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

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

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Osjetljivost i rezistencija bakterija na antibiotike u Republici Hrvatskoj u 2016. g.

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PREDGOVOR:

Nakon obilježavanja dvadesete godišnjice rada Odbora za praćenje rezistencije bakterija na antibiotike prošle godine, ove godine s ponosom ističemo objavljivanje ove, dvadesete publikacije o otpornosti bakterija na antibiotike u Hrvatskoj. Okosnicu ove publikacije već dvadeset godina čini izvješće o rezistenciji kliničkih izolata najčešćih bakterijskih vrsta u različitim regijama Hrvatske. Tom izvješću se ubrzo pridružilo i izvješće Nacionalnog referentnog laboratorija za tuberkulozu Hrvatskog zavoda za javno zdravstvo, a broj centara koji su doprinosili publikaciji svojim rezultatima je već prvih godina praćenja dosegao skoro apsolutan broj te rezultati objavljeni u ovoj publikaciji obuhvaćaju više od 90% hrvatske populacije. Potaknuti europskim inicijativama krajem 1990-tih za praćenje rezistencije u invazivnih izolata (projekt European Antimicrobial Resistance Surveillance System, EARSS) i za praćenje potrošnje antibiotika (projekt European Surveillance of Antimicrobial Consumption, ESAC), Odbor je oformio radne grupe koje su se uključile u ove europske projekte. Od tada i ova izvješća čine sastavni dio publikacije, ali istovremeno nas i povezuju s europskim projektima koji su 2010. i 2011. g. prerasli u kontinuirane programe Europskog centra za prevenciju i kontrolu bolesti (European Center for Disease Prevention and Control, ECDC). U okviru Odbora osnovana je 2003.g. i hrvatska podružnica internacionalne organizacije The Alliance for the Prudent Use of Antibiotics (APUA) što je daljnje produbilo međunarodnu izmjenu informacija. Iako je Ministarstvo zdravstva (MZ) od početka imalo svog predstavnika u Odboru, 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. Od samog početka praćenja rezistencije, vanjska kontrola kvalitete čini bitan dio rada mreže laboratorija i poglavlje o rezultatima vanjske kontrole čini neizostavni dio ove publikacije i vrijedan izvor pučnog materijala za usavršavanje rada u rutini. Izazovi u detekciji sojeva s novim mehanizmima rezistencije su se tijekom vremena mijenjali, ali sinhronizirani rad mreže laboratorija omogućio je uspješno otkrivanje prvih takvih izolata i njihovo praćenje što je opisano u novije pridruženom poglavlju o izolatima posebnog značaja. Pomno usklađivanje hrvatskih laboratorija sa standardima europskog odbora The European Committee for Antimicrobial Sensitivity Testing (EUCAST) osigurava Povjerenstvo za metodologiju određivanja osjetljivosti na antibiotike (hrvatski „National Antibiotic Committee, NAC") osnovano 2011.g. unutar Odbora za praćenje rezistencije. Praćenje rezistencije i izdavanje godišnje publikacije dobilo je svoj puni smisao osnutkom Interdisciplinarne sekcije za kontrolu rezistencije na antibiotike (ISKRA) pri MZ 2006.g. kada su aktivnosti praćenja rezistencije postale integralni dio nacionalne strategije za kontrolu širenja rezistencije i podloga za razvijanje kliničkih smjernica, intenzivniju interdisciplinarnu suradnju, održavanje javnih kampanja i drugih intervencija usmjerenih na kontrolu širenja rezistentnih bakterija. Publikacija o rezistenciji bakterija u Hrvatskoj, dostupna u današnjem opsegu, rezultat je dugogodišnjeg rada i iskustva mnogih mikrobiologa, konzultacija s mikrobiolozima i kliničarima unutar i izvan Odbora te izmjene iskustava i znanja s vodećim međunarodnim institucijama.

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

PREFACE:

After celebrating the Croatian Committee for Antibiotic Resistance Surveillance 20th anniversary last year, this year we proudly present the 20th publication on antimicrobial resistance in Croatia. The core of this publication is a chapter describing resistance in clinical isolates from different regions in Croatia that is being published every year for 20 years now. Soon after the first edition this publication was enriched by the report of the national tuberculosis reference laboratory of the Croatian Public Health Institute. The number of centers contributing to national data reached almost absolute number already in the early years of surveillance so that data presented in this publication cover more than 90% of Croatian population. Working groups for antimicrobial resistance surveillance in invasive isolates and for antimicrobial consumption surveillance were formed to follow the European initiatives in the late 1990s (the European Antimicrobial Resistance Surveillance System, EARSS and the European Surveillance of Antimicrobial Consumption, ESAC projects) and ever since reports on resistance in invasive isolates and on antibiotic consumption are integral part of this publication and at the same time important link with the European projects that evolved into the European Center for Disease Prevention and Control (ECDC) continuous programs in 2010 and 2011. In 2003 the Croatian Chapter of The Alliance for the Prudent Use of Antibiotics (APUA) was established within the Committee for Antibiotic Resistance Surveillance to further promote international collaboration. Although the Ministry of Health (MoH) was represented by a delegate in the Committee from the very beginning, a deeper collaboration started with establishment of the MoH Reference Center for Antibiotic Resistance Surveillance at the University Hospital for Infectious Diseases "Dr. Fran Mihaljevic" in 2003. The Reference Center provides technical support for the surveillance network. From the very beginning external quality assurance (EQA) proved to be a very important part of the surveillance network and a chapter on EQA results is an important part of this publication and a valuable source of material for professional education. Challenges in detection of resistance mechanisms were changing with time and synchronized work of the laboratory network enabled successful detection of emergence and spread of resistant isolates which is described in a recently added chapter on alert organisms. The Croatian National Antibiotic Committee (NAC) was founded in 2011 as a body within the Committee for Antibiotic Resistance Surveillance and it takes care that every year Croatian antibiotic sensitivity testing standards are updated according to the current European Committee for Antimicrobial Sensitivity Testing (EUCAST) standards. Antibiotic resistance surveillance and yearly data publication gained its full meaning when the Croatian Intersectoral Coordination Mechanism (ICM), the Interdisciplinary Section for Antimicrobial Resistance Control (ISKRA) was established at the Ministry of Health in 2006. ISKRA coordinates all the activities related to antimicrobial resistance control and antibiotic resistance surveillance became one of the important components of the national strategy to control antimicrobial resistance and the basis for development of national guidelines on antibiotic use, better interdisciplinary collaboration, public campaigns and other interventions aiming to control antibiotic resistance. Publication on antibiotic resistance in Croatia in its current shape is a result of a long time work and experience of many microbiologists, wide consultations with microbiologists and clinicians and exchange of knowledge and experience with leading international institutions.

Arjana TambiĆ AndraġeviĆ
President of the Committee for Antibiotic Resistance Surveillance in Croatia

POGLAVLJE / CHAPTER 1.

REZISTENCIJA BAKTERIJSKIH IZOLATA U 2016. GODINI

ANTIBIOTIC RESISTANCE IN 2016

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UVOD

Praćenje rezistencije na antibiotike u Hrvatskoj organizirano je na dobrovoljnoj osnovi, no svi sudionici u praćenju 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 prati novosti u standardima European Committee for Antimicrobial Sensitivity Testing (EUCAST) i na zimskom sastanku Odbora donosi preporuke o standardima važećim za narednu godinu. Zahvaljujući redovitim sastancima Odbora i djelovanju nacionalnog povjerenstva za antibiotike postignut je visok stupanj standardizacije u mikrolaboratorijskom 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

Antibotic resistance surveillance in Croatia is organized on voluntary basis but all participants 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) antimicrobila resistance (AMR) surveillance at the national level became obligatory for all European Union Member States including Croatia. Croatian national antibiotic committee (NAC) for sensitivity testing methodology is a subcommittee of the Committee for antibiotic resistance surveillance closely follows developments within the European Committee for Antimicrobial Sensitivity Testing (EUCAST) and updates sensitivity testing standards accordingly every year at the Committee winter meeting. Due to the regular Committee meetings and NAC activity a high level of interlaboratory standardization is achieved and the EQAS results demonstrate high reproducibility of delivered resistance data. Although this chapter reports aggregated national resistance data, these data represent a compilation of isolate based data analysed at the level of a local laboratory and great attention is given to exclusion of copy isolates and testing of all isolates to the well defined panel of antibiotics throughout the surveillance period. The pittfal of this surveillance sheme is that patient demographic data are not available at the national level but analysis of a large number of clinical isolates enables consistent monitoring of trends in resistance and timely notification of isolates with novel resistance mechanisms.

MATERIJALI I METODE

Globalno praćenje rezistencije

U praćenje su uključeni svi izolati dogovorenih bakterijskih vrsta izolirani iz kliničkih materijala u razdoblju od 1.10. do 31.12.2016.g. Od 2016.g. u ispitivanje osjetljivosti po prvi puta su uključeni i klinički izolati *Candida* spp. Rezultati za izolate streptokoka grupe A, salmonela, šigela, anaerobnih bakterija i kandida prikupljaju se, zbog malog broja izolata, tijekom cijele godine, od 1.1. do 31.12.2016. Podatke za 2016.g. podnijelo je 38 centara (popis u legendi za tablice), što obuhvaća >90% populacije u Hrvatskoj.

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

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

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

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

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

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

1. pneumokoke rezistentne na norfloksacin
2. stafilokoke rezistentne na vankomicin i / ili linezolid
3. enterokoke rezistentne na vankomicin
4. *H.influenzae* rezistentan na ko-amoksiklav i / ili cefalosporine III generacije (engl. „beta-lactamase negative ampicillin resistant", BLNAR sojeve)
5. enterobakterije rezistentne na bilo koji od karbapenema

Tijekom 2016.g. korišteni su za testiranje i interpretaciju nalaza standardi europskog odbora, European Committee for Antimicrobial Sensitivity Testing (EUCAST) standardi (Breakpoint Table 6.0 za bakterije i Antifungal Clinical Breakpoint Table 7.1 za *Candida* spp.). U testiranju 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, za određivanje osjetljivosti stafilokoka na glikopeptide te pseudomonasa i acinetobaktera na kolistin. Preporuka Odbora je da se izolati *A. baumannii* i *P. aeruginosa* rezistentni na jedan, ali ne i oba karbapenema retestiraju određujući MIK za imipenem i meropenem U 2016.g. osjetljivost *P.aeruginosa* na ceftolozan + tazobaktam ispitana je u deset centara (PU ZZJZ, RI KBC, SB ZZJZ, ST KBC, ĐI ZZJZ, VŽ ZZJZ, ZG KBC, ZG KBD, ZG KBM i ZG KIB) određivanjem MIK vrijednosti (E-test, BioMerieux).

Disk difuzijska metoda se primjenjuje prema tekuć im EUCAST standardima. Minimalne inhibitorne koncentracije se odreĽuju korigtenjem gradijent testova (Etest, bioMérieux; MIC Test Strip, Liofilchem) ili mikrodilucije u bujonu.

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

U 2016.g. po prvi puta su analizirani podaci o rezistenciji *Candida* spp. na antifungalne lijekove. Za interpretaciju osjetljivosti korigteni su standardi EUCAST Antifungal clinical breakpoint table v.7.0.

Ciljane studije

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

U 2016.g. po prvi puta su u praćenje rezistencije uključ eni i klinič ki 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 obraĽuje 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 obraĽuje demografske podatke pacijenata, a u svrhu detaljnije analize invazivni izolati enterokoka, stafilokoka i *P. aeruginosa* ğalju se u Zavod za klinič ku i molekularnu mikrobiologiju Klinič kog bolnič kog centra Zagreb, a invazivni izolati pneumokoka, *E. coli*, *K. pneumoniae* i *Acinetobacter baumannii* u Zavod za klinič ku mikrobiologiju Klinike za infektivne bolesti ñDr. F. Mihaljević ò. RC za praćenje rezistencije ğalje podatke o invazivnim izolatima u The European Surveillance System (Tessy) Europskog centra za kontrolu bolesti (engl. òEuropean Center for Disease Controlò, ECDC). Podaci o invazivnim izolatima od poč etka praćenja do 2016.g. prikazani su u zasebnom poglavlju ove publikacije.

Od 2001.g., uključ ivanjem u europski projekt European Surveillance of Antimicrobial Consumption (ESAC), a potom i ESAC-Net, Hrvatska prati potroğnju antibiotika izraģenu u definiranim dnevnim dozama na 1000 stanovnika dnevno (DDD/TID). Podaci o bolnič koj i izvanbolnič koj potroğnji antimikrobnih lijekova se takoĽer ğalju u Tessy sustav ECDC-a. Podaci o potroğnji antibiotika u Hrvatskoj u 2016.g. su objavljeni kao posebno poglavlje ove publikacije, a uključ uju i detaljniju analizu bolnič ke potroğnje antibiotika koja se detaljnije poč ela 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 moğe uoč iti problem multiplorezistentnih bakterija u Hrvatskoj s obzirom da se rijetki izolati s novim mehanizmima rezistencije č esto ne prikazuju kao znač ajan postotak u velikom broju izolata obraĽenih u masovnom praćenju.

MATERIALS AND METHODS

Global surveillance

Global antibiotic resistance surveillance includes all clinical isolates of designated bacterial species isolated from 1 October till 31 December, 2016. In 2016 for the first time clinical isolates of *Candida* spp. were included in surveillance. Data on group A streptococci, salmonellae, shigellae, anaerobic bacteria and *Candida* spp. are collected throughout the year, from 1 January to 31 December, 2016 due to the small number of isolates. In 2016 thirtyeight centers took part in antibiotic resistance surveillance (names of the centers are listed in the legend to the tables) which makes a catchment population of >90%.

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

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

b. antibiotics designated to a particular bacterial species are listed on the antibiotic resistance surveillance form for the current year

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

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

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

1. pneumococci resistant to norfloxacin
2. staphylococci resistant to vancomycin and / or linezolid
3. vancomycin resistant enterococci
4. *H.influenzae* resistant to co-amoxiclav and / or III generation cephalosporins (beta-lactamase negative ampicillin resistant, BLNAR strains)
5. enterobacteriaceae resistant to any carbapenem

In 2016 EUCAST standards (Breakpoint Table 6.0 for bacteria and Antifungal Clinical Breakpoint Table 7.1 for *Candida* spp.) were used as official methodology. Disk diffusion method is the most widely used sensitivity testing method in Croatia and minimal inhibitory concentration (MIC) testing is used for testing anaerobic bacteria and detection of penicillin and ampicillin resistance in penicillin non-susceptible pneumococci, glycopeptide resistance in staphylococci and colistin resistance in pseudomonas and acinetobacter. The Committee recommendation is that for *A. baumannii* and *P. aeruginosa* isolates resistant to one but not to both carbapenems MICs of imipenem and meropenem should be determined In 2016 susceptibility of *P.aeruginosa* to ceftolozane + tazobactam was tested in ten centers (PU ZZJZ, RI KBC, SB ZZJZ, ST KBC, ĠI ZZJZ, VÇ ZZJZ, ZG KBC, ZG KBD, ZG KBM and ZG KIB) using MIC gradient strip method (E-test, BioMerieux).

Disk diffusion method is performed according to the current EUCAST standards. Minimal inhibitory concentrations are determined by gradient tests (Etest, bioMérieux; MIC Test Strip, Liofilchem) or microbroth dilution.

Bacterial species and antibiotics tested are listed in tables in further text.

In 2016 data on *Candida* spp. resistance to antifungal agents were analysed for the first time. For sensitivity interpretation EUCAST Antifungal clinical breakpoint table v.7.0. was used.

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.

In 2016 gonococci were for the first time included in antibiotic resistance surveillance. Data were analyzed at the Department of Bacteriology of the Croatian Public Health Institute and are described in a separate chapter of this publication.

Data on invasive isolates (isolates from blood and cerebrospinal fluid) of *S. pneumoniae*, *S. aureus, E. faecalis, E. faecium, E. coli*, *K. pneumoniae, P. aeruginosa* and *Acinetobacter baumannii* were first collected within the European Antimicrobial Resistance Surveillance System (EARSS) project and afterwards within the EARS-Net program. For these isolates Reference center (RC) for resistance surveillance collects and analyses patient demographic data and for the purpose of more detailed analysis invasive isolates of enterococci, staphylococci and *P.aeruginosa* are regularly sent to the Institute for Clinical and Molecular Microbiology, Clinical Hospital Centre Zagreb and invasive pneumococci, *E. coli*, *K. pneumoniae* and *A.baumannii* are sent to the Department of Clinical Microbiology, University Hospital for Infectious Diseases ñDr. F. MihaljeviÍ ò. RC for resistance surveillance is obliged to send Croatian resistance data to The European Surveillance System (Tessy), a global European Center for Disease Control (ECDC) surveillance network. Data on invasive isolates from the beginning of surveillance until 2016 are presented in a separate chapter of this publication.

Croatia started to analyze 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 2016 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 is still not seen as significant increase in resistance rates.

REZULTATI

U praćenju rezistencije u 2016.g. sudjelovalo je 38 centara u Hrvatskoj. Prosječni rezultati za Hrvatsku i rezultati za pojedinačne centre prikazani su u tablicama i grafovima u daljnjem tekstu. Rezultati laboratorija koji su prijavili manje od 30 izolata pojedine bakterijske vrste smatraju se nepouzdanim podacima za taj centar, ali su uvrštteni u tablice i uključeni su u zbirne rezultate za RH. Podaci o izolatima malo vjerojatnog fenotipa koji nisu potvrđeni u jednom od centralnih laboratorija označeni su zvjezdicom kao nepotvrđeni i ne smatraju se vaćećima.

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

- ČK ZZJZ je za *A. baumannii* prikazao rezultate za cijelu godinu
- GS ZZJZ je za sve vrste prikazao rezultate za cijelu godinu
- IG ZZJZ je za *BHS – A* prikazao rezultate za razdoblje 1.10. – 31.12.2016., za *Enterococcus faecalis* i *A. baumannii* je prikazao rezultate za cijelu godinu
- KA ZZJZ je za *E. faecium* prikazao rezultate za cijelu godinu
- PU ZZJZ je za *H.influenzae* i *A. baumannii* prikazao rezultate za cijelu godinu
- PČ ZZJZ je za sve vrste prikazao rezultate za cijelu godinu
- VK ZZJZ je za *S. pneumoniae, S. aureus*/MSSA, *S. aureus*/MRSA, *H. influenzae i A. baumannii* prikazao rezultate za cijelu godinu (izolati iz OB Vinkovci)
- SB ZZJZ je za *S. pneumoniae* i *H.influenzae* prikazao rezultate za cijelu godinu

Četiri laboratorija su prijavili izolaciju šigela: ČK ZZJZ *Sh. sonnei* (2); OG OB *Sh.sonnei* (1); RI NZZJZ *Sh.sonnei* (3) i DU ZZJZ *Sh.flexneri* (1). Ukupno je tijekom 2016.g. izolirano sedam šigela.

U 2016.g. ukupno je obrađeno 860 anaerobnih bakterija, 487 gram-pozitivnih i 373 gram-negativnih anaeroba iz 19 centara : ČK ZZJZ gram-pozitivni anaerobi (20), gram-negativni anaerobi (35); KA ZZJZ gram-pozitivni anaerobi (2), gram-negativni anaerobi (1); KC ZZJZ gram-pozitivni anaerobi (1); KT MAGD. gram-pozitivni anaerobi (4); gram-negativni anaerobi (2); OS ZZJZ gram-pozitivni anaerobi (5), gram-negativni anaerobi (10); PU ZZJZ gram-pozitivni anaerobi (1), gram-negativni anaerobi (8); RI KBC gram-pozitivni anaerobi (55), gram-negativni anaerobi (31); SB ZZJZ gram-pozitivni anaerobi (15), gram-negativni anaerobi (18); SK ZZJZ gram-pozitivni anaerobi (2), gram-negativni anaerobi (4); ST KBC gram-pozitivni anaerobi (100), gram-negativni anaerobi (52); ŠI ZZJZ gram-pozitivni anaerobi (13), gram-negativni anaerobi (14); VK ZZJZ gram-pozitivni anaerobi (3), gram-negativni anaerobi (8); VT ZZJZ gram-pozitivni anaerobi (1), gram-negativni anaerobi (13); VČ ZZJZ gram pozitivni anaerobi (105), gram-negativni anaerobi (61); ZD ZZJZ gram-pozitivni anaerobi (9), gram-negativni anaerobi (10); ZG KBM gram-pozitivni anaerobi (26), gram-negativni anaerobi (31); ZG KIB gram-pozitivni anaerobi (3), gram-negativni anaerobi (8); ZG KDB gram-pozitivni anaerobi (17), gram-negativni anaerobi (28); ZG KBSD gram-pozitivni anaerobi (105), gram-negativni anaerobi (39).

Osamnaest laboratorija je prijavilo izolaciju *Candida* spp.: ĻK ZZJZ *C. glabrata* (1); KA OB *C. glabrata* (41), *C. tropicalis* (10); OS ZZJZ *C. parapsilosis* (7), *C. krusei* (1); PU ZZJZ *C. krusei* (1); RI KBC *C. glabrata* (40), *C. parapsilosis* (10), *C. krusei* (12), *C. tropicalis* (13); SB ZZJZ *C. glabrata* (1), *C. parapsilosis* (5); SK *ZZJZ C. parapsilosis* (2); ST KBC *C. glabrata* (1), *C. parapsilosis* (20); ĠI ZZJZ *C. glabrata* (5), *C. krusei* (1), *C. dubliniensis* (1), *C. tropicalis* (1); VK ZZJZ *C. parapsilosis* (2); VĢ ZZJZ *C. parapsilosis* (1); ZG KBC *C. glabrata* (8), *C. parapsilosis* (18); ZG KBD *C. glabrata* (2), *C. parapsilosis* (3), *C. krusei* (1); ZG KBM *C. glabrata* (4), *C. parapsilosis* (3), *C. tropicalis* (3), *C. kefyr* (1); ZG KBCSM *C. glabrata* (2), *C. parapsilosis* (2); ZG KZT *C. parapsilosis* (4); ZG KIB *C. parapsilosis* (1); ZG KBSD *C. krusei* (1). Ukupno je tijekom 2016.g. izolirano 229 *Candida* spp.

RESULTS

Thirtyeight centers took part in antibiotic resistance surveillance in Croatia in 2016. Average data for Croatia and results for individual laboratories are presented in tables and figures further in the text. Results of the laboratories that reported less than 30 isolates of a single bacterial species were included in tables as to add to the total number for Croatia, but were flagged as not reliable resistance rate data for that individual centre. Where isolates of less probable phenotype were reported without being sent to a central laboratory for retesting, data were flagged as not retested centrally and these data are not considered to be reliable.

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

- ĻK ZZJZ reported data for *A. baumannii* for the whole year
- GS ZZJZ reported data for all species for the whole year
- IG ZZJZ reported data for GAS for the period 1.10. ï 31.12.2016., for *Enterococcus faecalis* and *A. baumannii* for the whole year
- KA ZZJZ reported data for *E. faecium* for the whole year
- PU ZZJZ reported data for *H.influenzae* and *A. baumannii* for the whole year
- PĢ ZZJZ reported data for all species for the whole year
- VK ZZJZ reported data for *S. pneumoniae, S. aureus*/MSSA, *S. aureus*/MRSA, *H. influenzae* and *A. baumannii* for the whole year (isolates from OB Vinkovci)
- SB ZZJZ reported data for *S. pneumoniae* and *H.influenzae* for the whole year

Four laboratories reported shigella isolates: ĻK ZZJZ *Sh. sonnei* (2); OG OB *Sh.sonnei* (1); RI NZZJZ *Sh.sonnei* (3); DU ZZJZ *Sh.flexneri* (1). Altogether seven shigella isolates were reported in 2016.

In 2016 altogether 860 anaerobic bacteria were isolated, 487 gram-positives and 373 gram-negatives. They were isolated in 19 centers: ĻK ZZJZ gram-positive anaerobes (20), gram-negative anaerobes (35); KA ZZJZ gram-positive anaerobes (2), gram-negative anaerobes (1); KC ZZJZ gram-positive anaerobes (1); KT MAGD gram-positive anaerobes (4), gram-negative anaerobes (2); OS ZZJZ gram-positive anaerobes (5), gram-negative anaerobes (10); PU ZZJZ gram-positive anaerobes (1), gram-negative anaerobes (8); RI KBC gram-positive anaerobes (55), gram-negative anaerobes (31); SB ZZJZ gram-positive anaerobes (15), gram-negative anaerobes (18); SK ZZJZ gram-positive anaerobes (2), gram-negative anaerobes (4); ST KBC gram-positive anaerobes (100), gram-negative anaerobes (52); ĠI ZZJZ gram-positive anaerobes (13), gram-negative anaerobes (14); VK ZZJZ gram-positive anaerobes (3), gram-negative anaerobes (8); VT ZZJZ gram-positive anaerobes (1), gram-negative anaerobes (13); VĢ ZZJZ gram-positive anaerobes (105), gram-negative anaerobes (61); ZD ZZJZ gram-positive anaerobes (9), gram-negative anaerobes (10); ZG KBM gram-positive anaerobes (21), gram-negative anaerobes (10); ZG KBM gram-positive anaerobes (26), gram-negative anaerobes (31); ZG KIB gram-positive anaerobes (3), gram-negative anaerobes (8); ZG KDB gram-positive anaerobes (17), gram-negative anaerobes (28); ZG KBSD gram-positive anaerobes (105), gram-negative anaerobes (39).

Eighteen laboratories reported *Candida* spp. isolates: LK ZZJZ *C. glabrata* (1); KA OB *C. glabrata* (41), *C. tropicalis* (10); OS ZZJZ *C. parapsilosis* (7), *C. krusei* (1); PU ZZJZ *C. krusei* (1); RI KBC *C. glabrata* (40), *C. parapsilosis* (10), *C. krusei* (12), *C. tropicalis* (13); SB ZZJZ *C. glabrata* (1), *C. parapsilosis* (5); SK *ZZJZ C. parapsilosis* (2); ST KBC *C. glabrata* (1), *C. parapsilosis* (20); GI ZZJZ *C. glabrata* (5), *C. krusei* (1), *C. dubliniensis* (1), *C. tropicalis* (1); VK ZZJZ *C. parapsilosis* (2); VG ZZJZ *C. parapsilosis* (1); ZG KBC *C. glabrata* (8), *C. parapsilosis* (18); ZG KBD *C. glabrata* (2), *C. parapsilosis* (3), *C. krusei* (1); ZG KBM *C. glabrata* (4), *C. parapsilosis* (3), *C. tropicalis* (3), *C. kefyr* (1); ZG KBCSM *C. glabrata* (2), *C. parapsilosis* (2); ZG KZT *C. parapsilosis* (4); ZG KIB *C. parapsilosis* (1); ZG KBSD *C. krusei* (1). Altogether 229 *Candida* spp. isolates were reported in 2016.

DISKUSIJA

Beta-hemolitički streptokok grupe A (BHS-A) je glavni uzročnik bakterijskih upala grla, no može i asimptomatski kolonizirati sluznicu ždrijela. Izolacija BHS-A iz uzorka rane, naprotiv, uvijek predstavlja patološki nalaz jer BHS-A posjeduje naglašeni potencijal za izazivanje infekcija kože i mekih tkiva. Rezistencija BHS-A na penicilin još nije opisana te je ovaj antibiotik prvi lijek izbora u liječenju streptokoknih infekcija. Kod grlobolje, makrolidi su alternativa penicilinu u osoba preosjetljivih na penicilin, no stečena rezistencija na makrolide može ugroziti ishod terapije. Rezistencija BHS-A na makrolide u 2016.g. iznosi 7% i nije se zadnjih godina značajnije mijenjala (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 bila konstitutivna u 3% izolata i inducibilna u 3% izolata, što je slično prošlogodišnjim stopama (5% i 2%). Prema EUCAST standardima izolati s inducibilnom rezistencijom su se do 2014.g. izdavali kao osjetljivi na klindamicin uz upozorenje da se izbjegava dugotrajnija terapija, a od 2014.g. se takvi izolati interpretiraju kao rezistentni na klindamicin uz opasku da se klindamicin još uvijek može primijeniti u kratkotrajnom liječenju ili u liječenju blažih infekcija kože i mekih tkiva. Klindamicin se preporuča i u kombiniranoj terapiji s penicilinom kod teških nekrotizirajućih infekcija s obzirom da djeluje brže od beta-laktama i sprječava sintezu toksina. Utjecaj inducibilne rezistencije na uspjeh u kombiniranoj terapiji nije posebno proučen no s obzirom na naglu narav širenja nekroze u takvim slučajevima vjerojatno je uputno u početku terapije uključiti klindamicin.

Infekcije višnih puteva su pretežno uzrokovane virusima no u česte respiratorne patogene, uključuju se i pneumokoki, *Haemophilus influenzae* i *Moraxella catarrhalis*. Ove bakterije mogu uzrokovati izvanbolnički pneumoniju, upalu srednjeg uha i sinusitis, ali često se nalaze i kao dio fiziološke mikrobiote gornjih dišnih puteva u zdravih ljudi ili tijekom virusne infekcije gornjih dišnih puteva. Brisevi nazofarinksa, stoga, pokazuju nisku specifičnost i osjetljivost, često zavode u kliničkom rasuđivanju i ne preporučuju se kao uzorci za dijagnosticiranje etiologije infekcija gornjih dišnih puteva. U Hrvatskoj se brisevi nazofarinksa sve manje uzimaju, čemu doprinose i smjernice Hrvatskog društva za kliničku mikrobiologiju, te se broj prijavljenih pneumokoka i hemofilusa sve više smanjuje. Izolati pneumokoka i hemofilusa opisani u ovom poglavlju potječu, ipak, još uvijek pretežno iz briseva nazofarinksa i predstavljaju pretežno kolonizirajuću mikrobiotu. Neinvazivni pneumokoki često pokazuju veće stope rezistencije negoli invazivni izolati. Rezistencija invazivnih pneumokoka opisana je u poglavlju o invazivnim izolatima i mjerodavnija je kao putokaz za primjenu antimikrobne terapije. Stope rezistencije ukupnih pneumokoka imaju, međutim, epidemiološko značenje jer ukazuju na trendove u širenju rezistencije. U Hrvatskoj, parenteralni penicilin je još uvijek lijek izbora u liječenju pneumokoknih pneumonija jer visoka rezistencija na penicilin iznosi i dalje 3%. Empirijsko liječenje pneumonije treba, međutim, započeti višim dozama penicilina kako bi se učinkovito djelovalo na pneumokoke koji pokazuju intermedijarnu rezistenciju. Ukupno, stopa smanjene osjetljivosti na penicilin u 2016.g. iznosi 24%, što znači i da se ne nastavlja trend smanjenja neosjetljivosti uočen prošlih godina (22% u 2015.g., 23% u 2014.g., 31% u 2013%.g., 30% u 2012.g., 29% u 2011.g., 24% u 2010.g., 29% u 2009.g., 30% u 2008.g., 26% u 2007.g.). Infekcije uzrokovane pneumokokima smanjene osjetljivosti na penicilin nisu dostupne liječenju oralnim penicilinom, a u slučaju da zahvaćaju središnji živčani sustav ni parenteralnim penicilinom. Pneumonije uzrokovane izolatima intermedijarne osjetljivosti na penicilin mogu se liječiti parenteralnim penicilinom u dozama prilagođenima visini minimalnih inhibitornih koncentracija (MIK). Prema rasponu MIK-ova penicilina registriranih u 2016.g. 97% svih pneumokoka ima MIK penicilina ≤2.0 mg/L i reagirat će na dozu od 6x2.4g (6x4MIU), 94% pneumokoka ima MIK penicilina ≤1.0 mg/L i reagirat će na dozu od 4x2.4g (4x4MIU) ili 6x1.2g (6x2MIU), a 89% pneumokoka ima MIK penicilina ≤0.5 mg/L i reagirat će na dozu od 4x1.2g (4x2MIU). Zbog povoljnijih farmakodinamskih osobina i dobre djelotvornosti na pneumokoke i hemofiluse, amoksicilin/ampicilin se češće od penicilina upotrebljava u liječenju upale uha, sinusitisa i pneumonija. EUCAST standardi imaju oštrije granične

koncentracije za ampicilin negoli američki standardi te smo prelaskom na EUCAST poželi registrirati veći postotak na ampicilin visoko (3% u 2016.g., 2015.g. i 2014.g.) i intermedijarno (9% u 2016.g. i 2015.g. i 11% u 2014.g.) rezistentih pneumokoka, što se vjerojatno može nadvladati primjenom viših doza ampicilina. Prelaskom na EUCAST poželi su se primjenjivati i oštriji kriteriji za detekciju rezistencije hemofilusa na ampicilin te se lagani porast rezistencije nakon 2010.g. može dijelom pripisati i promjeni standarda (9% u 2006.g., 11% u 2007.g., 8% u 2008.g., 10% u 2009.g., 11% u 2010.g., te nakon prelaska na EUCAST 13% u 2011.g. i 2012.g., 17% u 2013.g., 14% u 2014.g., 20% u 2015.g., 24% u 2016.g.). Rezistencija pneumokoka na makrolide (35%) je identična prošlogodišnjoj stopi, a rezistencija na ko-trimoksazol (23%) i tetraciklin (22%) je slična prošlogodišnjim stopama (26% i 22%). Dugoročno gledajući i rezistencija na ko-trimoksazol pokazuje trend pada (43% u 2010.g., 35% u 2011.g., 29% u 2012.g., 27% u 2013.g., 29% u 2014.g., 26% u 2015.g., 23% u 2016.g.). Otpornost pneumokoka na respiratorne kinolone je još uvijek niska (<1%).
Staphylococcus aureus je glavni uzročnik infekcija kože i mekih tkiva. Rezistencija na penicillin se proširila još 1940-tih godina i danas su još samo rijetki izolati osjetljivi na penicilin. Osim uobičajene rezistencije na penicilin, meticilin senzitivni *Staphylococcus aureus* (MSSA) sojevi ne pokazuju značajnije stope rezistencije na druge antistafilokokne antibiotike, no 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 povoljnog trenda pada udjela MRSA sojeva uočenog nakon 2010.g. stopa MRSA je, nažalost, opet počela rasti (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.). Udio MRSA sojeva s inducibilnom rezistencijom na klindamicin (16% u 2014.g., 21% u 2015.g., 28% u 2016.g) raste, što bi mogao biti indirektni pokazatelj porasta izvanbolničkih MRSA. Rezistencija MRSA na gentamicin je u daljnjem padu (91% u 2006.g., 81% u 2009.g., 77% u 2010.g., 69% u 2011.g., 64% u 2012.g., 59% u 2013.g., 43% u 2014.g., 38% u 2015.g., 32% u 2016.g.). Rezistencija na tigeciklin, linezolid i vankomicin nije uočena. Distribucija MIK-ova vankomicina je podjednaka prošlogodišnjim vrijednostima. Udio izolata s MIK-om od 2.0 mg/L je iznosio 8% u 2016.g., 7% u 2015.g. te 16% i 20% u 2014.g. i 2013.g.

Enterokoki su prirodno rezistentni na mnoge grupe antibiotika, a gotovo svi izolati *Enterococcus faecium* pokazuju rezistenciju na ampicilin. Svi enterokoki pokazuju uroĎenu rezistenciju niskog stupnja na aminoglikozide, ali se aminoglikozidi kod divljih tipova enterokoka još uvijek mogu upotrebljavati u terapiji kombiniranoj s ampicilinom ili glikopeptidima. Kod sojeva visoko rezistentnih na aminoglikozide, ovi se antibiotici ne mogu upotrebljavati niti u kombiniranoj terapiji. Udio sojeva s visokom rezistencijom na aminoglikozide iznosi 27% za *E.faecalis* i 60% za *E.faecium*, što je podjednako prošlogodišnjim stopama. Rezistencija na vankomicin je još uvijek rijetka u *E.faecalis* (<1%), ali je i dalje u porastu u *E. faecium* (1% u 2012.g., 5% u 2013.g., 7% u 2014.g., 15% u 2015.g., 17% u 2016.g.). Od 2015.g. vankomicin rezistentni *E. faecium* (VRE) izolati se počinju s većom učestalošću javljati i izvan Zagreba, u brojnim drugim regijama Hrvatske. 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. Rezistencija na kinolone u *E. faecalis* (19%) i *E. faecium* (80%) podjednaka je prošlogodišnjim stopama (20% i 72%).

Escherichia coli je najčešći uzročnik infekcija mokraćnog sustava (IMS), a ostale enterobakterije često uzrokuju komplicirane IMS ili infekcije raznih sustava povezane s bolničkom skrbi. Enterobakterije su i sastavni dio fiziološke mikrobiote te nalaz ovih bakterija u primarno nesterilnim uzorcima treba pažljivo tumačiti u sklopu cjelokupne kliničke slike. S obzirom da su enterobakterije dio fiziološke mikrobiote često su izložene primjeni antibiotika, a širenje jednom nastalih mutanti teško je učiniti i kontrolirati. Od početka praćenja *E. coli* pokazuje visoku rezistenciju na ampicilin (50% u 2016.g.), ali amoksicilin s dodatkom klavulanske kiseline pokazuje dobru djelotvornost jer klavulanska kiselina uspješno blokira

beta-laktamaze ġirekog spektra i veĺinu beta-laktamaza proġirenog spektra (engl. ñextended spectrum beta-lactamases, ESBLò). Kombinacija s klavulanskom kiselinom, meĽutim, ograniļava primjenu amoksicilina u visokim dozama, kakve su ļesto potrebne kod ozbiljnih sistemnih infekcija. U 2014.g. EUCAST je po prvi puta razdvojio interpretaciju osjetljivosti na amoksicilin s klavulanskom kiselinom ovisno o tome radi li se o nekompliciranoj IMS ili drugim oblicima infekcije. Nakon te podjele, stope rezistencije su ostale podjednake ako se interpretiraju za primjenu kod nekompliciranih IMS (7% u 2013.g. i 2014.g., 9% u 2015.g., 10% u 2016.g.) no znatno su se povisile ako se interpretiraju za primjenu kod ostalih infekcija (16% u 2014.g. i 2015.g., 15% u 2016.g.). Rezistencija na cefalosporine treĺe generacije (6% do 9%) je u daljnjem laganom porastu, ali rezistencija na karbapeneme je i dalje izuzetno rijetka i ne odraġava se u stopama rezistencije. Rezistencija na kinolone je, takoĽer, u daljnjem laganom porastu (14% u 2012. i 2013.g., 17% u 2014.g., 18% u 2015.g., 19% u 2016.g.), a rezistencije na ko-trimoksazol (27%), gentamicin (9%), amikacin (1%) i nitrofurantoin (3%) su sliļne ili jednake proġlogodiġnjim stopama.

Proteus mirabilis joġ uvijek izaziva preteġno izvanbolniļke infekcije i prirodno bi trebao biti bakterijska vrsta dobro osjetljiva na sve beta-laktamske antibiotike usmjerene na gram-negativne bakterije. Naġalost, rezistencija na beta-laktamske antibiotike je veĺ dosegla visoke stope i u 2016.g. iznosi za ampicilin 48%, za ko-amoksiklav 23%, za piperacilin/tazobaktam 2%, za cefalosporine 3.generacije od 17% do 19% i za cefepim 4%. Rezistencija na ciprofloksacin (24%), gentamicin (21%), amikacin (11%) i ko-trimoksazol (42%) je podjednaka proġlogodiġnjim stopama. Zbog svoje uroĽene otpornosti na kolistin, tigeciklin te niġe osjetljivosti na imipenem *Proteus mirabilis* i drugi *Proteus* spp. bi u buduĺnosti mogli predstavljati sve veĺi problem, naroļito kod uroloġkih bolesnika i infekcija povezanih s bolniļkom skrbi.

Klepsijele i enterobakteri ļesto uzrokuju infekcije povezane s bolniļkom skrbi te veĺ dugi niz godina pokazuju visoke stope rezistencije. *Klebsiella pneumoniae* je prirodno rezistentna na ampicilin no rezistencija na ostale beta-laktame je steļena uslijed dugotrajnog izlagnja antibioticima. Stope rezistencije na cefalosporine treĺe i ļetvrte generacije (21% za ceftibuten do 32% za ceftriakson) i ko-amoksiklav (35%) su sliļne proġlogodiġnjima. Nakon ġto je broj klepsijela rezistentnih na karbapeneme po prvi puta u 2014.g. dosegao razinu vidljivu kao postotak rezistencije na imipenem i meropenem, te su se stope zadrġale i u 2016.g. (1% rezistentnih i 1% intermedijarnih izolata).

Enterobakteri, citrobakteri i seracije ļine grupu enterobakterija koje prirodno posjeduju inducibilne cefalosporinaze i s izuzetkom *Citrobacter koseri* pokazuju rezistenciju ne samo na ampicilin veĺ i na ko-amoksiklav i cefalosporine prve generacije. Cefuroksim samo marginalno djeluje na ovu grupu enterobakterija i prema EUCAST standardima ne postoji kliniļka interpretacija osjetljivosti na cefuroksim za ovu grupu bakterija. Divlji sojevi su osjetljivi na treĺu generaciju cefalosporina, no u tijeku terapije cefalosporinima moġe doĺi do probira derepresiranih mutanti koji stabilno hiperproduciraju AmpC cefalosporinaze i time uvjetuju rezistenciju i na cefalosporine treĺe generacije. Udio mutanti rezistentnih na cefalosporine treĺe i ļetvrte generacije (8% za cefepim do 28% za cefiksim) se nije bitno mijenjao u odnosu na proġlu godinu. Stopa rezistencije enterobaktera na imipenem i meropenem postala je vidljiva 2013.g. (1%), no u 2015.g. i 2016.g. ponovno je <1. Stope rezistencije na ciprofloksacin (11%), gentamicin (14%) i ko-trimoksazol (18%) se nisu znaļajnije promijenile u odnosu na prethodnu godinu.

Multiplorezistentni *Pseudomonas aeruginosa* veĺi dugi niz godina predstavlja veliki problem u Hrvatskoj. Neosjetljivost (visoka i umjerena rezistencija) *P.aeruginosa* na imipenem (20%) i meropenem (21%) se nije bitno promijenila u odnosu na prethodnu godinu (19% i 20%). Rezistencija na piperacilin/tazobaktam (10%), ceftazidim (14%), cefepim (9%), gentamicin (22%), amikacin (9%) i ciprofloksacin se takoĽer nije znaļajnije mijenjala S obzirom da se za sada osjetljivost na ceftolozan + tazobaktam moġe odrediti samo testiranjem MIK vrijednosti,

osjetljivost na ovaj novi antibiotik testirana je probno u deset centara. Testiranih 978 konsekutivnih izolata *P.aeruginosa* je pokazalo najbolju osjetljivost na ceftolozan + tazobaktam (94%), zatim na piperacillin + tazobaktam (88%), cefepime (88%) i amikacin (83%), a osjetljivost na ostale antibiotike (uključujući i karbapeneme) je bila Ò80%. MIC_{50} za ceftolozan + tazobaktam je iznosio 1.0 mg/L a MIC_{90} 2.0 mg/L.

Rezistencija na karbapeneme kod *Acinetobacter baumannii* se u Hrvatskoj naglo progirila od 2008.g. i u 2016.g. su se zadrgale visoke stope neosjetljivosti na imipenem (85%) i meropenem (86%), podjednake proglogodignjima. Prema EUCAST standardima ne postoje jasni dokazi o uginkovitosti ampicilin/sulbaktama na acinetobaktere, no kako je to jedan od rijetkih antibiotika koji jog pokazuju djelotvornost *in vitro*, ovaj antibiotik se u Hrvatskoj testira i interpretira prema amerigkim standardima. Neosjetljivost (visoka i umjerena rezistencija) na ampicilin/sulbaktam se zadrgala na visokim vrijednostima (33% u 2013.g., 43% u 2014.g., 55% u 2015.g., 49% u 2016.g.). Osjetljivost na kolistin se moge ispitati samo odreĎivanjem minimalnih inhibitornih koncentracija te se osjetljivost na kolistin zasada odreĎuje samo kod pseudomonasa i acinetobaktera rezistentnih na karbapeneme. Iako su registrirani pojedinagni izolati acinetobaktera i pseudomonasa rezistentni na kolistin, to se jog ne prikazuje kao postotak rezistencije.

Rezistencija salmonella na ampicilin dugo nije prelazila 10%, no u 2014., 2015.g. i 2016.g iznosi 14%, 16% i 14%. ESBL sojevi su i dalje rijetki meĎu salmonelama, ali u 2016.g. se već prikazuju i kao postotak rezistencije na cefalosporine 3. generacije (1%). Rezistencija na ko-amoksiklav (3%), ko-trimoksazol (2%) i ciprofloksacin (3%) je niska i identigna ili sligna proglogodignjim stopama. Do 2013.g. osjetljivost salmonela na ciprofloksacin na razini Hrvatske je bila 100%, a na nalidiksingu kiselinu, koja je bolji pokazatelj niske razine rezistencije na kinolne, do 2%. Od 2014.g. EUCAST je uveo testiranje osjetljivosti na kinolone (ciprofloksacin) preko pefloksacinskog diska gto je vjerojatno utjecalo na registriranje stopa rezistencije na ciprofloksacin od 2% u 2014.g., 4% u 2015.g i 3% u 2016.

Rezistencija u *Campylobacter coli* i *Campylobacter jejuni* se prati od 2013.g. Rezistencija na ciprofloksacin (60% za obje vrste) je u 2016.g. porasla u odnosu na proglogodignje vrijednosti (52% i 50%). Rezistencija na eritromicin iznosi 3% i 1%, gto je sligno proglogodignjim stopama. Rezistencija na tetraciklin (35% i 28%) je takoĎer negto viga negoli progle godine (32% i 21%).

Tijekom 2016.g. registrirano je sedam izolata gigela, gest izolata *Shigella sonnei* i jedan izolat *Shigella flexneri*. Iako je zbog malog broja izolata teško govoriti o stopama rezistencije, rezistencija je visoka na ampicilin (43%) i kotrimoksazol (67%), a ove godine rezistencija na ko-amoksiklav, cefalosporine treće generacije i ciprofloksacin nije zabilgena.

Stope rezistencije se kod anaerobnih bakterija nisu znagajnije mijenjale. MeĎu gram-negativnim anaerobima rezistencija je visoka na penicilin (84%) i klindamicin (28%), a kod gram-pozitivnih anaeroba rezistencija je visoka na metronidazol (61%). Rezistencija na ko-amoksiklav, piperacilin/tazobaktam i ertapenem je niska (Ò10%).

DISCUSSION

Group A streptococcus (GAS) is the most common agent causing bacterial sorethroat but can also asymptomatically colonize mucosa of the upper respiratory tract. When present in wound this organisms is always considered pathogenic because GAS has a marked potential for causing skin and soft tissue infections. Resistance to penicillin in GAS has not yet been described and penicillin is a drug of first choice in treating streptococcal infections. Macrolides are alternative therapy for sorethroat in patients with hypersensitivity to penicillin but acquired resistance may compromise the outcome of macrolide therapy. Resistance to macrolides in GAS in 2016 is 7% and does not demonstrate a significant change over the past few years (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 was constitutive in 3% and inducible in 3% of isolates which is similar to last year results (5% and 2%). Until 2014 the EUCAST standards recommended to report isolates with inducible clindamycin resistance as sensitive 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.

Respiratory tract infections are predominately caused by viruses but bacteria such as pneumococci, *Haemophilus influenzae* and *Moraxella catarrhalis* are also important respiratory pathogens. These bacteria can cause community acquired pneumonia, acute otitis media and sinusitis, but are also frequently found as part of the normal microbiota of the upper respiratory tract in healthy individuals or during a viral upper respiratory tract infection. Nasopharyngeal swabs have, therefore, low sensitivity and specificity, they can be misleading in clinical judgement and they are not recommended as samples for diagnosing aetiology of upper respiratory tract infections. In Croatia nasopharyngeal swabs are becoming less popular as diagnostic tool and their use is discouraged in guidelines of the Croatian Society of Clinical Microbiology so the number of reported pneumococcal and haemophilus isolates is decreasing. Most of the pneumococcal and haemophilus isolates reported in this chapter are still from nasopharyngeal swabs and aspirates and therefore mostly represent colonizing organisms. 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, parenteral penicillin is still a drug of first choice for treating pneumococcal pneumonia as high level resistance is still 3%. Empirical therapy of pneumonia should, however, include higher penicillin dosing to achieve efficacy against pneumococci with intermediate penicillin resistance. Altogether penicillin non-susceptibility rate in 2016 is 24% which means that the decreasing trend observed in the previous year (22% in 2015, 23% in 2014, 31% in 2013%, 30% in 2012, 29% in 2011, 24% in 2010, 29% in 2009, 30% in 2008, 26% in 2007) is interrupted. Infections caused by penicillin intermediately resistant pneumococci cannot be treated with oral penicillin and in case they involve central nervous system they cannot be treated with parenteral penicillin either. Pneumonia caused by pneumococci with intermediate penicillin resistance 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 2016, 97% of pneumococci have penicillin MIC Ò2.0 mg/L and will be covered by 6x2.4g (6x4MIU) dosing, 94% have penicillin MIC Ò1.0 mg/L and will be covered by 4x2.4g (4x4MIU) or 6x1.2g (6x2MIU) dosing and 89% have penicillin MIC Ò0.5 mg/L and will be covered by 4x1.2g (4x2MIU) dosing. Due to the better pharmacodynamic characteristics and good activity against

pneumococci and haemophilus amoxicillin / ampicillin is used in treatment of acute otitis media, sinusitis and pneumonia more frequently than penicillin. EUCAST standards have more rigorous breakpoint concentrations for ampicillin than American standards so when switching to EUCAST we started reporting higher proportions of ampicillin resistant (3% in 2016, 2015 and 2014) and intermediate (9% in 2016 and 2015 and 11% in 2014) pneumococci which can probably be overcome by higher ampicillin dosing. When switching to EUCAST we started to apply more rigorous ampicillin breakpoints for haemophilus as well and the increase in ampicillin resistance after 2010 can partially be attributed to the change of standards (9% in 2006, 11% in 2007, 8% in 2008, 10% in 2009, 11% in 2010, 13% in 2011 and 2012, 17% in 2013, 14% in 2014, 20% in 2015, 24% in 2016). Pneumococcal resistance to macrolides (35%) is identical to previous year rate and resistance to co-trimoxazole (23%) and tetracycline (22%) is similar (26% and 22%). Resistance to co-trimoxazole is showing decreasing trend (43% in 2010, 35% in 2011, 29% in 2012, 27% in 2013, 29% in 2014, 26% in 2015, 23% in 2016). Resistance of pneumococci to respiratory quinolones is still low (<1%). *Staphylococcus aureus* is a major skin and soft tissue pathogen. Penicillin resistance got widely spread already in the 1940s and today only rare isolates demonstrate susceptibility to penicillin. Apart from penicillin resistance methicillin sensitive *Staphylococcus aureus* (MSSA) do not demonstrate remarkable resistance rates to other antistaphylococcal antibiotics but methicillin resistant *Staphylococcus aureus* (MRSA) isolates are resistant to all beta-lactam antibiotics (except novel cephalosporins ceftaroline and ceftobiprole) and frequently show associated resistance to other antibiotic classes. Unfortunately, after a decrease observed after 2010, MRSA rates started to increase again (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). The rate of MRSA isolates with inducible clindamycin resistance (16% in 2014, 21% in 2015, 28% in 2016) is rising which could be an indirect indicator of rise in community acquired MRSA. Resistance to gentamicin is further decreasing (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). Resistance to tigecycline, linezolid and vancomycin was not recorded. Vancomycin MIC distribution is similar to previous year values. The rate of isolates showing MIC of 2.0 mg/L was 8% in 2016 and 7% in 2015 and 16% and 20% in 2014 and 2013.

Enterococci are naturally resistant to many antibiotic classes and *Enterococcus faecium* demonstrates high rate of resistance to ampicillin. All enterococci have low level of resistance to aminoglycosides. Aminoglycosides can still be used in combination with ampicillin or glycopeptides for treating wild type enterococci but not for strains with high level aminoglycoside resistance. High level aminoglycoside resistance rate in 2015 is 27% in *E.faecalis* and 60% in *E.faecium* which is similar to the previous year results. Resistance to vancomycin is still rare in *E.faecalis* (<1%) but is further increasing in *E.faecium* (1% in 2012, 5% in 2013, 7% in 2014, 15% in 2015, 17% in 2016). Since 2015 vancomycin resistant *E. faecium* (VRE) strains became more prevalent in many regions outside Zagreb as well. In 2014 EUCAST introduced testing sensitivity of enterococci to the quinolones with norfloxacin disk serving as an indicator of sensitivity to ciprofloxacin and levofloxacin. Quinolone resistance in *E.faecalis* (19%) and *E.faecium* (80%) is similar to previous year rates (20% and 72%).

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. Enterobacteriaceae are essential part of the normal human microbiota and clinical significance of finding these bacteria in primarily unsterile samples is difficult to estimate. As part of human microbiota enterobacteriaceae are frequently exposed to antibiotics and once the resistant mutants emerge they are difficult to spot and control. From the very beginning of surveillance resistance to ampicillin in *E. coli* (50% in 2016) is high but amoxicillin with clavulanic acid is still effective as clavulanic acid successfully blocks broad spectrum beta-lactamases and most extended spectrum beta-lactamases (ESBL). However, addition of clavulanic acid restricts the use of higher

amoxicillin dosing which is often required in severe infections. In 2014 EUCAST introduced different interpretation of amoxicillin/clavulanic acid sensitivity 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) but did change significantly if interpreted for other infections (16% in 2014 and 2015, 155 in 2016). Resistance to 3rd generation cephalosporins (6% to 9%) continues increasing slightly but resistance to carbapenems is still rare and bellow the rate of detection. Quinolone resistance is also slightly increasing (14% in 2012 and 2013, 17% in 2014, 18% in 2015, 19% in 2016), and resistance to co-trimoxazole (27%), gentamicin (9%), amikacin (1%) and nitrofurantoin (3%) is similar or identical to previous year rates.

Proteus mirabilis is still predominately a community acquired pathogen and wild type organisms are sensitive to all beta-lactams designed for gram-negatives. Unfortunately, resistance to beta-lactam antibiotics has already reached high rates and in 2016 resistance to ampicillin is 48%, co-amoxiclav 23%, piperacillin/tazobactam 2%, 3rd generation cephalosporins 17% to 19% and cefepime 4%. Resistance to ciprofloxacin (24%), gentamicin (21%), amikacin (11%) and co-trimoxazole is similar to previous year rates. Due to its innate resistance to colistin, tigecycline and low sensitivity to imipenem *Proteus mirabilis* and *Proteus* spp. may pose a growing problem in the future, especially in urology patients and in health care associated infections.

Klebsiellae 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. Resistance to 3rd and 4th generation cephalosporins (21% ceftibuten to 32% ceftriaxone) and co-amoxiclav (35%) is similar to previous year results. In 2014 the number of carbapenem resistant klebsiellae for the first time reached the level visible as percentage of resistance to imipenem and meropenem and until 2016 these rates remained the same (1% resistant and 1% intermediate isolates).

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. Cefuroxime is marginally active against this group of enterobacteriaceae and EUCAST standards do not include cefuroxime interpretation for this group of bacteria. Wild type isolates are susceptible to 3rd generation cephalosporins but resistant derepressed mutants that hyperproduce AmpC cephalosporinases often emerge during therapy. Resistance rates to 3rd and 4th generation cephalosporins (8% cefepime to 28% cefixime) did not change significantly. Resistance to imipenem and meropenem first became visible in 2013 (1%) but in 2015 and 2016 it is <1% again. Resistance to ciprofloxacin (11%), gentamicin (14%) and co-trimoxazole (18%) did not change significantly as compared to the previous year.

Multiply resistant *Pseudomonas aeruginosa* is a major problem in Croatia for many years. Non-susceptibility of *P.aeruginosa* to imipenem (20%) and meropenem (21%) did not change significantly as compared with the previous year (19% and 20%). Resistance to piperacillin/tazobactam (10%), ceftazidime (14%), cefepime (9%), gentamicin (22%), amikacin (9%) and ciprofloxacin (25%) did not change significantly either. As susceptibility to ceftolozane + tazobactam can be determined by MIC testing only, susceptibility to this new antibiotic was tested in ten centers. In the 978 consecutive *P.aeruginosa* isolates the highest susceptibility was recorded for ceftolozane + tazobactam (94%), followed by piperacillin + tazobactam (88%), cefepime (88%) and amikacin (83%), and susceptibility to other antibiotics (including carbapenems) was Ò80%. MIC_{50} for ceftolozane + tazobactam was 1.0 mg/L and MIC_{90} was 2.0 mg/L.

Carbapenem resistance in *A. baumannii* has rapidly spread throughout Croatia since 2008 and in 2016 non-susceptibility to imipenem (85%) and meropenem (86%) is maintained at high rates similar to last year results. According to 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 and therefore in Croatia American standards are used to test and interpret susceptibility of acinetobacter to ampicillin sulbactam. Non-susceptibility to ampicillin/sulbactam is maintained at high rates (33% in 2013, 43% in 2014, 55% in 2015, 49% in 2016). Susceptibility to colistin can only be detected by MIC test, so it is determined only in pseudomonas and acinetobacter isolates resistant to carbapenems. Although sporadic acinetobacter and pseudomonas isolates resistant to colistin have been reported, resistance did not reach visible resistance rate.

For many years resistance to ampicillin in salmonellae did not exceed 10% but in 2014, 2015 and 2016 it reached 14%, 15% and 14%. ESBL isolates are still rare among salmonellae but in 2016 this was already visible as a resistance rate of 1% to 3rd generation cephalosporins. Resistance to co-amoxiclav (3%), co-trimoxazole (2%) and ciprofloxacin (3%) is still low and identical or similar to the rates recorded in the previous year. Until 2013 susceptibility of salmonellae to ciprofloxacin in Croatia was 100% with 2% resistance to nalidixic acid, which is an indicator of low level resistance to quinolones. Since 2014 EUCAST introduced the use of pefloxacin disk as an indicator of susceptibility to ciprofloxacin which resulted in a ciprofloxacin resistance rate of 2% in 2014, 4% 2015 and 3% in 2016.

Resistance in *Campylobacter coli* and *Campylobacter jejuni* is reported since 2013. In 2016 resistance to ciprofloxacin (60% for both species) has increased compared to previous year rates (52% and 50%). Resistance to erythromycin is 3% and 1% which is similar to the rates recorded previously. Resistance to tetracycline (35% and 28%) is somewhat higher than last year (32% and 21%).

During 2016 seven shigella isolates were reported, 6 *Shigella sonnei* and one *Shigella flexneri* isolate. Due to the low number of isolates it is difficult to estimate resistance rates but resistance to ampicillin (43%), and co-trimoxazole (67%) appears high and this year no resistance to co-amoxiclav, 3rd generation cephalosporins or ciprofloxacin was recorded.

Resistance rates in anaerobic bacteria did not change significantly. Among gram-negative anaerobes resistance is high to penicillin (84%) and clindamycin (28%), and in gram-positive anaerobes high resistance is recorded for metronidazole (61%). Low rates of resistance (Ò10%) were recorded for co-amoxiclav, piperacillin/tazobactam and ertapenem.

LEGENDA ZA TABLICE */ LEGEND TO TABLES*

Šifra / *code*	**USTANOVE** /*CENTERS*
BJ ZZJZ	ZZJZ Bjelovarsko-bilogorske ġupanije, Bjelovar
ČK ZZJZ	ZZJZ MeĽimurske ġupanije, Ļakovec
DU ZZJZ	ZZJZ Dubrovaļko-neretvanske ġupanije, Dubrovnik
GS ZZJZ	ZZJZ Liļko-senjske ġupanije, GospiĹ
IG ZZJZ	ZZJZ Zagrebaļke ġupanije, IvaniĹ Grad
KA OB	OpĹa bonica Karlovac, Karlovaļka ġupanija
KA ZZJZ	ZZJZ Karlovaļke ġupanije, Karlovac
KC ZZJZ	ZZJZ Koprivniļko-kriġevaļke ġupanije, Koprivnica
KR ZZJZ*	ZZJZ Krapinsko-zagorske ġupanije , Krapina
KT MAGD.	Klinika za kardiovaskularne bolesti «Magdalena», Krapinske Toplice
NG OB	OpĹa bolnica Nova Gradiġka, Brodsko-posavska ġupanija
OG OB	OpĹa bolnica Ogulin, Karlovaļka ġupanija
OS ZZJZ	ZZJZ Osjeļko-baranjske ġupanije, Osijek
PU ZZJZ	ZZJZ Istarske ġupanije, Pula
PŽ OŽB**	OpĹa ġupanijska bolnica Poġega, Poġeġko-slavonska ġupanija
PŽ ZZJZ	ZZJZ Poġeġko-slavonske ġupanije, Poġega
RI KBC	Kliniļki bolniļki centar Rijeka, Rijeka
RI NZZJZ	Nastavni ZZJZ Primorsko-goranske ġupanije, Rijeka
SB ZZJZ	ZZJZ Brodsko-posavske ġupanije, Slavonski Brod
SK ZZJZ	ZZJZ Sisaļko-moslavaļke ġupanije, Sisak
ST KBC	Kliniļki bolniļki centar Split, Split
ST NZZJZ	Nastavni ZZJZ Splitsko-dalmatinske ġupanije, Split
ŠI ZZJZ	ZZJZ Ġibensko-kninske ġupanije, Ġibenik
VK ZZJZ	ZZJZ Vukovarsko-srijemske ġupanije, Vinkovci
VT ZZJZ	ZZJZ «Sveti Rok», Virovitiļko-podravske ġupanije, Virovitica
VŽ ZZJZ***	ZZJZ Varaġdinske ġupanije, Varaġdin
ZD ZZJZ	ZZJZ Zadarska ġupanije, Zadar
ZG KBC**	Kliniļki bolniļki centar «Zagreb», Zagreb
ZG KBD	Kliniļka bolnica «Dubrava», Zagreb
ZG KBM***	Kliniļka bolnica «Merkur», Zagreb
ZGKBCSM****	Kliniļki bolniļki centar «Sestre milosrdnice», Zagreb
ZG KZT	Klinika za traumatologiju, Zagreb
ZG KIB	Klinika za infektivne bolesti «Dr. F. MihaljeviĹ», Zagreb
ZG NZZJZ	Nastavni ZZJZ grada Zagreba, Zagreb
ZG HZZJZ	Hrvatski zavod za javno zdravstvo, Zagreb
ZG KDB	Klinika za djeļje bolesti Zagreb, Zagreb
ZG KBSD	Kliniļka bolnica «Sveti Duh», Zagreb
ZG SYNLAB	Poliklinika, Zagreb

* uklјuļuje podatke i za: OpĹu bolnicu Zabok
** uklјuļuje podatke i za: OpĹu ġupanijsku bolnicu, Pakrac
*** uklјuļuje podatke i za: Bolnicu za pluĹne bolesti i TBC, Klenovnik
**** uklјuļuje podatke i za: Kliniku za pluĹne bolesti ñJordanovacò, Zagreb
***** uklјuļuje podatke i za: Sveuļiliġnu Kliniku za dijabetes, endokrinologiju i bolesti metabolizma ñVuk Vrhovacò, Zagreb
****** uklјuļuje podatke i za: Institut za tumore, Zagreb

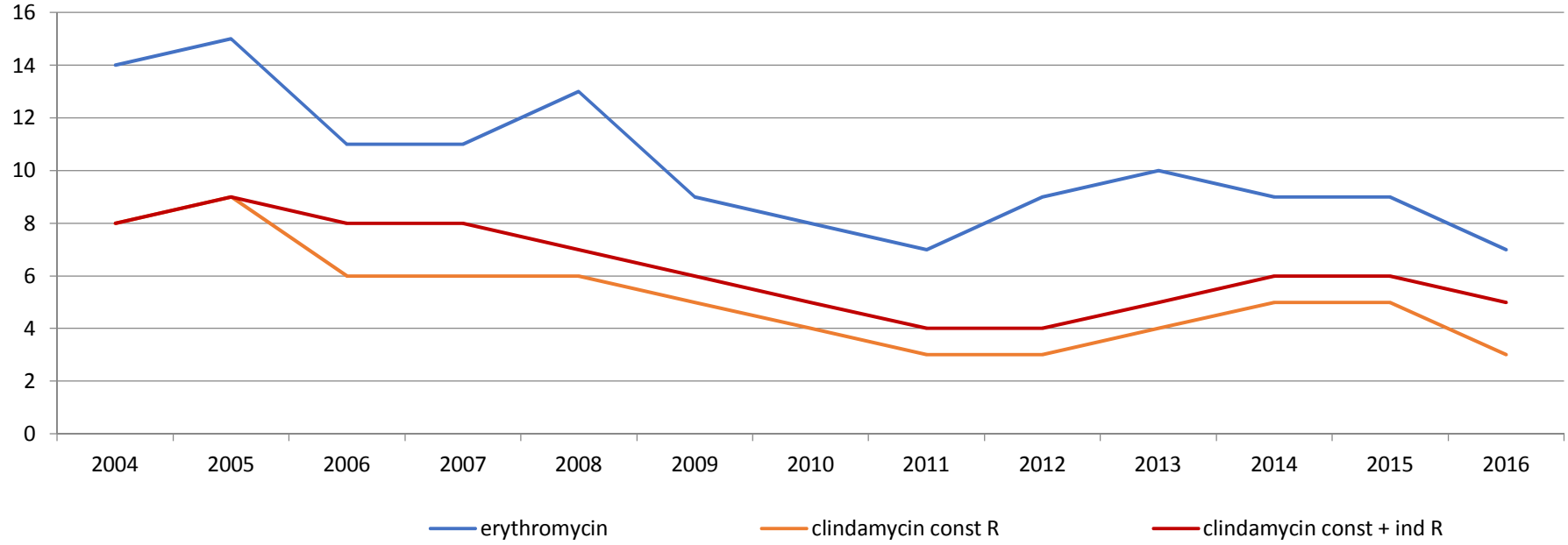
ANTIBIOTICI / *ANTIBIOTICS*

P $_{\textbf{parenteral}}$	*penicillin parenteral*
P $_{\textbf{oral}}$	*penicillin oral*
AMP	*ampicillin*
AMC	*amoxicillin + clavulanic acid*
AMC $_{\textbf{u}}$	*amoxicillin + clavulanic acid* $_{\textbf{uncomplicated urinary tract infection}}$
SAM	*ampicillin + sulbactam*
FOX	*cefoxitin*
CN	*cefalexin (I. gen. cephalosporins)*
CXM	*cefuroxime (II. gen. cephalosporins)*
CXM $_{\textbf{parenteral}}$	*cefuroxime parenteral*
CXM $_{\textbf{oral}}$	*cefuroxime oral*
CAZ	*ceftazidime (III. gen. cephalosporins)*
CRO	*ceftriaxone (III. gen. cephalosporins)*
CTB	*ceftibuten (III. gen. cephalosporins)*
CFM	*cefixime (III. gen. cephalosporins)*
CFEP	*cefepime (IV. gen. cephalosporins)*
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*
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*
CTZ	*ceftolozane + tazobactam*

UK = ukupan broj izolata / *total number of isolates*
No = broj izolata / *number of isolates*
I% = % intermedijarnih izolata / *% of intermediate isolates*
R% = % rezistentnih izolata / *% of resistant isolates*

Beta-hemolitički streptokok grupe A /
Group A streptococcus

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 2004. - 2016.



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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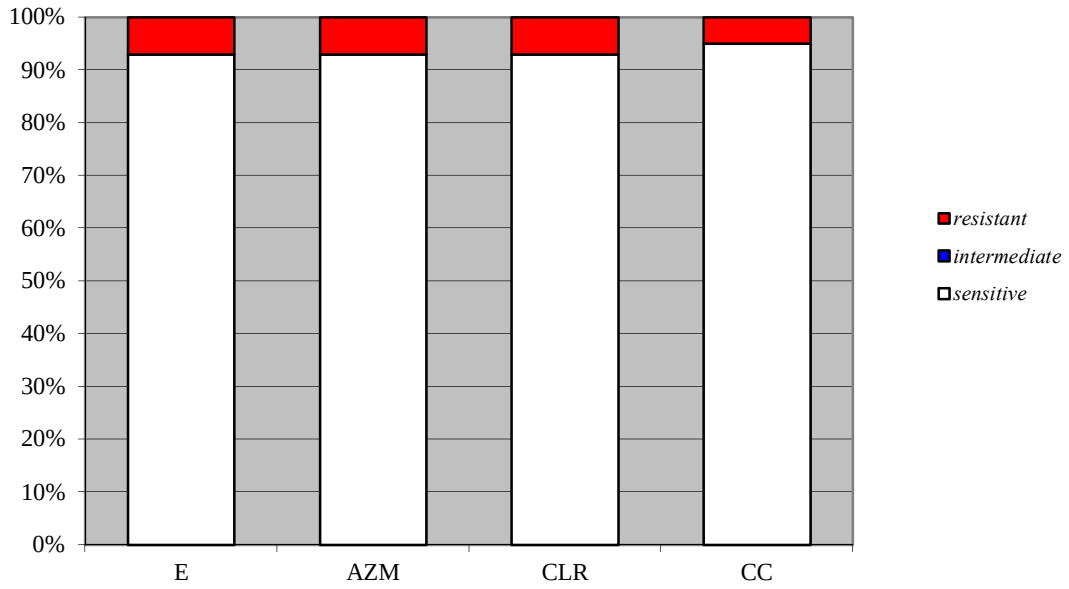
Beta-hemolitički streptokok grupe A /
Group A streptococcus

rezistencija na antibiotike u razdoblju od 1.01.- 31.12. 2016.,
zbirni prikaz izolata iz 38 centra u RH /
antibiotic resistance for the period 1.01. - 31.12. 2016,
summary results for the isolates from 38 centers in Croatia

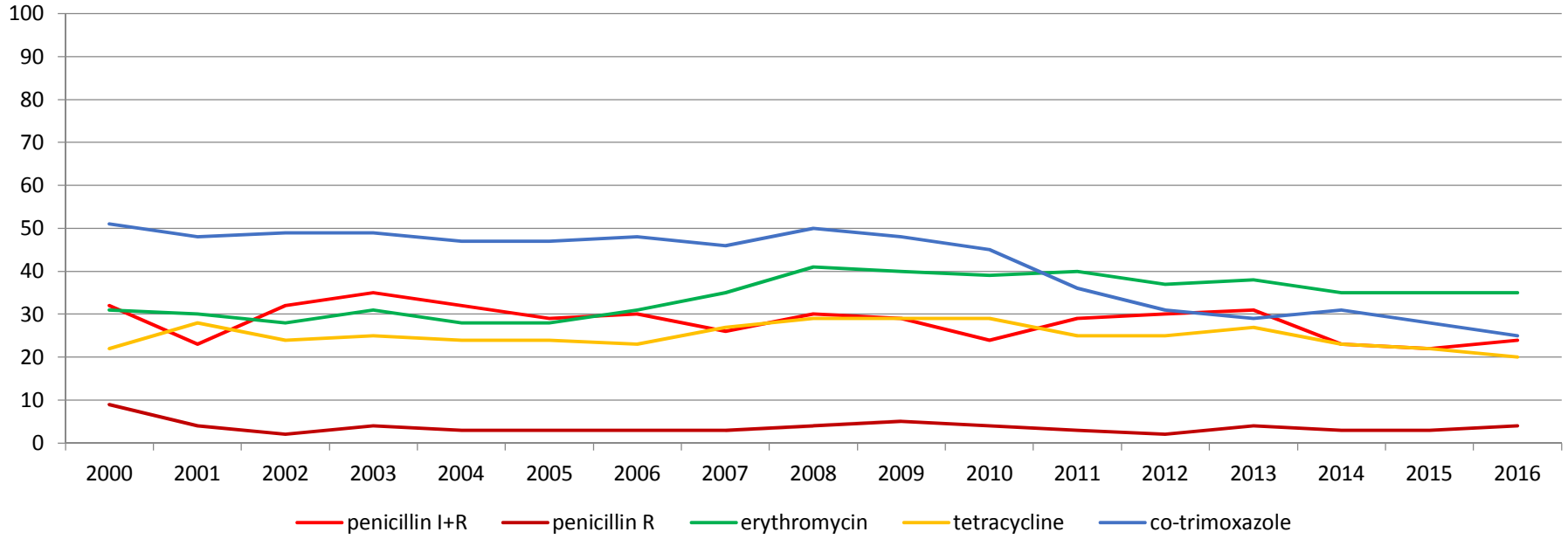
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Erythromycin	16 325	7 (0)	1 (0) - 19 (3)
Azithromycin	16 325	7 (0)	1 (0) - 19 (3)
Clarythromycin	16 325	7 (0)	1 (0) - 19 (3)
Clindamycin	16 325	5 (0)	
constitutive		3	0 - 11
inducible		3	0 - 15

*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

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2016.



R = visoka rezistencija / *high level resistance*
I = intermedijarna rezistencija / *intermediate resistance*

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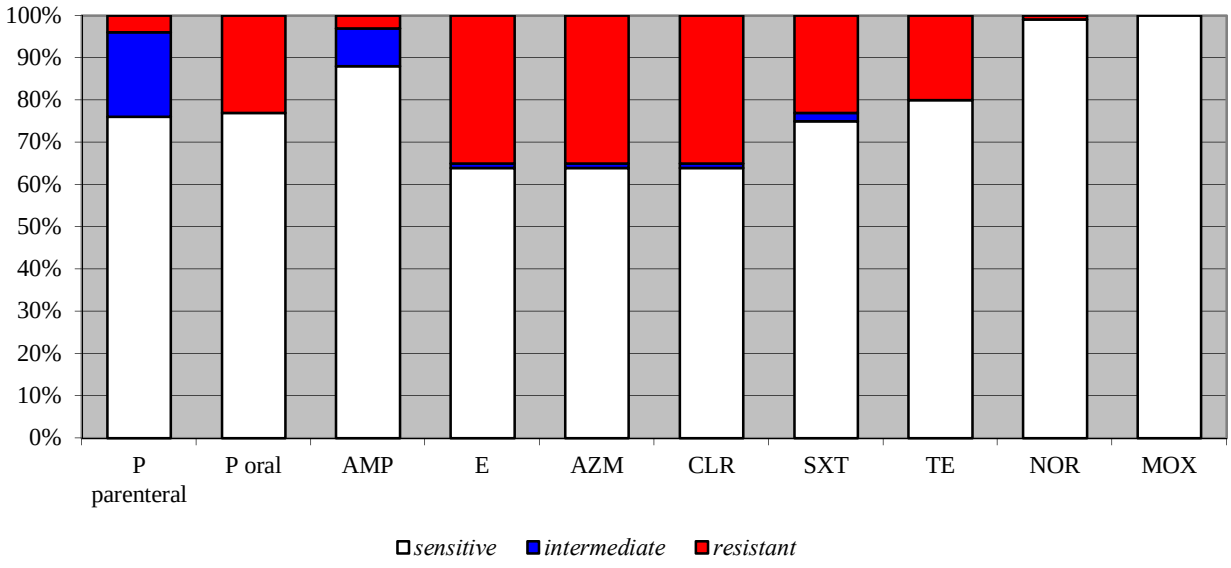
Streptococcus pneumoniae

rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2016.,
zbirni prikaz izolata iz 38 centra u RH /
antibiotic resistance for the period 1.10. - 31.12. 2016,
summary results for the isolates from 38 centers in Croatia

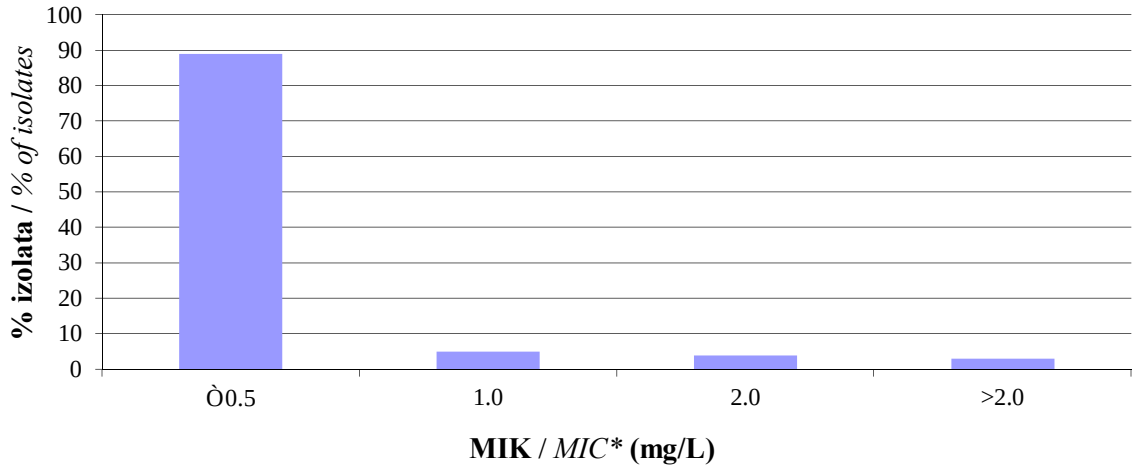
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Penicillin parenteral	1 971	4 (20)	0 (6) ï 8 (22)
Penicilin oral	1 971	23 (0)	2 (0) - 51 (0)
Ampicillin	1 663	3 (9)	0 (0) - 10 (5)
Erythromycin	1 911	35 (1)	17 (0) - 58 (0)
Azithromycin	1 911	35 (1)	17 (0) - 58 (0)
Clarythromycin	1 911	35 (1)	17 (0) - 58 (0)
Co-trimoxazole	1 908	23 (2)	6 (0) - 39 (0)
Tetracycline	1 744	20 (0)	3 (0) - 42 (0)
Norfloxacin	1 834	1 (0)	0 (0) - 21 (0)
Moxifloxacin	1 909	0 (0)	0 (0) - 6 (0)

* rezultati centara s malim brojem izolata (<32) 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, (1 830 *S. pneumoniae* izolata) /
Penicillin MIC distribution, (1 830 S. pneumoniae isolates), 1.10. ï 31.12. 2016.



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

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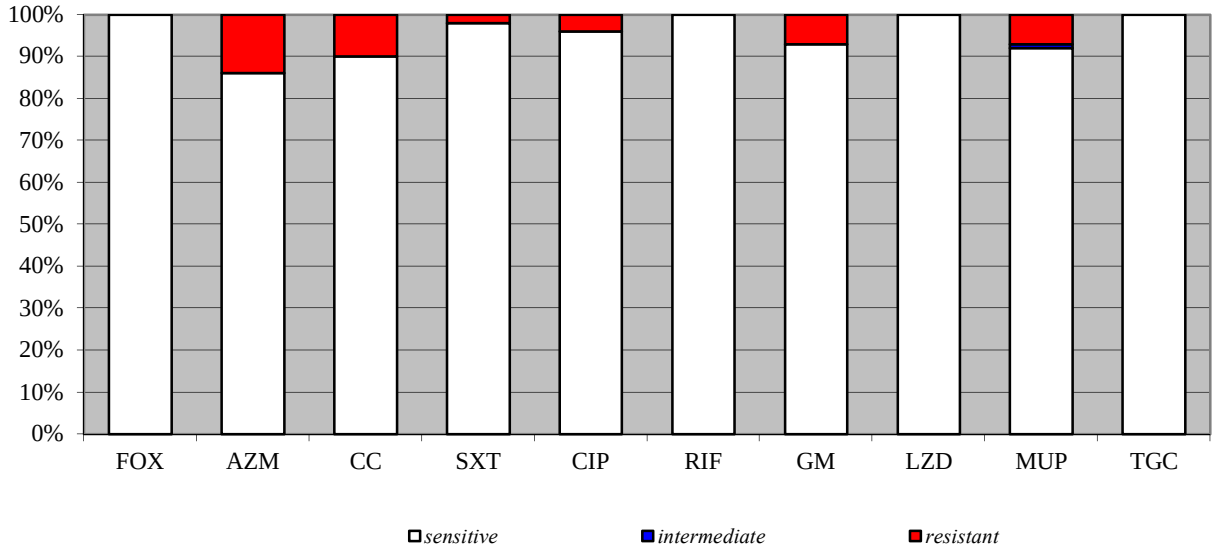
Staphylococcus aureus / MSSA

rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2016.,
zbirni prikaz izolata iz 38 centra u RH /
antibiotic resistance for the period 1.10. - 31.12. 2016,
summary results for the isolates from 38 centers in Croatia

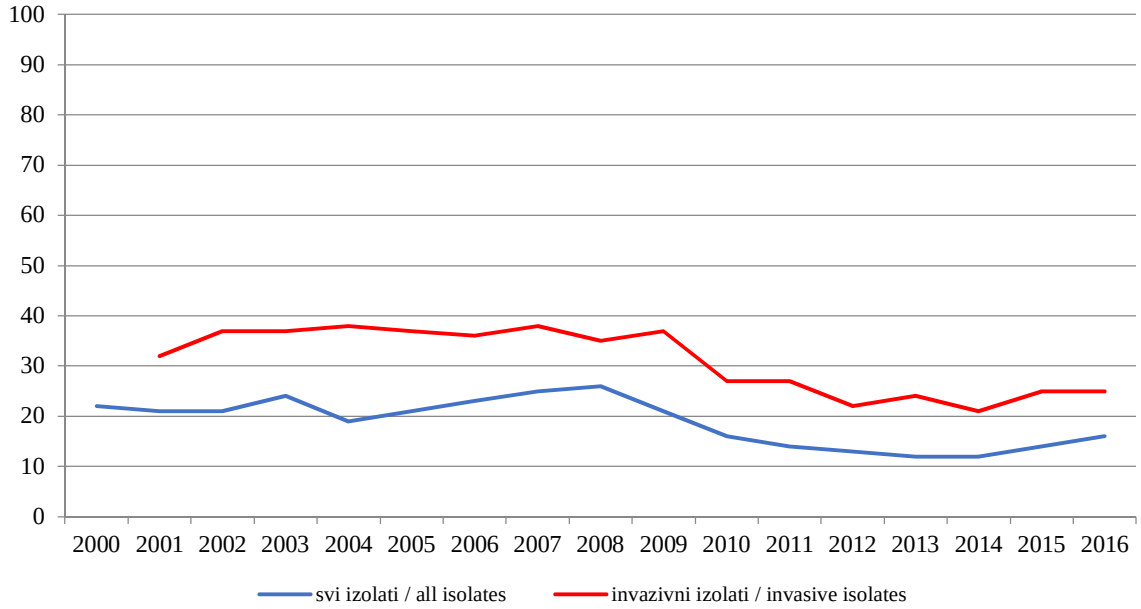
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Cefoxitin/ Methicillin	3 739	0 (0)	0 (0) - 0 (0)
Azithromycin	3 651	14 (0)	4 (0) - 26 (0)
Clindamycin	3 648	10 (0)	
constitutive		6	0 - 16
inducible		4	0 - 12
Co-trimoxazole	3 676	2 (0)	0 (0) - 7 (0)
Ciprofloxacin	3 249	4 (0)	0 (0) - 13 (0)
Rifampicin	3 004	0 (0)	0 (0) - 3 (0)
Gentamicin	3 648	7 (0)	0 (0) - 24 (0)
Linezolid	3 217	0 (0)	0 (0) - 0 (0)
Mupirocin	3 074	7 (1)	0 (0) - 23 (0)
Tigecycline	3 022	0 (0)	0 (0) - 0 (0)

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

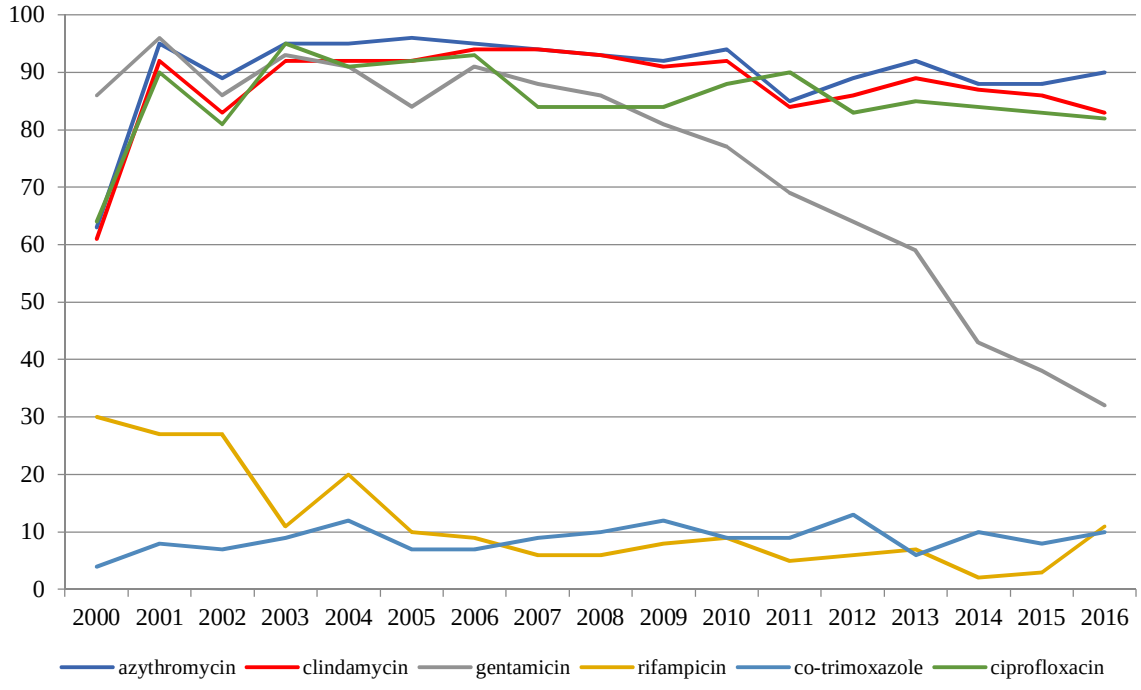


Staphylococcus aureus / MRSA

Methicillin resistant *Staphylococcus aureus* (MRSA) – stope / *rates*, 2000. - 2016.



neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2016.



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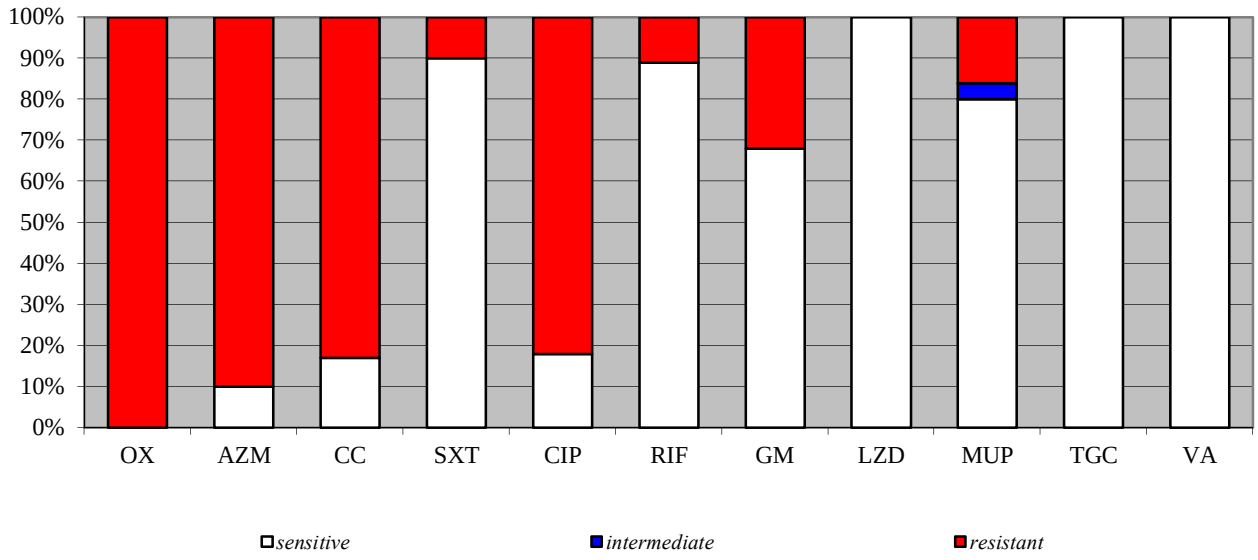
Staphylococcus aureus / MRSA

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2016.,
zbirni prikaz izolata iz 38 centra u RH /
antibiotic resistance for the period 1.10. - 31.12. 2016,
summary results for the isolates from 38 centers in Croatia

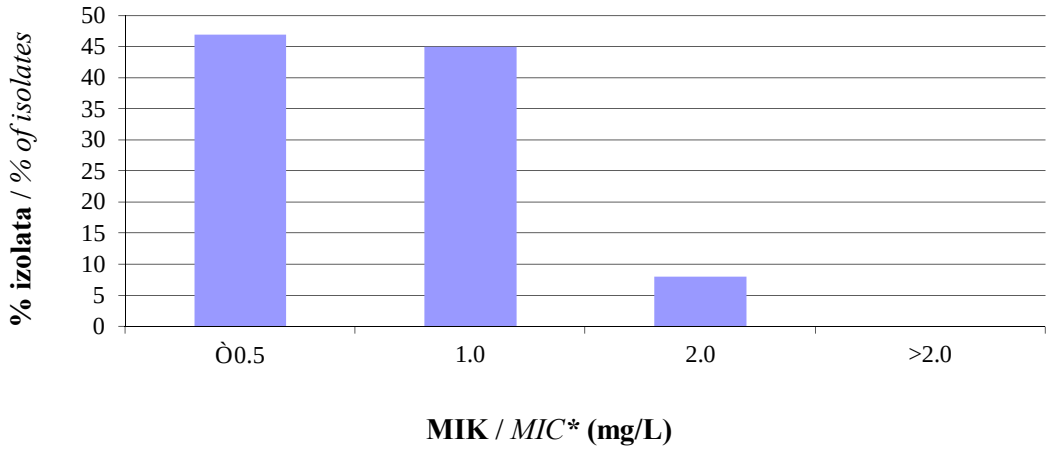
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Cefoxitin/ Methicillin	712	100 (0)	100 (0) - 100 (0)
Azithromycin	706	90 (0)	85 (0) - 100 (0)
Co-trimoxazole	710	10 (0)	0 (0) - 41 (5)
Clindamycin	706	83 (0)	85 (0) - 100 (0)
constitutive		55	3 - 85
inducible		28	0 - 97
Ciprofloxacin	705	82 (0)	26 (0) - 100 (0)
Rifampicin	702	11 (0)	0 (0) - 100 (0)
Gentamicin	706	32 (0)	2 (0) - 75 (0)
Linezolid	708	0 (0)	0 (0) - 0 (0)
Mupirocin	575	16 (4)	0 (0) - 55 (0)
Tigecycline	552	0 (0)	0 (0) - 0 (0)
Vankomicin	617	0 (0)	0 (0) - 0 (0)

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



Staphylococcus aureus / MRSA

Distribucija MIK-ova vankomicina, (617 MRSA izolata) /
Vancomycin MIC distribution, (617 MRSA isolates), 1.10. ï 31.12. 2016.



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

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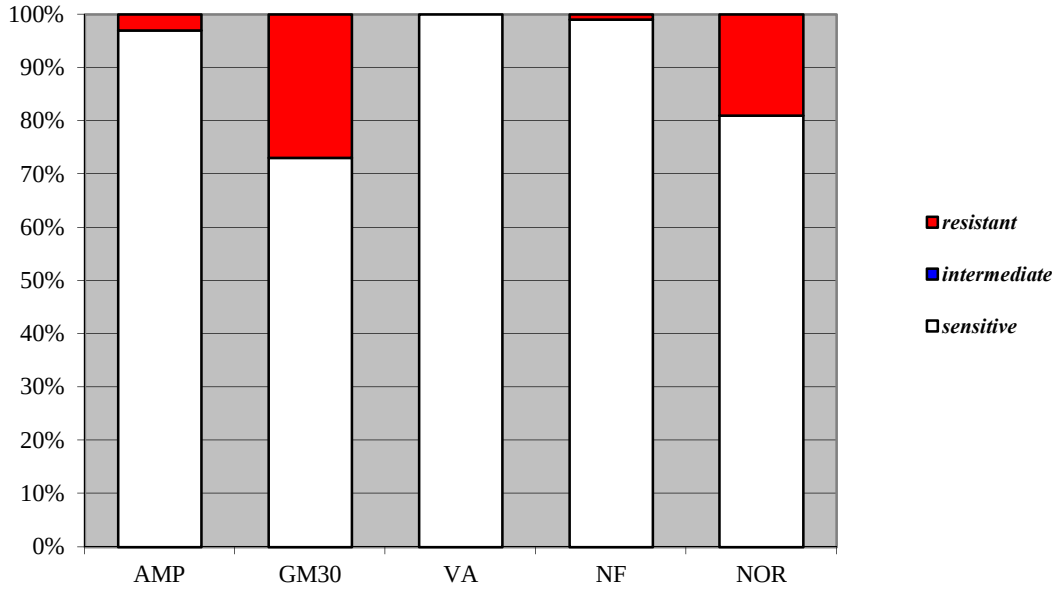
Enterococcus faecalis

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2016.,
zbirni prikaz izolata iz 38 centra u RH /
antibiotic resistance for the period 1.10. - 31.12. 2016,
summary results for the isolates from 38 centers in Croatia

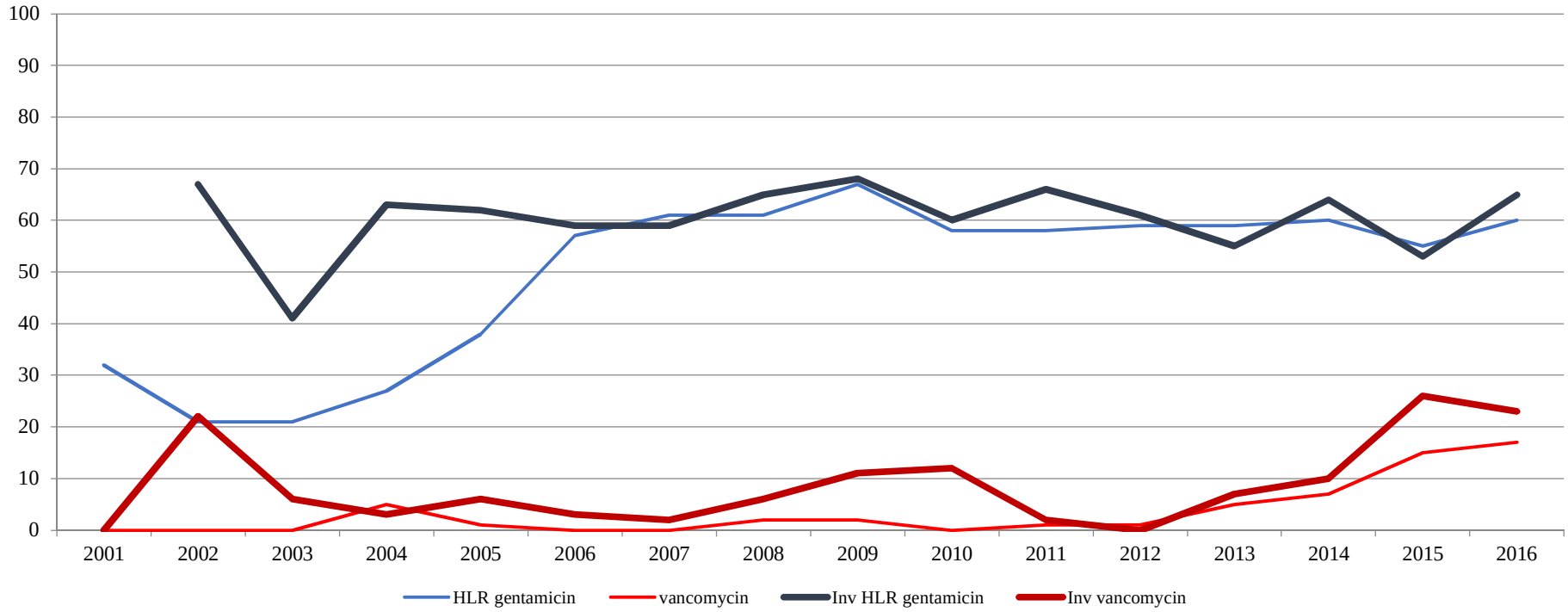
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	5 117	3 (0)	0 (0) - 82 (11)
Gentamicin	5 111	27 (0)	8 (0) - 57 (0)
Vancomycin	5 115	0 (0)	0 (0) -1 (0)
Nitrofurantoin	5 025	1 (0)	0(0) - 7 (0)
Norfloxacin	5 030	19 (0)	0 (0) - 37 (0)

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



Enterococcus faecium

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2001. - 2016.



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

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Enterococcus faecium

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2016.,
zbirni prikaz izolata iz 38 centra u RH /
antibiotic resistance for the period 1.10. - 31.12. 2016,
summary results for the isolates from 38 centers in Croatia

ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	736	92(0)	57 (0) - 100 (0)
Gentamicin	731	60 (0)	35 (0) - 71 (0)
Vancomycin	745	17 (0)	5 (0) - 49 (0)
Norfloxacin	569	80 (0)	22 (0) - 100 (0)

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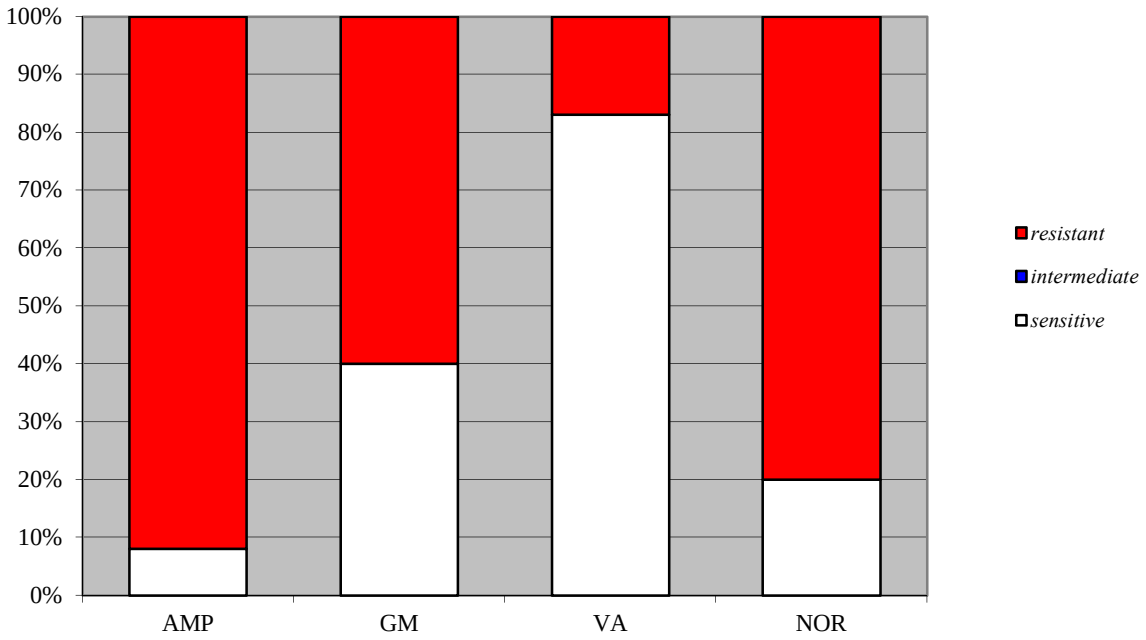
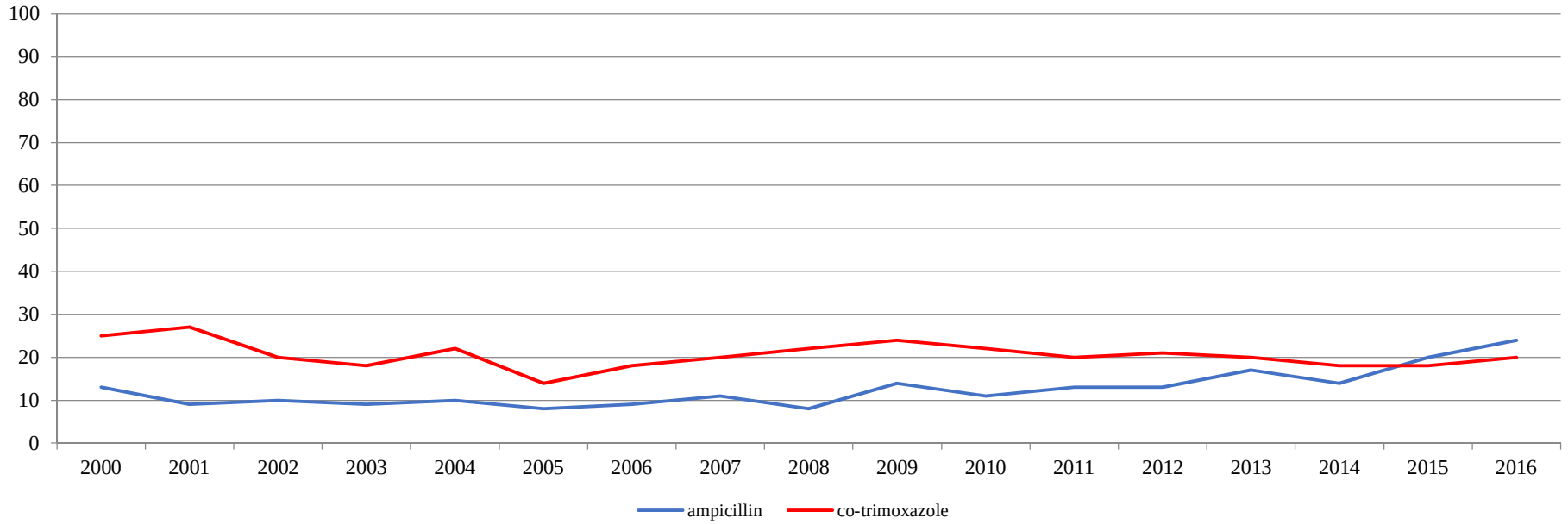
results from the centers with small number of isolates (<30) were not taken into consideration



Haemophilus influenzae

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2016.



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Haemophilus influenzae

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2016.,
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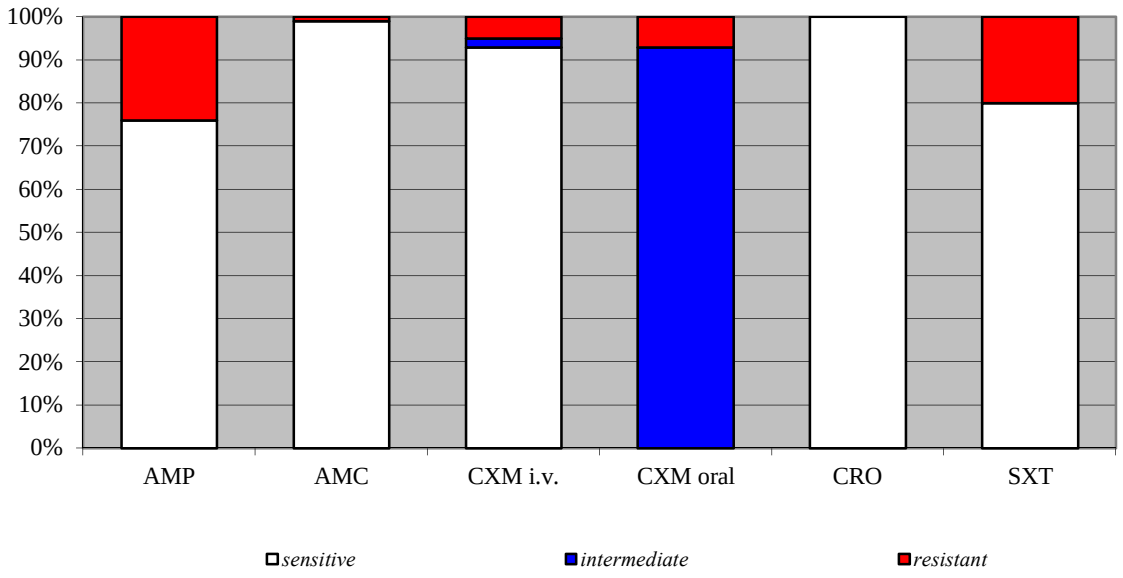
antibiotic resistance for the period 1.10. - 31.12. 2016,
summary results for the isolates from 38 centers in Croatia

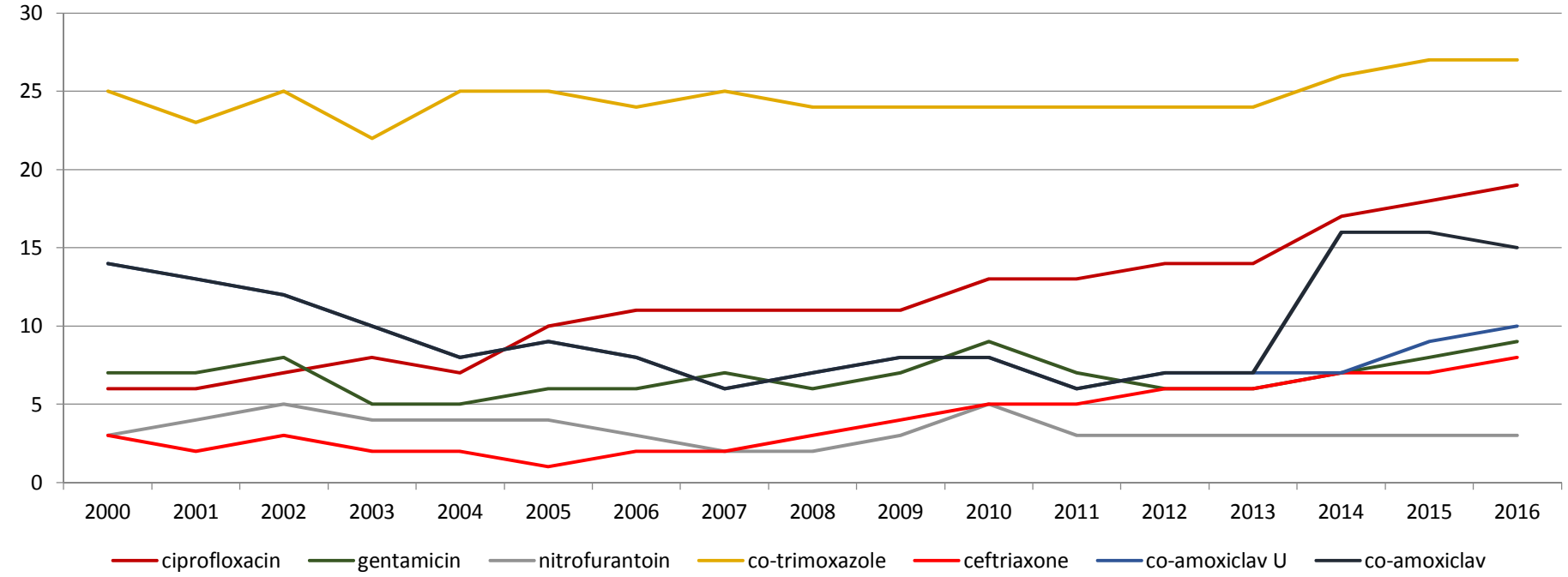
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	1 444	24 (0)	0 (0) - 72 (0)
Amoxicillin + clav. acid	1 449	1 (0)	0 (0) - 8 (0)
Cefuroxime i.v.	1 393	5 (2)	0 (0) - 29 (13)
Cefuroxime oral	1 393	7 (93)	0 (100) - 42 (58)
Ceftriaxone	1 315	0 (0)	0 (0) - 0 (0)
Co-trimoxazole	1 441	20 (0)	6 (0) - 35 (2)

*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

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2016.



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

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Escherichia coli

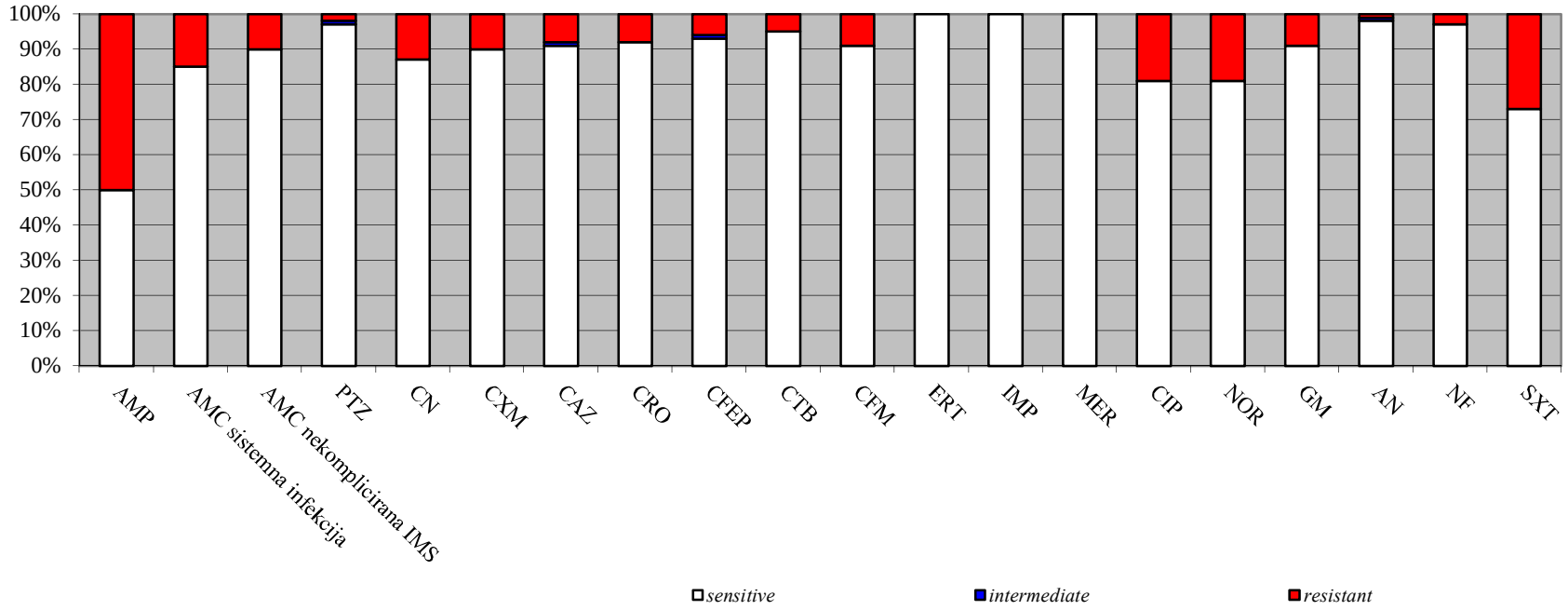
rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2016.,
zbirni prikaz izolata iz 38 centra u RH /
antibiotic resistance for the period 1.10. - 31.12. 2016,
summary results for the isolates from 38 centers in Croatia

ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	19 037	50 (0)	32 (0) - 78 (0)
Amoxicillin + clav. acid sistemna infekcija	18 464	15 (0)	6 (0) - 25 (0)
Amoxicillin + clav. acid nekomplicirana IMS	18 453	10 (0)	2 (0) - 21 (0)
Piperacillin + tazobactam	18 979	2 (1)	0 (0) - 9 (3)
Cephalexin	18 195	13 (0)	5 (0) - 59 (0)
Cefuroxime	18 998	10 (0)	2 (0) ï 19 (0)
Ceftazidime	19 031	8 (1)	0 (1) - 17 (0)
Ceftriaxone	19 034	8 (0)	1 (0) - 19 (0)
Cefepime	18 983	6 (1)	0 (0) - 19 (0)
Ceftibuten	18 066	5 (0)	0 (0) - 15 (0)
Cefixime	18 846	9 (0)	2 (0) - 19 (0)
Ertapenem	18 942	0 (0)	0 (0) - 1 (0)
Imipenem	18 984	0 (0)	0 (0) - 1 (0)
Meropenem	18 984	0 (0)	0 (0) - 1 (0)
Ciprofloxacin	19 035	19 (0)	7 (2) - 36 (0)
Norfloxacin	18 445	19 (0)	8 (1) - 33 (0)
Gentamicin	19 029	9 (0)	2 (0) - 22 (8)
Amikacin	18 735	1 (1)	0 (0) - 10 (0)
Nitrofurantoin	18 361	3 (0)	0 (0) - 7 (0)
Co-trimoxazole	19 027	27 (0)	20 (0) - 44 (0)

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

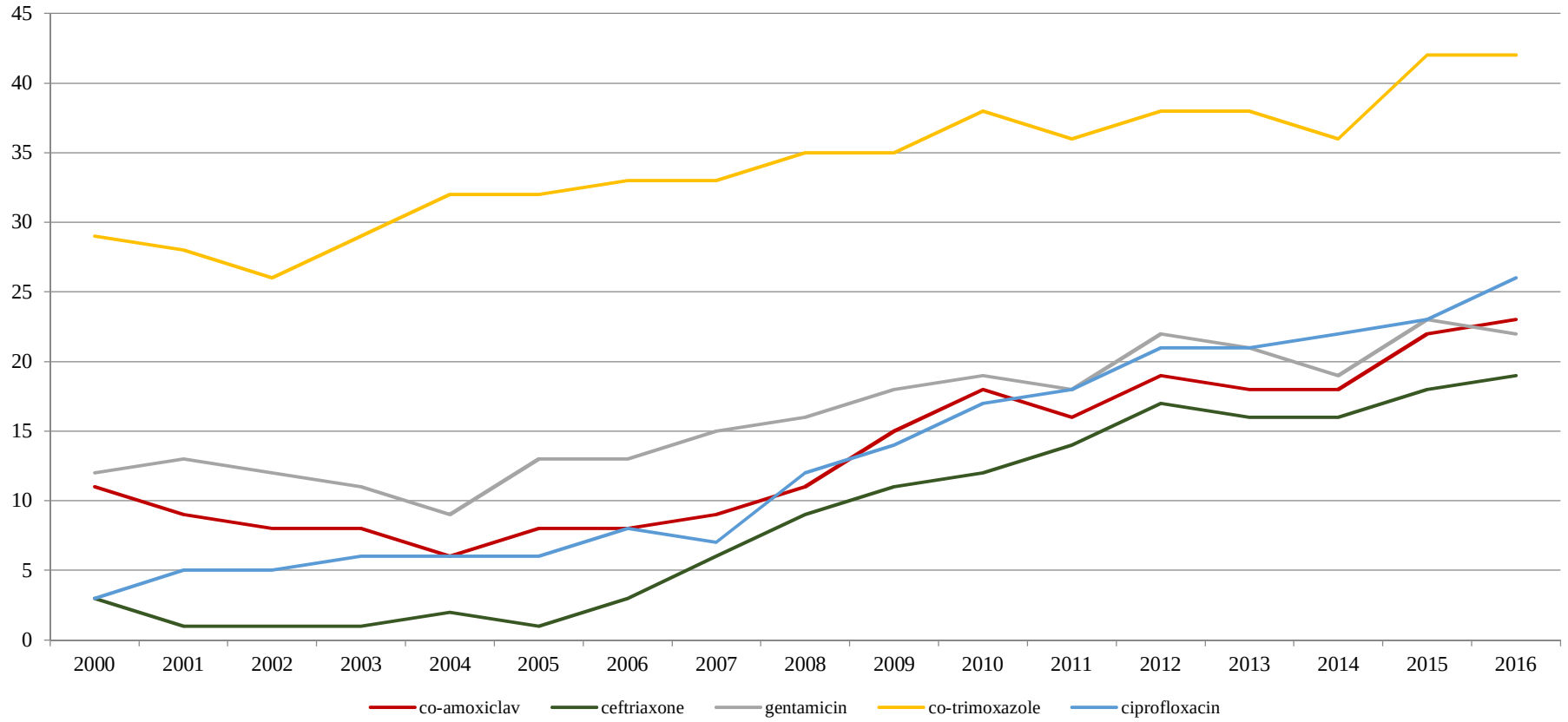
Escherichia coli

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. ï 31.12.2016.



Proteus mirabilis

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. ï 2016.



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Proteus mirabilis

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2016.,
zbirni prikaz izolata iz 38 centra u RH /
antibiotic resistance for the period 1.10. - 31.12. 2016,
summary results for the *isolates from 38 centers in Croatia*

ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	4 202	48 (0)	33 (0) - 69 (0)
Amoxicillin + clav. acid	4 202	23 (0)	6 (0) - 52 (0)
Piperacillin + tazobactam	4 151	2 (1)	0 (0) - 11 (0)
Cephalexin	3 978	24 (0)	7 (0) - 69 (0)
Cefuroxime	4 203	22 (0)	4 (0) - 51 (0)
Ceftazidime	4 178	18 (1)	2 (0) - 37 (7)
Ceftriaxone	4 174	19 (0)	2 (0) ï 52 (0)
Cefepime	4 151	4 (32)	0 (0) - 23 (0)
Ceftibuten	3 850	17 (0)	0 (0) - 35 (0)
Cefixime	3 984	19 (0)	2 (0) - 47 (0)
Ertapenem	4 154	0 (0)	0 (0) - 1 (0)
Meropenem	4150	0 (0)	0 (0) - 0 (0)
Ciprofloxacin	4 201	24 (2)	0 (0) - 56 (1)
Norfloxacin	3 994	23 (2)	4 (0) - 45 (5)
Gentamicin	4 202	21 (1)	10 (0) - 48 (3)
Amikacin	4 119	11 (0)	0 (0) - 27 (0)
Co-trimoxazole	4 170	42 (0)	14 (0) - 85 (0)

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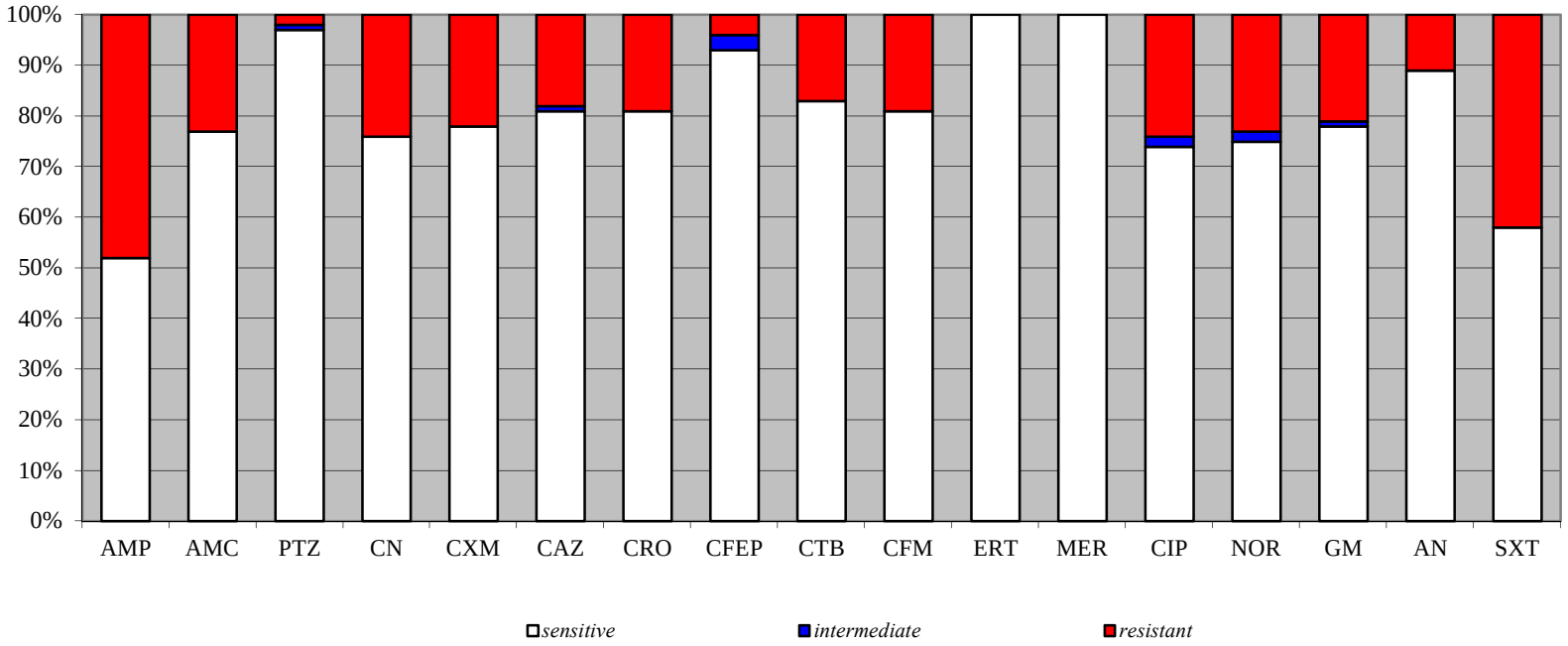
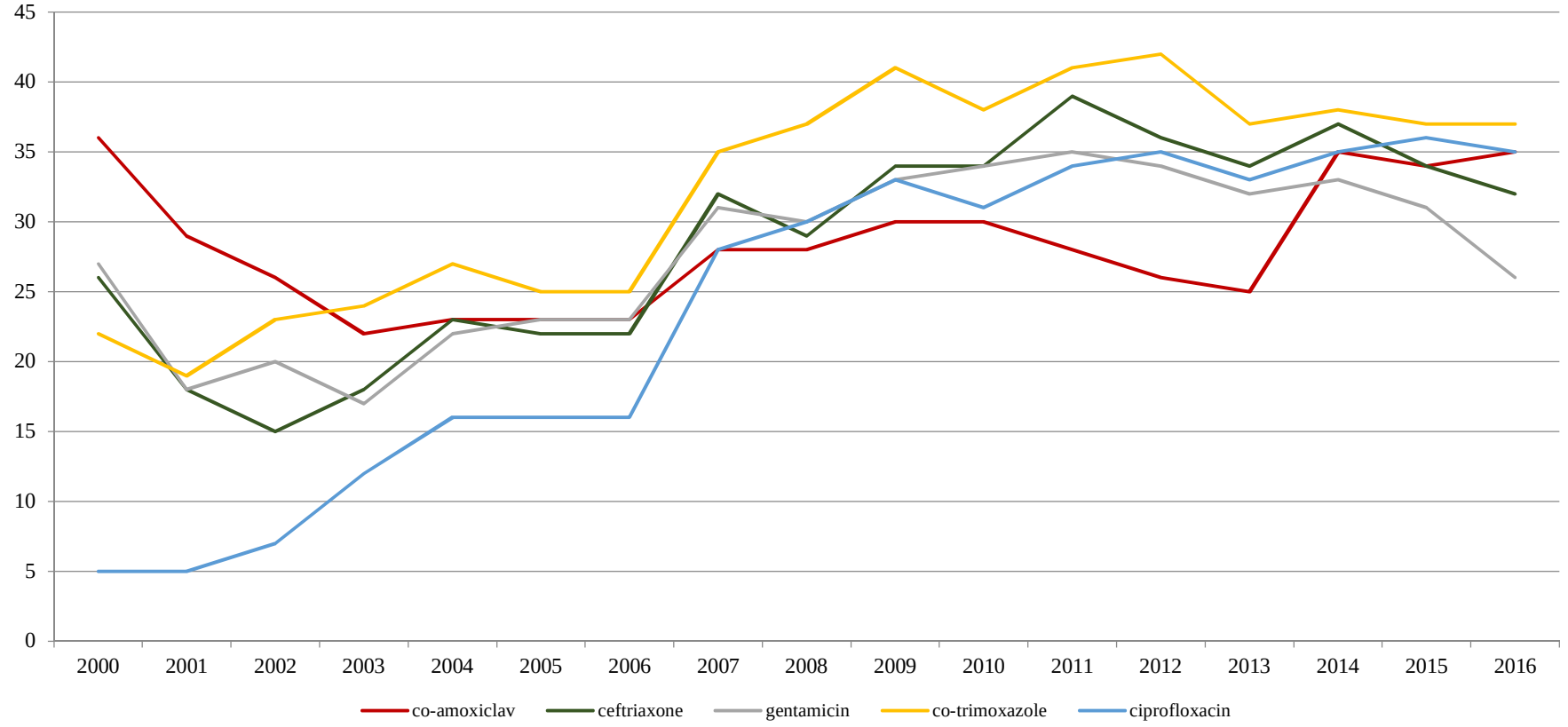
Proteus mirabilis

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia,* 1.10. ï 31.12.2016.



Klebsiella pneumoniae

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2016.



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Klebsiella pneumoniae

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ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	4 723	100 (0)	100 (0) - 100 (0)
Amoxicillin + clav. acid	4 722	35 (0)	16 (0) - 66 (0)
Piperacillin + tazobactam	4 693	17 (7)	2 (6) - 38 (1)
Cephalexin	4 395	36 (0)	13 (0) - 62 (0)
Cefuroxime	4 722	35 (0)	13 (0) - 65 (0)
Ceftazidime	4 722	31 (1)	9 (0) - 57 (2)
Ceftriaxone	4 722	32 (0)	9 (0) - 59 (1)
Cefepime	4 693	26 (3)	4 (0) - 54 (3)
Ceftibuten	4 276	21 (0)	5 (0) - 42 (0)
Cefixime	4 587	32 (0)	11 (0) - 59 (0)
Ertapenem	4 692	3 (1)	0 (0) - 18 (1)
Imipenem	4 693	1 (1)	0 (0) - 5 (6)
Meropenem	4 693	1 (1)	0 (0) - 6 (9)
Ciprofloxacin	4 721	33 (2)	9 (0) - 60 (2)
Norfloxacin	4 454	32 (2)	9 (0) - 60 (4)
Gentamicin	4 723	25 (1)	2 (29) - 63 (1)
Amikacin	4 615	2 (2)	0 (0) - 7 (8)
Co-trimoxazole	4 721	36 (1)	16 (0) - 61 (0)

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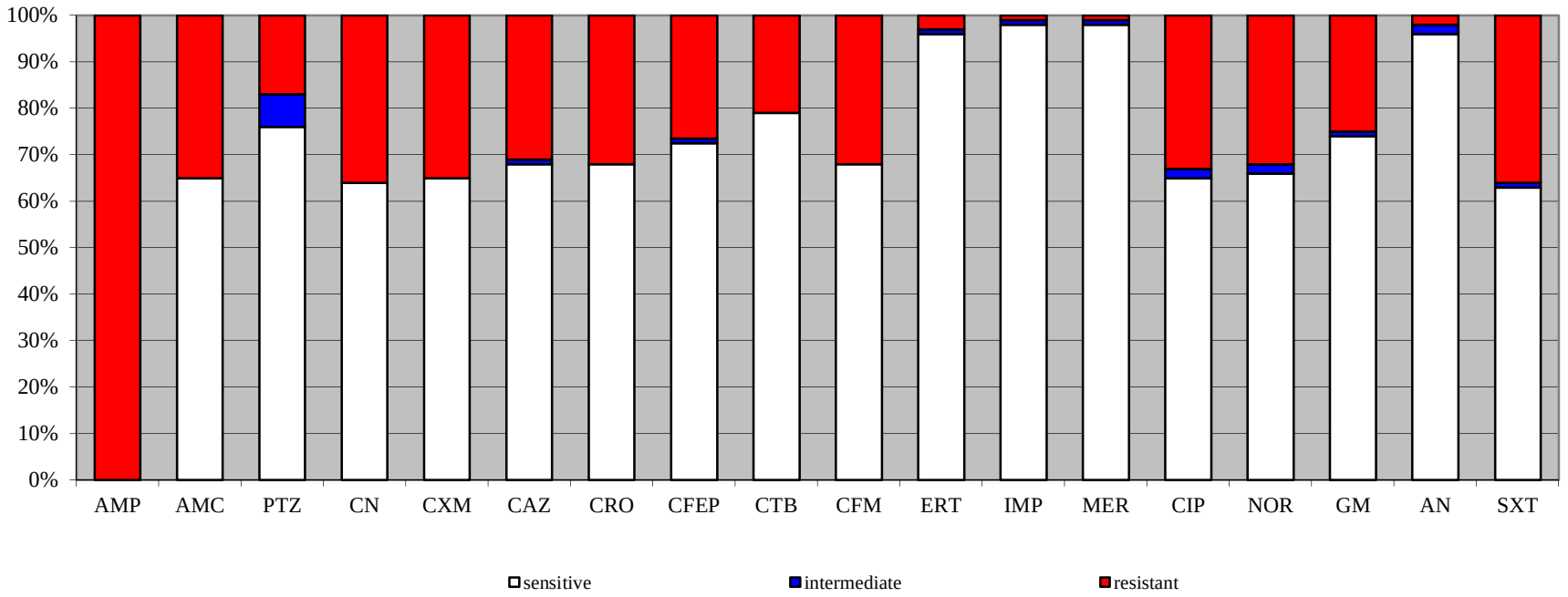
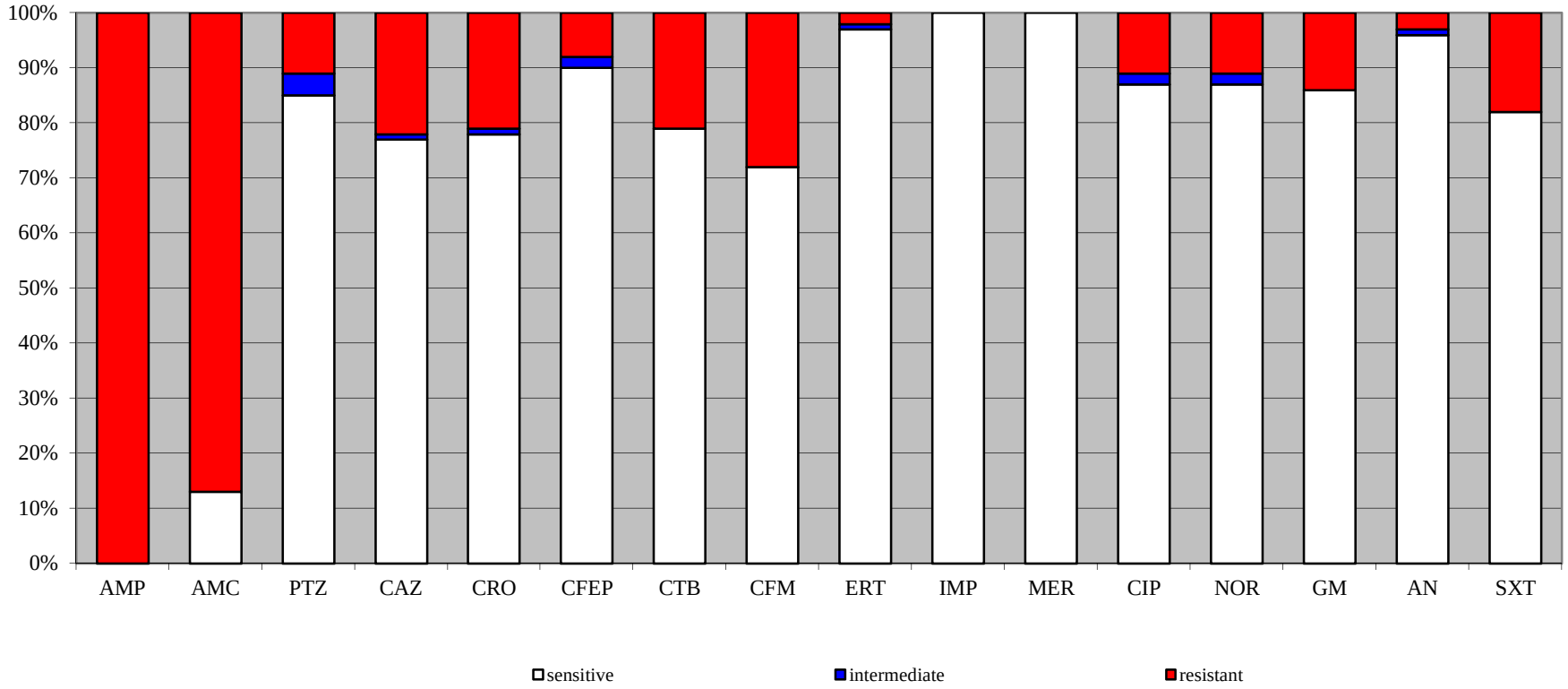
Klebsiella pneumoniae

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. ï 31.12.2016.



Enterobacter spp., *Serratia* spp., *Citrobacter* spp.

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia,* 1.10. ï 31.12.2016.



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Enterobacter spp., *Serratia* spp., *Citrobacter* spp.

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2016.,
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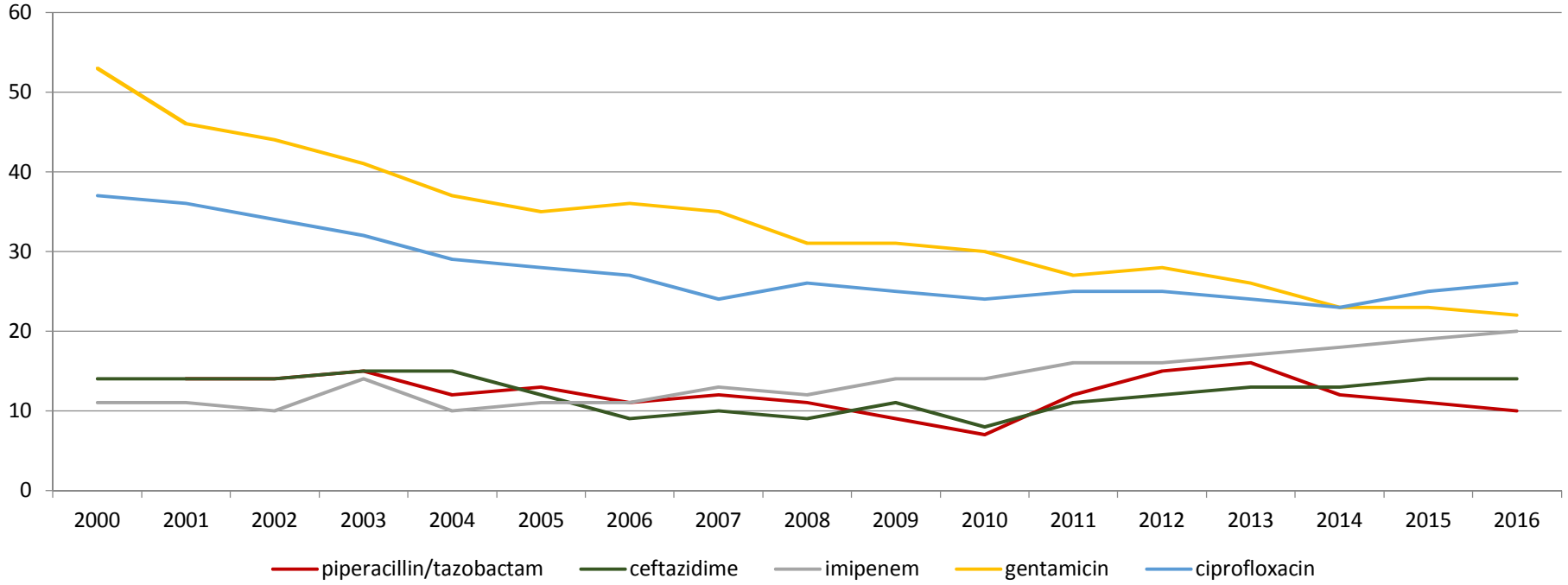
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	3 709	100 (0)	80 (0) - 100 (0)
Amoxicillin + clav. acid	3 709	87 (0)	431 (0) - 100 (0)
Piperacillin + tazobactam	3 675	11 (4)	0 (0) - 88 (0)
Ceftazidime	3 702	22 (1)	7 (0) - 34 (0)
Ceftriaxone	3 701	22 (1)	4 (0) - 33 (0)
Cefepime	3 673	8 (2)	0 (0) - 25 (0)
Ceftibuten	3 003	21 (0)	2 (0) - 35 (0)
Cefixime	3 191	28 (0)	4 (0) - 41 (0)
Ertapenem	3 663	2 (1)	0 (0) - 8 (2)
Imipenem	3 673	0 (0)	0 (0) - 2 (0)
Meropenem	3 675	0 (0)	0 (0) - 2 (2)
Ciprofloxacin	3 706	11 (2)	0 (0) - 20 (0)
Norfloxacin	3 087	11 (2)	0 (0) ï 22 (0)
Gentamicin	3 706	14 (0)	2 (0) - 25 (0)
Amikacin	3 625	3 (1)	0 (0) - 17 (0)
Co-trimoxazole	3 223	18 (0)	2 (0) - 33 (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

Pseudomonas aeruginosa

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2016.



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Pseudomonas aeruginosa

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antibiotic resistance for the period 1.10. - 31.12. 2016,
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ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Piperacilin + tazobaktam	4 407	10 (0)	2 (0) - 27 (0)
Ceftazidim	4 406	14 (0)	2 (0) - 34 (0)
Cefepim	4 414	9 (0)	0 (0) - 57 (0)
Imipenem	4 410	18 (2)	0 (0) - 36 (4)
Meropenem	4 412	17 (2)	0 (0) - 36 (6)
Ciprofloxacin	4 413	25 (1)	2 (0) - 36 (1)
Gentamicin	4 413	22 (0)	8 (0) - 45 (0)
Amikacin	4 347	9 (2)	2 (7) - 21 (6)
Colistin	857	0 (0)	0 (0) - 0 (0)

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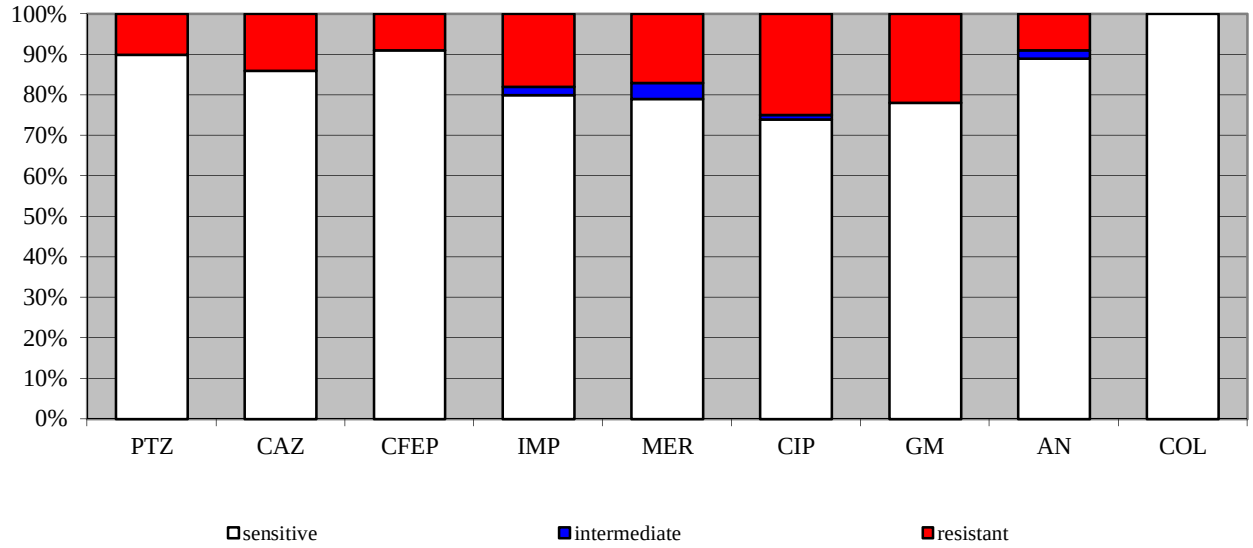
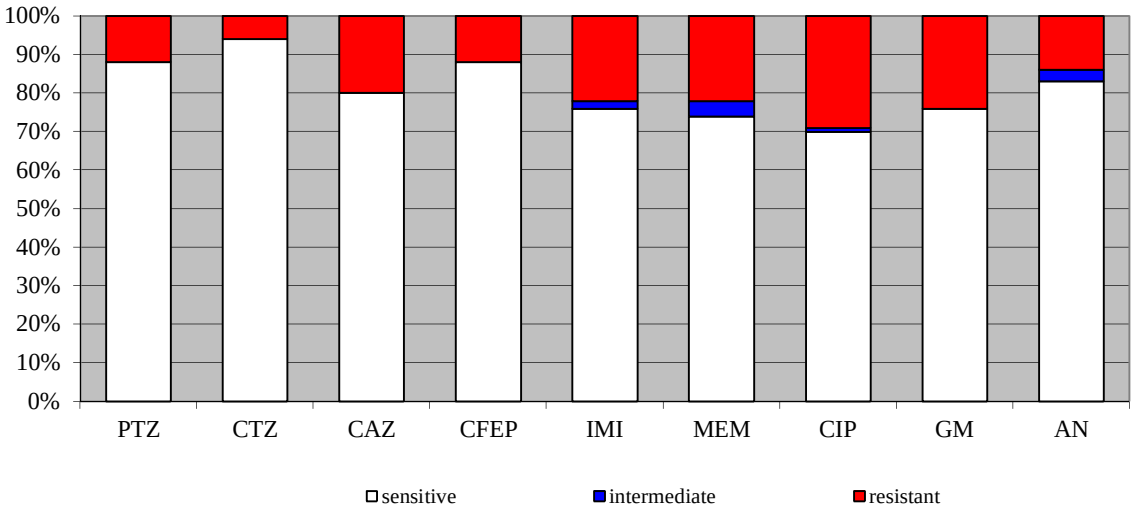
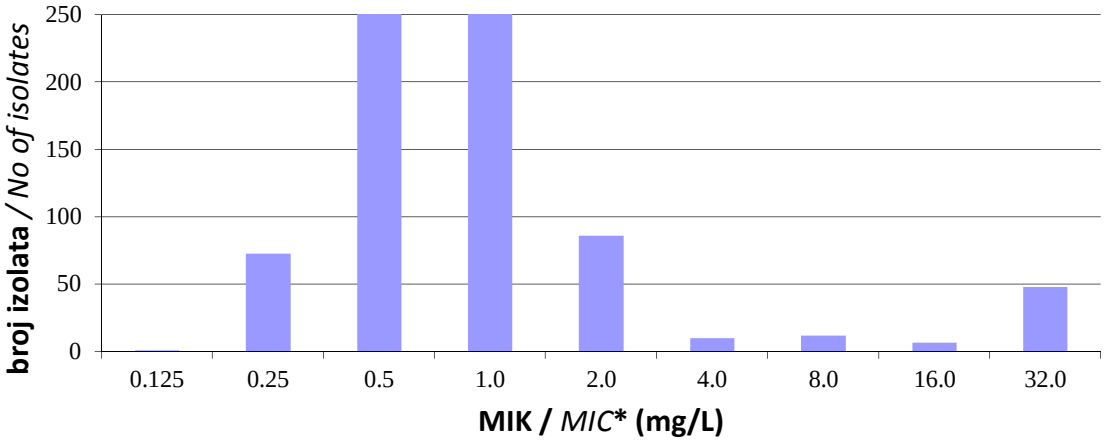


Pseudomonas aeruginosa

978 izolata, 10 centara, 2016. */ 978 isolates, 10 centers, 2016*
osjetljivost na ceftolozan + tazobaktam i druge antibiotike / *sensitivity to ceftolozane + tazobactam and other antibiotics*



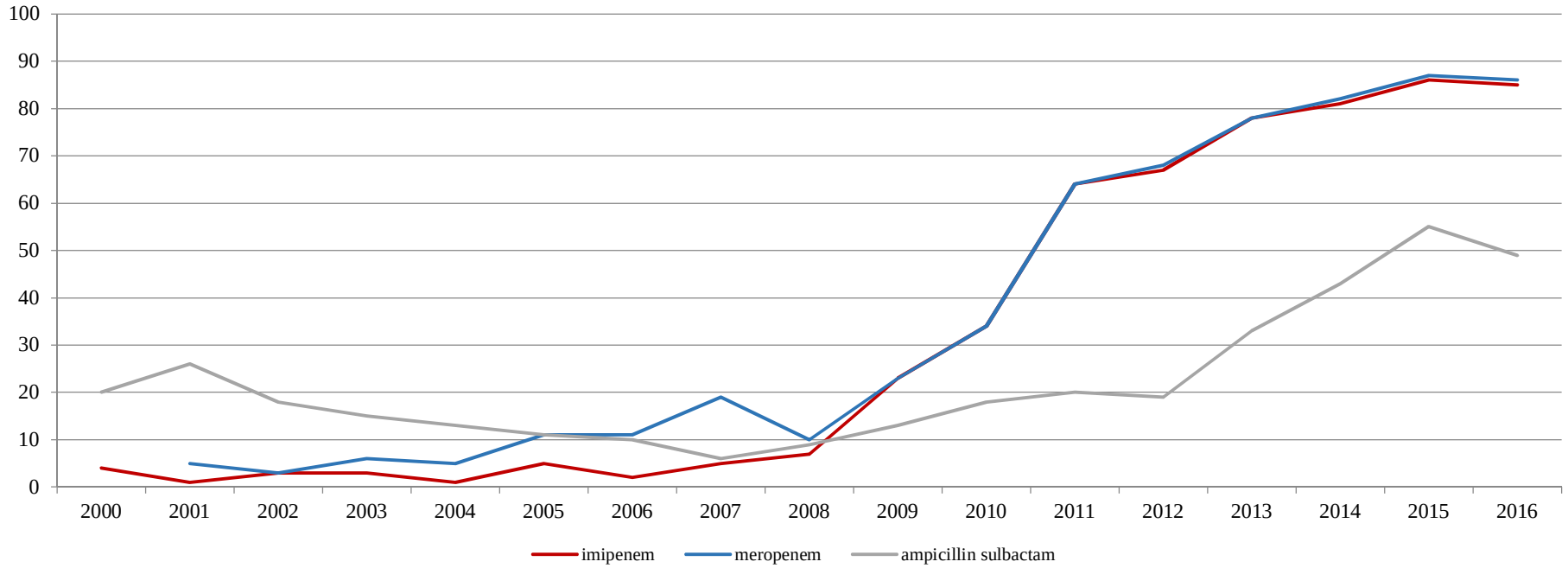
ceftolozan + tazobactam: raspon MIK-ova / *ceftolozane + tazobactam: MIC range*



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

Acinetobacter baumannii

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2016.



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Acinetobacter baumannii

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ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin + sulbactam	1 422	36 (13)	0 (3) - 86 (0)
Meropenem	1 518	86 (1)	58 (0) - 98 (0)
Imipenem	1 518	85 (0)	58 (0) - 98 (0)
Ciprofloxacin	1 509	90 (0)	38 (0) - 100 (0)
Gentamicin	1 518	81 (0)	56 (0) - 100 (0)
Amikacin	1 511	79 (1)	56 (0) - 94 (4)
Co-trimaxazole	1 430	76 (4)	41 (3) - 100 (0)
Colistin	1 220	0 (0)	0 (0) - 0 (0)

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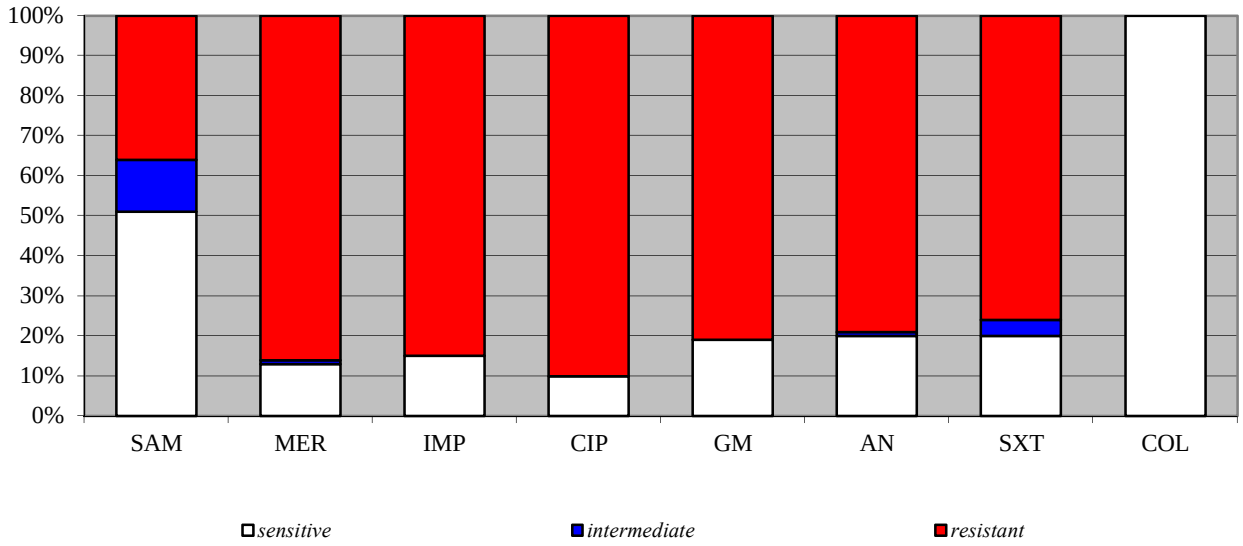

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Salmonella spp.

rezistencija na antibiotike u razdoblju od 01.01. - 31.12. 2016.,
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antibiotic resistance for the period 01.01. - 31.12. 2016,
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ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	2 455	14 (0)	3 (0) - 30 (0)
Amoxicillin + clav. acid	2 459	3 (0)	0 (0) - 21 (0)
Ceftazidim	2 459	1 (0)	0 (0) - 4 (0)
Ceftriaxone	2 459	0 (0)	0 (0) - 4 (0)
Ciprofloxacin	2 987	3 (0)	0 (0) - 10 (0)
Co-trimoxazole	2 459	2 (0)	0 (0) - 9 (0)

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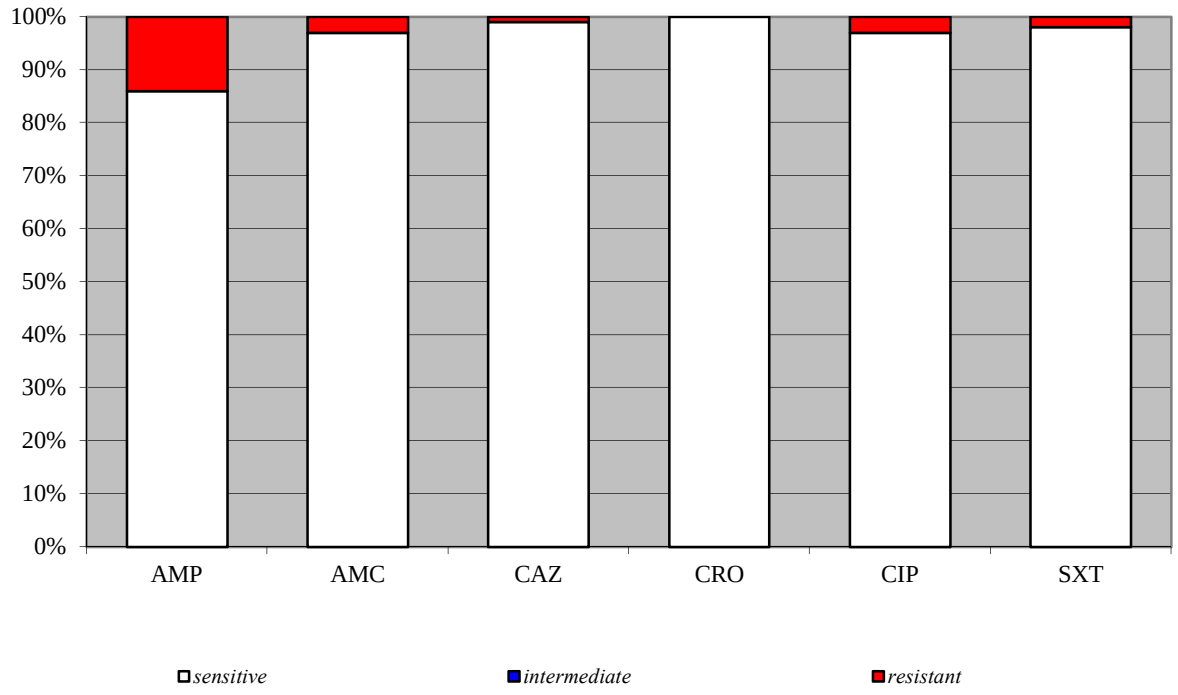

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Campylobacter jejuni

rezistencija na antibiotike u razdoblju od 1.01.- 31.12. 2016.,
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ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ciprofloxacin	2 841	60 (0)	43 (0) - 74 (0)
Erythromicin	2 841	1 (0)	0 (0) - 8 (0)
Tetracycline	2 842	28 (0)	14 (0) - 51 (0)

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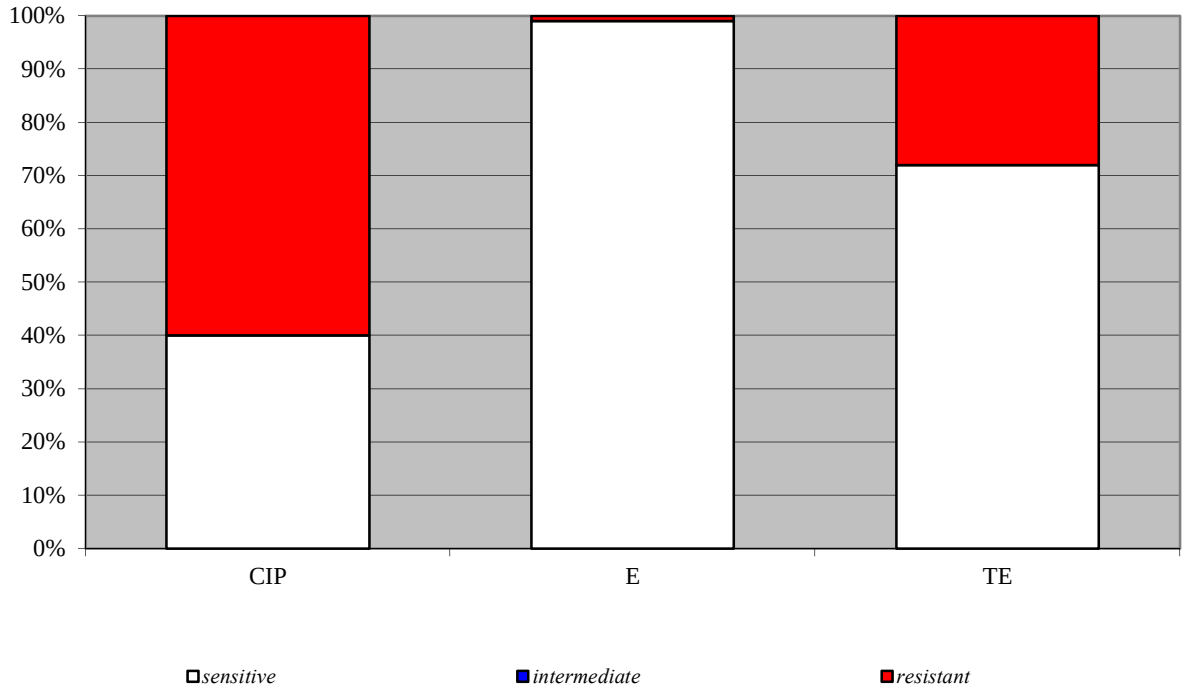

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Campylobacter coli

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ANTIBIOTIK / ANTIBIOTIC	Broj izolata / No. of isolates	% rezistentnih (% intermedijarnih) izolata / % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* / Range of local results*
Ciprofloxacin	606	60 (0)	38 (0) - 76 (0)
Erythromicin	606	3 (0)	0 (0) - 12 (0)
Tetracycline	606	35 (0)	23 (0) - 75 (0)

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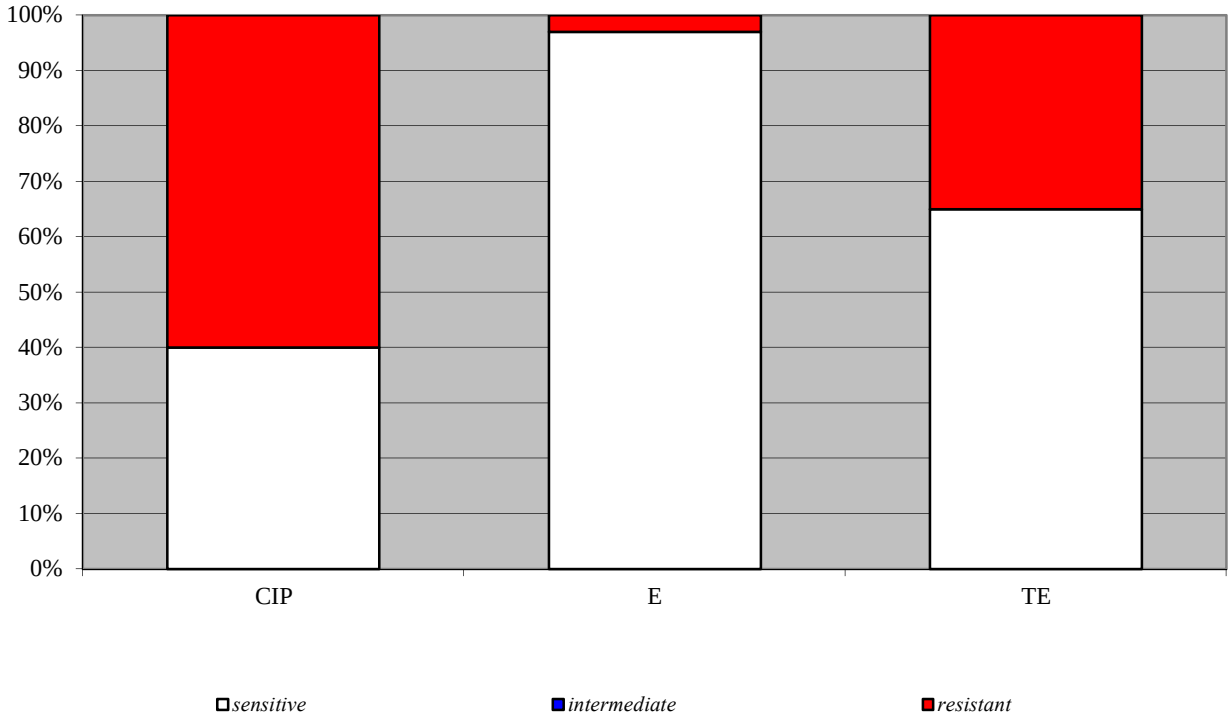

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Shigella spp.

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia,* 1.01 ï 31.12.2016.

***Shigella* spp.**	**AMP**			**AMC**			**CAZ**			**CRO**			**CIP**			**SXT**		
	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**
Shigella sonnei*	6	0	**50**	6	0	**0**	6	0	**0**	6	0	**0**	6	0	**0**	5	0	**80**
Shigella flexneri*	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**
UKUPNO* / *TOTAL**	7	0	**43**	7	0	**0**	7	0	**0**	7	0	**0**	7	0	**0**	6	33	**67**

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

Anaerobne bakterije / *Anaerobes*

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia,* 1.01 - 31.12.2016.

Anaerobne bakterije / *Anaerobes*	**P**			**AMC**			**PTZ**			**ERT***			**MTZ**			**CC**		
	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R%**	No	I %	**R %**	No	I %	**R %**
Gram-pozitivni anaerobi osim *C. difficile* / *Gram-positive anaerobes except C. difficile*	479	2	**9**	426	0	**1**	309	0	**1**	447	0	**0**	486	0	**61**	483	0	**17**
Gram-negativni anaerobi / *Gram-negative anaerobes*	365	0	**84**	339	2	**10**	266	2	**3**	337	0	**2**	373	0	**13**	360	0	**28**
UKUPNO / *TOTAL*	844	1	**41**	771	1	**5**	575	1	**2**	784	0	**1**	859	0	**40**	843	0	**22**

* OS ZZJZ rezistenciju na karbapeneme testirali preko imipenema / *OS ZZJZ carbapenem resistance tested with imipenem*

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Candida spp.

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia,* 1.01. ï 31.12.2016.

	FLUKONAZOL			**VORIKONAZOL**			**AMFOTERICIN B**			**ANIDULAFUNGIN**		
***Candida* spp.**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**
Candida glabrata	105	70	**7**	NA*	NA*	**NA***	105	4	**0**	25	0	**0**
Candida parapsilosis	78	4	**38**	78	5	**28**	78	0	**0**	32	81	**3**
Candida krusei*	NA*	NA*	**NA***	NA*	NA*	**NA***	19	0	**5**	13	0	**0**
Candida dubliniensis*	1	0	**0**	NA*	NA*	**NA***	NA*	NA*	**NA***	NA*	NA*	**NA***
Candida tropicalis*	27	7	**7**	17	0	**0**	27	11	**0**	7	0	**0**
Candida kefyr*	1	0	**0**	NA*	NA*	**NA***	NA*	NA*	**NA***	NA*	NA*	**NA***

*nije primjenjivo/ *not applicable*
**podatak o postotku rezistencije nepouzdan zbog premalo izolata / *resistance rate data unreliable due to small number of isolates*

OSJETLJIVOST *M. TUBERCULOSIS* U HRVATSKOJ U 2016. GODINI

SENSITIVITY OF M. TUBERCULOSIS IN CROATIA, 2016

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Mikobakterije izolirane u Hrvatskoj u 2016. godini

Podaci Registra za tuberkulozu Sluġbe za epidemiologiju Hrvatskog zavoda za javno zdravstvo ukazuju na stagnaciju trenda sniġenja broja oboljelih od tuberkuloze. Stopa uļestalosti od 11/100.000 u 2016. godini je na razini vrijednosti iz 2015. Razlike u pobolu po ġupanijama su u rasponu od 4,1 ï 19,7 na 100.000 stanovnika. U 2016., kao niti u prethodnih deset godina, nije zabiljeġen niti jedan sluļaj tuberkuloznog meningitisa u dobi izmeĽu 0 i 19 godina.

Za analizu podataka o bakteriološkoj dijagnostici tuberkuloze u Hrvatskoj u 2016. godini koristio se ĂUpitnik o radu TBC laboratorija u 2015. godiniñ. Ukupno je pregledano 38.616 kliniļkih uzoraka na tuberkulozu ġto je na razini broja pregledanih u 2015. godini. Mreġa TBC laboratorija je ostala nepromijenjena (15 laboratorija). U devet laboratorija je broj uzorka bio ispod 2.000, ġto je preporuļeni minimum broja uzoraka. ObraĽeni broj uzoraka u pet laboratorija je bio ļak ispod 1.000 uzoraka. Nadalje, svi naġi laboratoriji joġ uvijek ne koriste tekuĆe podloge za sve uzorke nego samo za paucibacilarne ili izvanpluĆne uzorke. U 5,2% uzoraka kultivacijom su otkrivene mikobakterije, a raspon pozitivnih kultura meĽu laboratorijima se kretao od 0,4 do 17,6% pozitivnih uzoraka. Ukupno je izolirano 2.021 sojeva mikobakterija ġto je za 6,7% viġe izolata nego u 2015. godini (Tablica 1).

Oļekivano se *M. tuberculosis* najļeġće izolira iz pluĆnih uzoraka, a od izvanpluĆne bakteriološki dokazane tuberkuloze najļeġća je bila tuberkuloza pleure (N=16), limfoglandularna tuberkuloza (N=8) te tuberkuloza urinarnog sustava (N=5).

MeĽutim, iako je *M. tuberculosis* i dalje dominantna mikobakterija s 1.587 (78,5%) izolata, udio netuberkuloznih mikobakterija (NTM) sve je veĆi te ove godine iznosi 21,2% (Tablica 1).

Tijekom 2016. godine iz humanih kliniļkih materijala nije izoliran *M. bovis*, a zabiljeġeno je pet izolata *M. bovis* ï BCG soja. Nastavlja se trend visokog broja izolata NTM i broja moguĆih bolesnika s mikobakteriozom. Osobe s izolatima NTM se biljeġe od 1982. godine, a kod viġekratnih izolacija se utvrĽuju mikrobiološki kriteriji za mikobakterioze i popunjava obrazac za NTM. U 2016. godini je otkriveno 51 osoba sa zadovoljenim mikrobiološkim kriterijima za dijagnozu mikobakterioze (dva i viġe izolata). Kod 14 bolesnika izoliran je *M. xenopi,* slijede ga *M. avium* koji je izoliran kod deset bolesnika te *M. malmoense* kod ġest. Kod po pet bolesnika naĽene su brzorastuĆe mikobakterije *M. chelonae* i *M. fortuitum,* dok je *M. abscessus* naĽen kod tri bolesnika. Kod po tri bolesnika izolirane su spororastuĆe mikobakterije, *M. kansasii* i *M. intracellulare*. *M. gordonae* kao saprofitna mikobakterija je identificiran u 28,5% izolata NTM. Najļeġće se radi o kontaminaciji uzoraka, sluļajnim nalazima i prolaznim kolonizacijama. MeĽu uvjetno patogenim NTM u Hrvatskoj i dalje prevladavaju izolati *M. xenopi* (16,4%), *M. avium* (11,7%) i *M. intracellulare* (5,1%), a meĽu brzorastuĆim *M. fortuitum* (13,8%) i *M. chelonae* (6,5%) i (Tablica 2).

Nastavljen je izrazito povoljan trend broja rezistentnih sojeva *M. tuberculosis*, a time i bolesnika s rezistentnom tuberkulozom. Od 1.587 izoliranih sojeva *M. tuberculosis* samo je 79 (5,0%) bilo rezistentno na prvu liniju antituberkulotika, a otkriveni su kod 21 bolesnika s rezistentnom tuberkulozom (Tablica 3). MeĽu bolesnicima s rezistentnim oblikom tuberkuloze, njih 20 (95%) je imalo monorezistentni oblik, dok je kod jednog bolesnika otkrivena tuberkuloza rezistentna na 2 i viġe antituberkulotika iz prve linije (Tablica 4). Monorezistencija na izoniazid je utvrĽena kod osam

bolesnika, a monorezistencija na streptomicin kod 12 bolesnika. U 2016. godini nismo izolirali niti jedan multirezistentan soj.

Mycobacteria isolated in Croatia in 2016

According to the data obtained from the Epidemiology Service at the Croatian National Institute of Public Health, the decreasing trend of TB incidence is stagnating. TB incidence in 2016 is at the 2015 level, with a rate of 11/100,000 inhabitants. The difference in morbidity between different counties is 4.1-19.7/100.000 inhabitants. In 2016, same as in previous ten years, there were no cases of tuberculous meningitis in the age group 0 to 19 years.

To analyze data on TB bacteriological diagnostics, the ñQuestionnaire on the work of TB laboratories in 2016ò was used. A total of 38.616 clinical samples were analyzed for tuberculosis, similar to the number in year 2015. The TB laboratory network remained unchanged (15 laboratories). The number of processed samples was still under recommended minimum of 2000 samples in a total of nine laboratories and under 1000 samples in five laboratories.

Furthermore, all laboratories still donôt use liquid media for all samples, but only for paucibacillar or extrapulmonary samples. In 5.2% of samples, cultivation detected mycobacteria and the range of positivity of cultivation in different laboratories was from 0.4 to 17.6%. A total of 2.021 mycobacterial isolates were cultivated, which represents a 6.7% increase in the number of isolates compared to 2015. As expected, *M. tuberculosis* is most frequently isolated from pulmonary samples. Among bacteriologically confirmed extrapulmonary TB, the most frequent forms were pleural TB (N=16), lymphoglandular TB (N=8), and urinary tract TB (N=5).

Although *M. tuberculosis* remained the predominant mycobacterium with 1,587 (78.5%) isolates, the number of **nontuberculous** mycobacteria (NTM) is increasing, accounting for 21.2% of all isolates in 2016. There were no *M. bovis* strains isolated from human clinical samples, while there were five *M. bovis* - BCG strains isolated (Table 1). The number of NTM isolates is continuously increasing, as well as the number of potential patients. Patients with NTM isolates are systematically documented since 1982, and in case of multiple isolates, microbiological criteria for mycobacterioses are established and a questionnaire for NTM is used. In 2016, a total of 51 cases that fulfilled the microbiological criteria for mycobacteriosis (two or more isolates) were documented. In 14 patients, *M. xenopi* was isolated, *M. avium* was isolated in ten patients, and *M. malmoense* in six.

The cause of mycobacteriosis in five patients each were rapidly growing NTMs, *M. chelonae* and *M. fortuitum*, whereas *M. abscessus* was isolated in three patients. Slowly growing NTM *M. kansasii* and *M. intracellulare* were isolated in three patients each. *M. gordonae*, a saprophytic mycobacterium, was identified in 28.5% of all NTM isolates (Table 2). In most cases, the isolation was the result of specimen contamination, accidental finding and transient colonization. Among conditionally pathogenous NTM in Croatia still prevail *M. xenopi* (16.4%), *M. avium* (11.7%), and *M. intracellulare* (5.1%), while *M. fortuitum* (13.8%) and *M. chelonae* (6.5%) were most frequently isolated rapidly growing NTMs (Table 2).

The number of resistant *M. tuberculosis* strains and, by extension, number of resistant TB cases has demonstrated a continuous favorable decreasing trend. Of the 1,587 isolated *M. tuberculosis* strains, only 79 (5.0%) were resistant to the first line antituberculotics, isolated in 21 patients with resistant TB (Table 3). Among patients with resistant TB, 20 patients (95%) had monoresistant strains, while 1 patient was infected with *M. tuberculosis* isolate resistant to 2 or more first-line antituberculotics (Table 4). Monoresistance to isoniazid was established in eight patients and monoresistance to streptomycin in 12 patients. In 2016, there were no multiresistant strains isolated.

Tablica /*Table* **1.**
Mikobakterije izolirane u Hrvatskoj, 2006. – 2016. /
Mycobacteria strains isolated in Croatia, 2006-2016

Godina	Ukupno mikobakterija	*M. tuberculosis*		*M. bovis*		Netuberkulozne mikobakterije	
		Broj	%	*M. bovis*	BCG soj	Broj	%
2006.	3959	3717	93.9	-	2	240	6,1
2007.	3217	2920	90.8	1	4	292	9,1
2008.	3665	3299	90,0	-	1	365	9,9
2009.	3197	2763	86,4	-	-	434	13,6
2010.	2712	2283	84,2	-	1	429	15,8
2011.	2351	2000	85,0	-	4	347	14,8
2012.	2108	1807	85,7	1	6	294	14,0
2013.	2153	1748	81,2	-	1	402	18,8
2014.	1969	1541	78,3	-	1	423	21,5
2015.	1880	1505	80,1	-	6	375	19,9
2016.	2021	1587	78,5	-	5	428	21,2

Tablica / *Table* **2.**
Netuberkulozne mikobakterije (NTM) izolirane u Hrvatskoj u 2016. /
Nontuberculous mycobacteria (NTM) isolated in Croatia in 2016

	Vrsta	**Broj**	**%**
Uvjetno patogene mikobakterije	*M. avium*	50	11,7
	M. intracellulare	22	5,1
	M. kansasii	10	2,3
	M. xenopi	70	16,4
	M. malmoense	10	2,3
	M. intermedium	3	0,7
	M . szulgai	1	0,2
	M. fortuitum	59	13,8
	M. chelonae	28	6,5
	M. abscessus	14	3,3
	M. mucogenicum	7	1,6
	M. shimoidei	3	0,8
	M. celatum	4	0,9
Saprofitne mikobakterije	*M. gordonae*	122	28,5
	M. lentiflavum	3	0,7
	ostalo	22	5,1
Ukupno		428	100,0

Tablica /- *Table* **3.**
Osjetljivost sojeva *M. tuberculosis* na antituberkulotike u Hrvatskoj, 2016. /
Drug susceptibility testing of M. tuberculosis strains in Croatia, 2016

Ustanova / *Institution*	***M. tuberculosis* /** *M. tuberculosis*	**Osjetljivi /** *Sensitive*	**Rezistentni /** *Resistant*
ZJZ Ļakovec	22	22	-
SB Klenovnik	601	558	43
OĢB Poģega	41	41	-
OB N. Gradiģka	22	22	-
ZJZ Osijek	120	119	1
ZJZ Pula	45	45	-
ZJZ Rijeka	32	29	3
ZJZ Slavonski Brod	36	36	-
KB Split	73	73	-
ZJZ Split	4	4	-
ZJZ Ġibenik	22	22	-
ZJZ Virovitica	15	15	-
ZJZ Zadar	43	43	-
KBC Zagreb	147	145	2
HZJZ	364	334	30
Ukupno	1587	1508	79

Tablica / *Table* **4.**
Bolesnici s rezistentnom tuberkulozom u Hrvatskoj, 2016. /
Resistant tuberculosis in Croatia, 2016

	Broj / *Number*	**%**
Ukupno bolesnika / *Patients total*	**21**	**100**
Monorezistencija / *Monoresistance*		
S	12	57,1
H	8	38,1
Polirezistencija / *Poliresistance*		
HSZ	1	4,8

POGLAVLJE / CHAPTER 3.

OSJETLJIVOST GONOKOKA U HRVATSKOJ U 2016. GODINI

SENSITIVITY OF GONOCOCCI IN CROATIA IN 2016

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Antimikrobna rezistencija u gonokoka izoliranih Hrvatskoj u 2105. i 2016. godini

Gonoreja je druga najļeġĺa spolno prenosiva infekcija (SPI) bakterijskog podrijetla danas. Ukoliko se ne provede pravilno lijeļenje, infekcija uzrokovana sa *Neisseria gonnorrhoeae* (NG) moġe dovesti do ozbiljnih komplikacija: upalne bolesti zdjelice (PID), izvanmaternilļne trudnoĺće, neplodnosti, epididimitisa ili ģirenja gonokokne infekcije na druge organe .

Poseban problem danas je i pojava sve veĺć otpornosti na antimikrobne lijekove (antimikrobna rezistencija (AMR). Upravo NG postaje sve viġe otporna na donedavno djelotvorne kinolone i cefalosporine viġih generacija. Lijeļenje gonoreje takoĽer predstavlja izazov jer gonokokna infekcija ne izaziva zaġtitni imunitet, a istovremeno moġe pospjeġiti i olakġati ģirenje infekcije uzrokovane virusom humane imunodeficijencije .

Podaci epidemiološkog praĺćenja Europskog centra za spreļavanje i kontrolu bolesti (ECDC) pokazuju trend porasta broja sluļajeva gonoreje u veĺćini drġava ļlanica EU/EEA posljednjih godina. Iako se kretanje gonoreje treba tumaļiti s oprezom zbog razliļitosti u sustavima praĺćenja u pojedinim zemljama i nepotpunim podacima, opĺća stopa oboljelih za cijelu EU/EEA porasla je 2014. godine za 79% u odnosu na 2008. godinu. Zabiljeġen je i porast AMR gonokoka posljednjih godina. Poveĺćanjeĺć stope oboljelih od gonoreje, dijelom se objaġnjava poveĺćanjem testiranja meĽu skupinama s veĺćim rizikom za zarazu.

U 2013. godini prijavljeno je gotovo 53 000 sluļajeva gonoreje (ģto ļini stopu od 16.9 na 100 000 stanovnika) iz 28 drġava EU/EEA (ne ukljuļuje podatke iz Njemaļke, Italije i Lihtenġtajna), ģto je za 5 500 veĺći broj prijava u odnosu na godinu prije. Viġe od jedne treĺćine (39%) oboljelih su mladi u dobi 15 do 24 godine, tri puta ļeġće se biljeġi meĽu muġkarcima, a od ukupnog broja prijava oko polovina (43%) je bilo meĽu muġkarcima koji imaju spolne odnose s muġkarcima (MSM).

U Hrvatskoj se prema prijavama zaraznih bolesti prosjeļno u zadnjih deset godina evidentira 16 sluļajeva gonoreje godiġnje (raspon od 10 do 22). U 2013. godini svi oboljeli su bili muġkarci, od ļega njih polovina iz dobne skupine 20-29 godina. U 2014. godini bilo je 22 prijava gonoreje ģto je za 8 viġe nego prethodne dvije godine. Prema podacima o utvrĽenim bolestima ili stanjima iz primarne zdravstvene zaġtite (djelatnost opĺće/obiteljske medicine) u 2014. godini evidentirano je 48 sluļajeva gonoreje (Hrvatski zdravstveno-statistiļki ljetopis za 2014. godinu, HZJZ).

Obzirom da je u zemljama zapadne Europe gonokokna infekcija sve ļeġća, a javlja se i problem AMR, u organizaciji ECDC-a, pokrenut je program: European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP). Temeljem podataka prikupljenih preko projekta, utvrĽena je smanjena osjetljivost na cefalosporine proġirenog spektra ģto je imalo za posljedicu neupjeh u lijeļenju.Navedeni podatak potaknuo je izradu europskog plana odgovora na viġestruku antimikrobnu otpornost NG.

U 2013. godini, Euro-GASP je proveden u 21 zemlji EU, a glavni zakljuļci bili su :

ÅRezistencija na cefiksim opaġena je u 4,7% testiranih izolata. To je poveĺćanje od 0,8 % u odnosu na 2012.g., ģto je rezultiralo padom trendova od 2010. g.

ÅSedam izolata otpornih na ceftriakson otkriveno je u Euro-GASP-u u usporedbi sa tri u 2012. godini.

ÅStope otpornosti ciprofloksacina i azitromicina neznatno su porasle u odnosu na 2012. g. Udio izolata otpornih na ciprofloksacin ostao je vrlo visok (52,9%); rezistencija azitromicina ostala je blizu 5% (5,4%).

Hrvatska se krajem 2014. ukljuļila u program: Euro-GASP, nakon ģto je u listopadu 2014. godine struļni tim ECDC-a bio u radnom posjetu Hrvatskom zavodu za javno zdravstvo (HZJZ). Na sastanku su sudjelovali struļnjaci iz Nastavnog zavoda za javno zdravstvo ĂDr. Andrija Ġtamparñ, Klinike za

infektivne bolesti ĂDr. F. Mihaljeviĺ ñ te Referentnog centra za praĺenje rezistencije bakterija na antibiotike Ministarstva zdravlja RH i HZJZ-a.
Struļna javnost je informirana o programu na 6. hrvatskom kongresu o urogenitalnim i spolno prenosivim infekcijama u listopadu 2014. godine u Opatiji. Na 39. sastanku Odbora za praĺenje rezistencije bakterija (svibanj 2015.) donesen je zakljuļak o ukljuļivanju praĺenja AMR u gonokoka u godiġnje izvijeġĺe o rezistenciji. Izolati NG iz svih laboratorija koji sudjeluju u praĺenju, ġalju se u Odjel za bakteriologiju Sluġbe za mikrobiologiju HZJZ-a u okviru koje djeluje Hrvatski Nacionalni Referentni Laboratoriji ECDC-a.
U HZJZ se potvrĽuje identifikacija NG metodama kultivacije i molekularnom metodom PCR te se provodi testiranje osjetjivosti na antibiotike (metoda E- test). Izolati koji zbog vrlo velike osjetljivosti NG zadrġe vijabilnost, proslijeĽuju se u suradnu ustanovu ECDC-a:
Antimicrobial resistance and healthcare associated infection, National Infection Service
Public Health England (United Kingdom) ili Örebro University Hospital (Sweden). Molekularna dijagnostika provodi se na ureĽaju ABI Prism sequence detection system 7000 (Applied Biosystems, USA) metodom Real time - PCR. Sekvence i poļetnice koji se koriste su
slijedeĺe:

Primer or probe	Sequence
opa-Fw	GTT GAA ACA CCG CCC GG
opa-Rv	CGG TTT GAC CGG TTA AAA AAA GAT
Probe opa-1	CCC TTC AAC ATC AGT GAA A-MGB
Probe opa-2	CTT TGA ACC ATC AGT GAA A-MGB

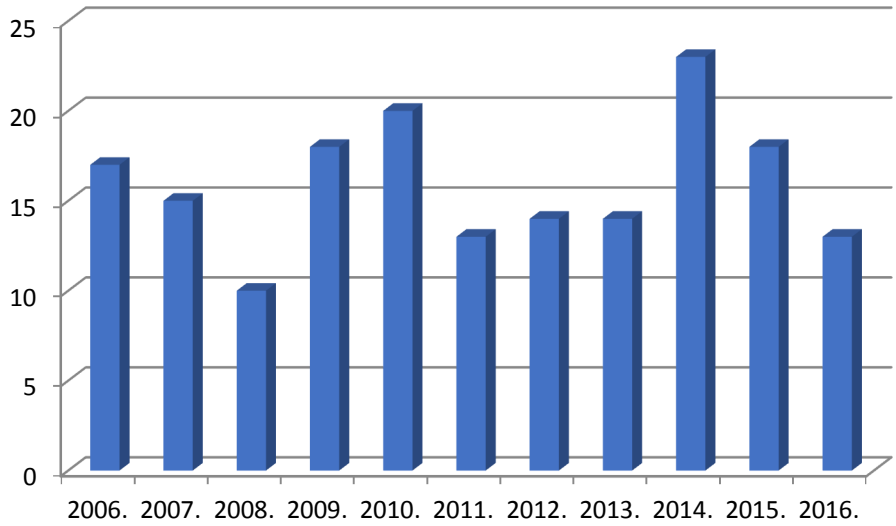
(izvor: J Clin Microbiol. Nov 2005; 43(11): 5653ï 5659. doi: 10.1128/JCM.43.11.5653-5659.2005).
U listopadu 2015. g. poslano je prvih deset uzoraka gonokoka na analizu u ECDC (Public Health England (United Kingdom)), a 2016. joġ 11 izolata NG.
U HZJZ je od 2007. do 2014 g. izolirano 69 izolata NG. Veĺina uzoraka dobivena je od mladih muġkaraca u dobi od 25 i viġe godina (97%). Uzorci su dobiveni od pacijenta koji su dolazili na pregled u Ambulantu Sluġbe za mikrobiologiju i u Savjetovaliġte HZJZ-a. Najviġe uzoraka dobiveno je iz spolno mokraĺnog sustava, ali je bilo i nekoliko uzoraka iz anorektalne regije i farinksa. Iako je rezistencija na cefalosporine viġih generacija u Europi u porastu, naġi rezultati u razdoblju 2007. do 2014 g. pokazali su dobru osjetljivost izolata na ceftriakson i cefiksim (>90%). Azitromicin i tetraciklin takoĽer su se pokazali djelotvornima na veĺinu izolata (>90%). Testirani sojevi su pokazali slabiju osjetljivost na ciprofloksacin (>50%), dok su gotovo svi izolati pokazali potpuno rezistenciju na penicillin.
U 2015.g. poļeli su stizati izolati NG ili samo podaci o osjetljivosti na NG (obzirom na zahtjevni transport i osjetljivost izolata) iz mikrobioloških laboratorija u RH koji sudjeluju u praĺenju rezistencije. Svi dobiveni rezultati su zaprimljeni, te su oni izolati koji su ostali vijabilni, retestirani.
Za 2015. god zaprimljeno je i analizirano ukupno podataka za 15 sojeva: 3 izolata iz Klinike za infektivne bolesti ñDr. F. Mihaljeviĺò, jedan iz Zavoda za javno zdravstvo Koprivniļko ï kriġevaļke ġupanije i 11 iz HZJZ (Tablica 2). U 2016. g. zaprimljeno je podataka za 35 sojeva iz viġe razliļitih ustanova (Tablica 3).
Iako je rezistencija na cefalosporine viġih generacija u Europi i dalje u porastu, naġi rezultati za 2015. pokazali su dobru osjetljivost na ceftriakson i cefiksim. Rezistentnih izolata na ceftriakson nije bilo, a na cefiksim je jedan izolat pokazao umjerenu osjetljivost (1/11, 9,1%).
Na tetraciklin bilo je 5 rezistentih izolata (5/15, 33,3%), a svih 15 izolata NG bilo je osjetljivo na azitromicin. Testirani sojevi pokazali su visoku rezistenciju na ciprofloksacin (8/15, 53,3%). Na penicilin bilo je 2/15 (13,3%) umjereno osjetljivih i 6/15 (40,0%) rezistentnih izolata. Kako se radi o vrlo malim brojevima, rezultate treba interpretirati s oprezom.
Podaci za 2016. pokazali su sliļne rezultate osjetljivosti, iako je ukupni broj prikazanih izolata bio veĺi u odnosu na prethodnu godinu. Ukupno je testirano 35 izolata:

- na penicillin 14/35 (40%) umjereno osjetljivih, 3/35, (8,6%) rezistentnih,
- na ceftriakson svi testirani osjetljivi (32/32, 100%)
- na cefiksim 5/29 (17,2%) rezistentnih,
- na azitromicin 5/33 (15,2%) rezistentnih,
- na ciprofloksacin 16/31(51,6%) rezistentnih izolata.

Iako je u praĺenje ukljuļeno 35 izolata, nije bilo moguĺe provesti testiranje svih izolata na sve antibiotike zbog tehniļkih razloga.

Osim navednih antimikrobnih lijekova, takoĽer je testirana osjetljivost na spektinomicin.U 2015.g. na spektinomicin testirano je 9 sojeva, a rezistencija je ustanovljena kod 3/9 (33,3%).
Uzevģi u obzir porast rezistencije na cefalosporinske antibiotike viģih generacija u EU, koje ļesto prati i unakriģna rezistencija na kinolone, potrebno je i u hrvatskim uvjetima podiĺi svijest o AMR na gonokoke. Naģi rezultati pokazuju dobru osjetljivost na cefalosporine, azitromicin i tetracikline, dok je na ciprofloksacin i penicillin utvrĽena rezistencija u veĺine sojeva. Prema preporukama ECDC-a potrebno bi bilo ujednaļiti metodologiju testiranja osjetljivosti, te usporediti izolate iz RH s onima u EU kako bi se toļno mogao pratiti razvoj AMR i predvidjeti uļinkovitost pojedinih antibiotika.

Tablica 1.
Broj prijavljenih bolesnika s *N. gonorrhoeae* u Hrvatskoj od 2006. do 2016.



Tablica 2.
Osjetljivost sojeva *N. gonorrhoeae* na antibiotike u Hrvatskoj, 2015.

Metoda MIK/E-test																					
	Penicilin			Ceftriaxon			Cefixim			Ciprofloxacin			Azithromycin			Tetracycline			Spektinomicin		
Ustanova	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)
ZG KIB	3	1 (33,3)	**0**	3	0	**0**	2	0	**0**	3	0	**2 (66,7)**	3	0	**0**	3	0	**0**			
ZG HZJZ	11	1 (9,1)	**6 (54,5)**	11	0	**0**	9	1 (11,1)	**0**	11	0	**5 (45,5)**	11	0	**0**	11	1 (9,1)	**4 (36,4)**			
KC ZZJZ	1	0	**0**	1	0	**0**				1	0	**1 (100)**	1	0	**1 (100)**	1	0	**1 (100)**			
Ukupno*	15	2 (13,3)	**6 (40,0)**	15	0	**0**	11	1 (9,1)	**0**	15	0	**8 (53,3)**	15	0	**1 (100)**	15	1(6.7)	**5(33.3)**	/	/	/

*Iako je u praćenje uključeno 15 izolata, nije bilo moguće provesti testiranje svih izolata na sve antibiotike zbog tehničkih razloga

Tablica 3.
Osjetljivost sojeva *N. gonorrhoeae* na antibiotike u Hrvatskoj, 2016.

Metoda MIK/E-test																					
	Penicilin			Ceftriaxon			Cefixim			Ciprofloxacin			Azithromycin			Tetracycline			Spektinomicin		
Ustanova	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)
ZG KIB	4	1 (25,0)	**0**	4	0	**0**	3	0	**0**	4	0	**4 (100)**	4	1 (25,0)	**1 (25,0)**	4	0	**1 (25,0)**			
ZG HZJZ	12	4 (33,3)	**1 (8,3)**	9	0	**0**	12	2 (16,7)	**5 (41,7)**	9	0	**5 (55,6)**	11	0	**2 (18,2)**	9	0	**4 (44,4)**	8	0	**3 (37,5)**
KC ZZJZ	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**1 (100)**	1	0	**0**	1	0	**0**			
ŠI ZZJZJ	1	0	**1 (100)**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**
SYNLAB	2	2 (100)	**0**	2	0	**0**	2	0	**0**	2	0	**2 (100)**	2	0	**0**	1	0	**0**			
KBC SM	1	1 (100)	**0**	1	0	**0**															
VŽ ZZJZ	1	1 (100)	**0**	1	0	**0**				1	0	**0**	1	0	**0**						
SB ZZJZ	1	1 (100)	**0**	1	0	**0**				1	0	**0**	1	0	**0**	1	0	**0**			
ČK ZZJZ	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**			
PU ZZJZ	2	0	**0**	2	0	**0**				2	0	**0**	2	0	**0**	2	0	**0**			
ZG ZZJZ	8	4 (50,0)	**1 (12,5)**	8	0	**0**	8	1 (12,5)	**0**	8	0	**3 (37,5)**	8	1 (12,5)	**2 (25,0)**	8	3 (37,5)	**1 (12,5)**			
ST NZJZZ	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**1 (100)**	1	0	**0**	1	0	**1 (100)**			
Ukupno*	35	14 (40)	**3 (8,6)**	32	0	**0**	29	0	**5 (17,2)**	31	0	**16 (51,6)**	33	2 (6,1)	**5 (15,2)**	29	0	**7 (24,1)**	9	0	**3 (33,3)**

*Iako je u praćenje uključeno 35 izolata, nije bilo moguće provesti testiranje svih izolata na sve antibitike zbog tehničkih razloga

Antimicrobial resistance in gonococci isolated in Croatia in 2015 and 2016

Gonorrhoea is today the second most frequent sexually transmitted infection (STI) of bacterial origin. Unless adequately treated, *Neisseria gonorrhoeae* (NG) infection can result in severe complications: pelvic inflammatory disease (PID), ectopic pregnancy, infertility, epididimytis or spread of gonococcal infection to other organs.

The present-day spread of antimicrobial resistance (AMR) additionally aggravates NG management, as NG has become increasingly resistant to quinolones and extended spectrum cephalosporins, that were efficient until recently. Another challenge is that not only does this infection not induce protective immunity, but it can also accelerate and facilitate the spread of human immunodeficiency virus infection.

Epidemiological surveillance data from the European Centre for Disease Prevention and Control (ECDC) reveal a growing trend of gonorrhea cases in majority of the EU/EEA countries over the last years.

Although gonorrhea trends need to be interpreted with caution due to differences in individual countriesô surveillance systems and to incomplete data, general EU/EEA morbidity rate in 2014 increased by 79% in comparison with that from 2008. A rise in gonococcal AMR has also been recorded in the last few years. A surge in the rate of persons affected by gonorrhea is partly explained by an increase in testing among high-risk groups.

Almost 53000 cases of gonorrhoea (rate of 16.9/100000 inhabitants) were registered in 28 EU/EEA countries (not including data from Germany, Italy and Lichtenstein) in 2013, which is an increase by 5500 records in comparison with the preceding year. More than one-third of persons affected (39%) were between 15 and 24 years of age; the infection was three times more frequent in men, and out of the total number of registered cases, about one half (43%) related to men who had sex with men (MSM).

According to a ten-year average of communicable disease registrations in Croatia, 16 cases of gonorrhoea (range 10 to 22) are registered annually. In 2013 all infected persons were men, and half among them were 20 to 29 years old. In 2014, 22 cases of gonorrhea were reported, 8 more than the previous two years.

According to primary care (general /family practice) data on diagnosed diseases or conditions, 48 gonorrhoea cases were registered in Croatia in 2014 (Croatian Health Statistics Yearbook 2014, CIPH).

In response to an increase in gonococcal infections and the spread of AMR in Western European countries, European Centre for Disease Prevention and Control (ECDC) initiated the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP). The collected data showed that a decrease in susceptibility to broad-spectrum cephalosporins was responsible for treatment failure. This finding resulted in the establishment of a European response plan to control and manage multidrug-resistant NG.

In 2013, Euro-GASP was implemented in 21 EU countries, and the major findings were:

ÅResistance to cefixime was observed in 4.7% of the tested isolates. Although this represented a 0.8% increase in comparison with 2012, the overall cefixime resistance trend decreased from 2010.

ÅSeven isolates with decreased susceptibility to ceftriaxone were detected by Euro-GASP compared to three isolates in 2012.

ÅRates of ciprofloxacin and azithromycin resistance slightly increased in comparison with 2012. The rate of ciprofloxacin-resistant isolates remained very high (52.9%), and azithromycin resistance remained close to 5% (5.4%).

Croatia has joined Euro-GASP in late 2014, after ECDC expert team paid a working visit to Croatian Institute of Public Health (CIPH), the national public health institute, in October 2014, gathering experts from the Teaching Institute of Public Health ñdr. Andrija Ġtamparò, Dr. Fran MihaljeviĺUniversity Hospital for Infectious Diseases, Reference Centre for Antimicrobial Resistance Surveillance of the Ministry of Health of the Republic of Croatia and the Croatian Institute of Public Health.

Professional community was informed about the programme at the Sixth Croatian Congress on Urogenital and Sexually Transmitted Infections in Opatija in October 2014. At its 39th meeting in May 2015, the Croatian Committee for Antibiotic Resistance Surveillance decided to include gonococcal AMR surveillance into the annual report on antibiotic resistance. NG isolates from all participating laboratories are sent to Croatian National Reference Laboratory - operating within the CIPH Department for Bacteriology of the Division for Microbiology. CIPH confirms NG identification by cultivation and PCR methods, and carries out antimicrobial susceptibility testing using the E-test method.

Isolates that maintain viability due to high NG susceptibility are forwarded to ECDCôs partner institutions - Antimicrobial resistance and healthcare associated infection, National Infection Service Public Health England (United Kingdom) or the Örebro University Hospital (Sweden). In CIPH, molecular diagnostics is performed on an ABI Prism sequence detection system 7000 (Applied Biosystems, USA) using real-time PCR assay. Sequences and primers used are as follows:

Primer or probe Sequence

- opa-Fw GTT GAA ACA CCG CCC GG
- opa-Rv CGG TTT GAC CGG TTA AAA AAA GAT
- Probe opa-1 CCC TTC AAC ATC AGT GAA A-MGB
- Probe opa-2 CTT TGA ACC ATC AGT GAA A-MGB

(Source: J Clin Microbiol. Nov 2005; 43(11): 5653ï 5659. doi: 10.1128/JCM.43.11.5653-5659.2005).

The first ten gonococcal isolates were sent to ECDC (Public Health England, United Kingdom) for analysis in October 2015, and another 11 in 2016.

Between 2007 and 2014, a total of 69 NG isolates were isolated in CIPH. The majority of samples were obtained from men aged 25 and above (97%). Samples were obtained from patients who presented at the Sample Collection Centre or the Counselling Centre of the Croatian Institute of Public Health. The site of specimen was mostly genitourinary, followed by anorectal and pharyngeal. Despite an increase in extended spectrum cephalosporins resistance in Europe, our results for the period 2007-2014 showed good susceptibility to ceftriaxone and cefixime (>90%). Azithromycin and tetracycline were also shown to be efficient in most isolates (>90%). The tested strains revealed a decreased susceptibility to ciprofloxacin (>50%), and almost all isolates were completely resistant to penicillin.

Microbiology laboratories from Croatia that participate in resistance surveillance programme began to submit NG isolates or data on NG susceptibility alone (due to demanding transport and sensitivity of isolates) in 2015. All results obtained were received and the isolates still viable were retested.

The following data on 15 strains were received and analysed in 2015: three isolates from Dr. F. MihaljeviĹ University Clinic for Infectious Diseases, one from Koprivnica-Kriġevci Institute of Public Health, and eleven from CIPH (Table 2). In 2016, data on 35 strains were received from different institutions (Table 3).

Although extended spectrum cephalosporins resistance in Europe increases, our results for the 2015 showed good susceptibility to ceftriaxone and cefixime. No ceftriaxone resistant isolates were detected, and one isolate showed moderate susceptibility to cefixime (1/11, 9.1%).

Five isolates were resistant to tetracycline (5/15, 33.3%), and all 15 NG isolates revealed susceptibility to azithromycin. The tested strains showed high resistance to ciprofloxacin (8/15, 53.3%). Moderate penicillin resistance was established in 2/15 (13.3%) isolates and high-level resistance was detected in 6/15 (40.0%) isolates. As the numbers are very small, these results should be interpreted with caution.

Data from 2016 showed similar results, although the total number of isolates presented was higher in comparison with the preceding year. Findings of antimicrobial resistance testing in a total of 35 isolates were as follows:

- penicillin - 14/35 (40%) moderately susceptible isolates, 3/35 (8.6%) resistant isolates,
- ceftriaxone - all tested isolates susceptible (32/32, 100%),
- cefixime - 5/29 (172%) resistant isolates,
- azithromycine - 5/33 (15.2%) resistant isolates,
- ciprofloxacin - 16/31(51,6%) resistant isolates.

Although surveillance included 35 isolates, not all of them could have been tested for resistance to all antibiotics for technical reasons.

Susceptibility to spectinomycin was additionally tested in nine strains collected in 2015, with resistance observed in 3/9 (33.3%) isolates.

In view of the increase in extended spectrum cephalosporins resistance in EU, which is frequently accompanied by cross-resistance to quinolones, awareness of gonococcal AMR needs to be increased in Croatia. Our results showed good susceptibility to cephalosporins, azithromycin and tetracyclines, but resistance to ciprofloxacin and penicillin in the majority of isolates. In accordance with ECDC recommendations, susceptibility testing techniques should be harmonised, and the isolates from Croatia compared with that from other EU countries to enable precise surveillance of AMR spread and anticipate efficacy of individual antibiotic drugs.

Table 1.
The number of registered patients with N. gonorrhoeae in Croatia, 2006-2016

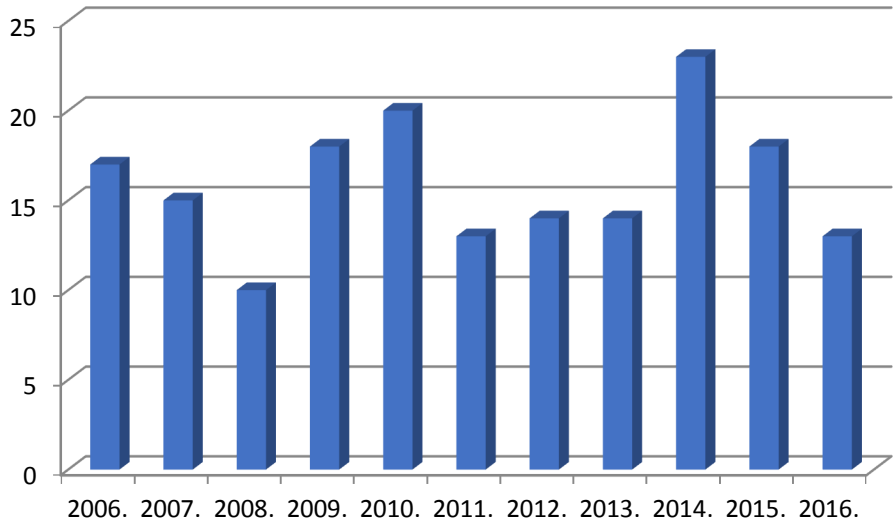


Table 2.
Antimicrobial susceptibility of N. gonorrhoeae strains to antibiotics in Croatia, 2016

Metoda MIK/E-test																					
	Penicilin			Ceftriaxon			Cefixim			Ciprofloxacin			Azithromycin			Tetracycline			Spektinomicin		
Ustanova	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)
ZG KIB	3	1 (33,3)	**0**	3	0	**0**	2	0	**0**	3	0	**2 (66,7)**	3	0	**0**	3	0	**0**			
ZG HZJZ	11	1 (9,1)	**6 (54,5)**	11	0	**0**	9	1 (11,1)	**0**	11	0	**5 (45,5)**	11	0	**0**	11	1 (9,1)	**4 (36,4)**			
KC ZZJZ	1	0	**0**	1	0	**0**				1	0	**1 (100)**	1	0	**1 (100)**	1	0	**1 (100)**			
Ukupno*	15	2 (13,3)	**6 (40,0)**	15	0	**0**	11	1 (9,1)	**0**	15	0	**8 (53,3)**	15	0	**1 (100)**	15	1(6.7)	**5(33.3)**	/	/	/

* Although 15 isolates were included in the monitoring, it was not possible to test all isolates on all antimicrobial agents, due to technical reasons

Table 3.
Antimicrobial susceptibility of N. gonorrhoeae strains to antibiotics in Croatia, 2016

Metoda MIK/E-test																					
	Penicilin			Ceftriaxon			Cefixim			Ciprofloxacin			Azithromycin			Tetracycline			Spektinomicin		
Ustanova	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)	UK	I (%)	R (%)
ZG KIB	4	1 (25,0)	**0**	4	0	**0**	3	0	**0**	4	0	**4 (100)**	4	1 (25,0)	**1 (25,0)**	4	0	**1 (25,0)**			
ZG HZJZ	12	4 (33,3)	**1 (8,3)**	9	0	**0**	12	2 (16,7)	**5 (41,7)**	9	0	**5 (55,6)**	11	0	**2 (18,2)**	9	0	**4 (44,4)**	8	0	**3 (37,5)**
KC ZZJZ	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**1 (100)**	1	0	**0**	1	0	**0**			
ŠI ZZJZJ	1	0	**1 (100)**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**
SYNLAB	2	2 (100)	**0**	2	0	**0**	2	0	**0**	2	0	**2 (100)**	2	0	**0**	1	0	**0**			
KBC SM	1	1 (100)	**0**	1	0	**0**															
VŽ ZZJZ	1	1 (100)	**0**	1	0	**0**				1	0	**0**	1	0	**0**						
SB ZZJZ	1	1 (100)	**0**	1	0	**0**				1	0	**0**	1	0	**0**	1	0	**0**			
ČK ZZJZ	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**0**			
PU ZZJZ	2	0	**0**	2	0	**0**				2	0	**0**	2	0	**0**	2	0	**0**			
ZG ZZJZ	8	4 (50,0)	**1 (12,5)**	8	0	**0**	8	1 (12,5)	**0**	8	0	**3 (37,5)**	8	1 (12,5)	**2 (25,0)**	8	3 (37,5)	**1 (12,5)**			
ST NZJZZ	1	0	**0**	1	0	**0**	1	0	**0**	1	0	**1 (100)**	1	0	**0**	1	0	**1 (100)**			
Ukupno*	35	14 (40)	**3 (8,6)**	32	0	**0**	29	0	**5 (17,2)**	31	0	**16 (51,6)**	33	2 (6,1)	**5 (15,2)**	29	0	**7 (24,1)**	9	0	**3 (33,3)**

* Although 35 isolates were included in the monitoring, it was not possible to test all isolates on all antimicrobial agents, due to technical reasons

PRAĆENJE REZISTENCIJE NA ANTIBIOTIKE U INVAZIVNIH IZOLATA
ANTIBIOTIC RESISTANCE SURVEILLANCE IN INVASIVE ISOLATES

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Važnost praćenja rezistencije u invazivnih izolata

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

Rezultati praćenja rezistencije u invazivnih izolata

U 2016.g. bilježimo približno isti broj prikupljenih izolata kao i prošle godine. Broj laboratorija i broj prikupljenih invazivnih izolata pojedinih vrsta prikazani su u Tablici 1.

Podaci o izolatima šalju se na formularu i obrađuju u Referentnom centru za praćenje rezistencije na antibiotike u Klinici za infektivne bolesti. Sa svrhom retestiranja izolata s rijetkim fenotipom i eventualne daljnje obrade invazivni izolati *S. pneumoniae, E. coli*, *K. pneumoniae* i *Acinetobacter* spp. se šalju u Referentni centar za praćenje rezistencije, a izolati *S. aureus, E. faecalis, E. faecium* i *P. aeruginosa* u Referentni centar za bolničke infekcije. Tijekom 2016.g. prikupljeno je 156 izolata *S. pneumoniae,* 1078 izolata *E. coli*, 339 izolata *K. pneumoniae*, 476 izolata *S. aureus,* 288 izolata enterokoka (183 *E. faecalis* i 105 *E. faecium* izolata), 269 izolata *P. aeruginosa* , te 188 izolata *Acinetobacter* spp. (Tablica 1).

Trend rasta rezistencije *P. aeruginosa* na karbapeneme je zabrinjavajući i u 2016. g. doseže visokih 41%. Rezistencija *Acinetobacter* spp. na karbapeneme je i dalje izuzetno visoka (95%).

Među invazivnim izolatima pneumokoka u 2016.g. neosjetljivost na penicilin (23%) je podjednaka prošlogodišnjoj stopi rezistencije dok je stopa rezistencije na makrolide skočila na 33% i time dosegla vrijednosti prijašnjih godina (2010.-2014.).
Udio MRSA izolata među invazivnim sojevima isti je kao i prošle godine (25%), još uvijek stabilno ispod razine stopa zabilježenih prije 2010.g. (>30%). Kod ukupnog broja izoliranih stafilokoka bilježimo porast MRSA izolata (16%).

Rezistencija na glikopeptide nije uočena u *E. faecalis,* a u *E. faecium* je stopa rezistencije i dalje vrlo visoka (23%). Stope visoke rezistencije na aminoglikozide su i dalje visoke u obje vrste enterokoka.

I dalje se nastavlja rast stopa rezistencije *E. coli* na 3. generaciju cefalosporina, što je pretežno uzrokovano proizvodnjom beta-laktamaza proširenog spektra (engl. "extended spectrum beta-lactamases", ESBL). Rezistencija na kinolone nastavlja svoj rast i u 2016.g. doseže 28%.

Udio *K. pneumoniae* izolata rezistentnih na 3. generaciju cefalosporina (46%) se nije bitno mijenjao, a stopa neosjetljivih izolata na karbapeneme (imipenem i/ili meropenem) je 2%. U sklopu EARS Net programa prijavljuje se neosjetljivost na imipenem i/ili meropenem, ali ne i ertapenem. U nagem nacionalnom praćenju evidentirano je još dodatnih 8 invazivnih izolata s dokazanom proizvodnjom karbapenemaza neosjetljivih na ertapenem, ali osjetljivih na imipenem i meropenem.

Stope rezistencije detaljno su prikazane u tablici 2.

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

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

Impact of antibiotic resistance surveillance in invasive isolates

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

Results of the antibiotic resistance surveillance in invasive isolates

The number of isolates collected in 2016 is similar to the previous year. Number of laboratories reporting and number of invasive isolates collected are shown in Table 1.

Forms with data for each isolate are sent to and analysed at the Reference Centre for Antimicrobial Resistance Surveillance at the University Hospital for Infectious Diseases. With a purpose of retesting and further analysis of isolates with unusual phenotype isolates of *S. pneumoniae*, *E. coli, K. pneumoniae* and *Acinetobacter* spp. are sent to the Reference Centre for Antimicrobial Resistance Surveillance while isolates of *S. aureus, E. faecalis, E. faecium* and *P. aeruginosa* are sent to the Reference Centre for Hospital Infections. During 2016 we have collected 156 isolates of *S. pneumoniae,* 1078 isolates of *E. coli*, 339 isolates of *K. pneumoniae*, 476 isolates of *S.aureus,* 288 enterococcal isolates (183 *E. faecalis* and 105 *E. faecium* isolates), 269 isolates of *P.aeruginosa* and 188 isolates of *Acinetobacter* spp. (Table 1).

The increasing trend of carbapenem resistance in *P. aeruginosa*, is highly disturbing, with resistance rates reaching 41% this year. Carbapenem resistance in *Acinetobacter* spp. remains extremely high (95%).

In 2016 we recorded 23% of invasive pneumococci non-susceptible to penicillin while resistance rates to macrolides (33%) went up, thereby reaching expected values recorded from years before (2010-2014). The rate of MRSA isolates stays the same as the previous year (25%), steadily under the values recorded before 2010 (>30%). MRSA rates observed in mass surveillance in 2016 increased to 16% (Chapter 1.).

Glycopeptide resistance was not observed in *E. faecalis* while glycopeptide resistance in *E. faecium* is still extremely high (26%). The rates of high level aminoglycoside resistance are still high in both species.

Resistance to 3rd generation cephalosporins in *E.coli* is continuously increasing, mostly due to the production of extended spectrum beta-lactamases (ESBL). Quinolone resistance in *E.coli* is still increasing and has reached as high as 28% in 2016.

Resistance to 3rd generation cephalosporins in *K. pneumoniae* remains stable (46%), and the rate of carbapenem non-susceptiblity (imipenem and/or meropenem) is 2%. When reporting carbapenem susceptibility to EARS-Net only imipenem and/or meropenem, not ertapenem data are considered. Within our national surveillance system, however, we collect isolates non-susceptible to any of the carbapenems (including ertapenem) and additional eight carbapenemase producing invasive isolates, non-susceptible to ertapenem but sensitive to imipenem and meropenem were detected.

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.-2016. /
Number of laboratories and number of isolates reported for the period 2001-2016

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

Tablica 2. / *Table 2.*
Udio izolata smanjene osjetljivosti na antibiotike izražen u postocima /
Proportion of antibiotic non-susceptible isolates in percent

PATOGEN / PATHOGEN	ANTIBIOTICI/ Antimicrobial classes	2006 %	2007 %	2008 %	2009 %	2010 %	2011 %	2012 %	2013 %	2014 %	2015 %	2016 %
S. pneumoniae	Penicillin R	1	1	4	6	7	1	1	4	1	1	1
	Penicillin I+R	18	18	17	19	21	18	23	27	26	20	22
	Macrolides I+R	16	8	14	8	29	24	28	34	28	19	33
S. aureus	Oxacillin/Met R	36	38	35	37	27	27	22	24	21	25	25
E. coli	Aminopenicillins R	51	51	53	55	55	55	52	54	54	56	57
	Aminoglycosides R	6	6	6	8	6	7	7	7	10	12	14
	Fluoroquinolones R	15	13	15	16	17	20	17	21	20	25	28
	3. gen Cef R	1	3	4	5	8	7	8	9	11	13	12
	ESBL						9	7	9	11	13	14
E. faecalis	Aminopenicillins I+R	3	2	5		5	1	5	9	6	4	7
	HL Aminoglycosides R	37	37	46	36	37	33	39	35	33	35	33
	Glycopeptides R	<1	<1	<1	<1	<1	1	<1	<1	0	0	0
E. faecium	Aminopenicillins I+R	69	78	79		82	98	98	90	94	97	98
	HL Aminoglycosides R	59	59	65	68	60	66	61	55	64	53	65
	Glycopeptides R	3	2	6	11	12	2	0	7	10	26	23
K. pneumoniae	Aminoglycosides R	33	38	51	47	49	43	45	51	48	40	31
	Fluoroquinolones R	23	34	44	51	48	43	43	45	46	50	44
	3. gen Cef R	34	40	54	53	56	50	44	50	48	46	42
	ESBL						51	52	50	48	47	46
	Carbapenems I+R						<1	<1	1	2	3	2
P. aeruginosa	Piperacillin R	38	30	34		23						
	Piperacllin/Tazobactam R					16	23	18	23	32	25	20
	Ceftazidime R	11	14	13	11	12	17	14	20	28	20	23
	Carbapenems R	25	26	30	31	26	30	21	25	35	37	41
	Aminoglycosides R	47	40	39	37	26	34	26	24	37	34	32
	Fluoroquinolones R	35	30	33	29	27	34	24	23	28	37	38
A. baumannii	Carbapenems R								91	88	89	95

Tablica 3. / *Table 3.*
Prikaz gram-pozitivnih invazivnih izolata u 2016.g. prema demografskim podacima pacijenata / *Selected details on gram-positive invasive isolates from the reporting period 2016*

	S.pneumoniae		***S.aureus***		***Enterococcus* spp.**	
	n=156		**n=476**		**n=288**	
	% tot	**% PNPS**	**% tot**	**% MRSA**	**% tot**	**% VRE**
UZORAK ***SAMPLE***						
Krv / Blood	85	20	99	25	100	8
Likvor / CSF	15	26	1	33	0	0
SPOL ***GENDER***						
M	57	18	62	23	63	7
Ç / F	39	26	36	27	32	13
Nepoznato / Unknown	4	17	2	38	5	0
DOB ***AGE***						
0-4	24	29	3	13	7	10
5-19	8	0	2	20	1	0
20-64	33	14	36	17	35	11
>65	24	37	57	36	56	7
Nepoznato / Unknown	11	6	2	0	1	0
ODJEL ***DEPARTMENT***						
Intenzivna / ICU	19	14	11	41	12	6
Interna / Medical	49	17	78	20	56	10
Kirurgija / Surgery	<1	0	7	39	9	15
Ostalo/ Other	32	32	4	33	23	5

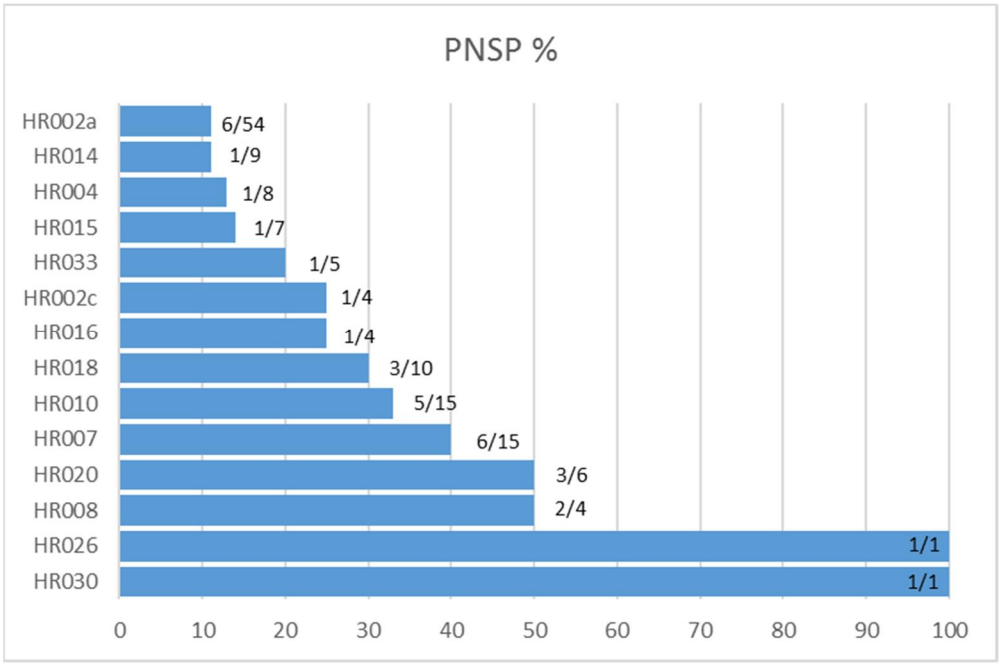
PNSP=Penicillin Non-Susceptible *S. Pneumoniae* MRSA=Methicillin Resistant *S.aureus* VRE=Vancomycin Resistant Enterococcus

Tablica 4. / *Table 4.*
Prikaz gram-negativnih invazivnih izolata u 2016.g. prema demografskim podacima pacijenata / *Selected details on gram-negative invasive isolates from the reporting period 2016*

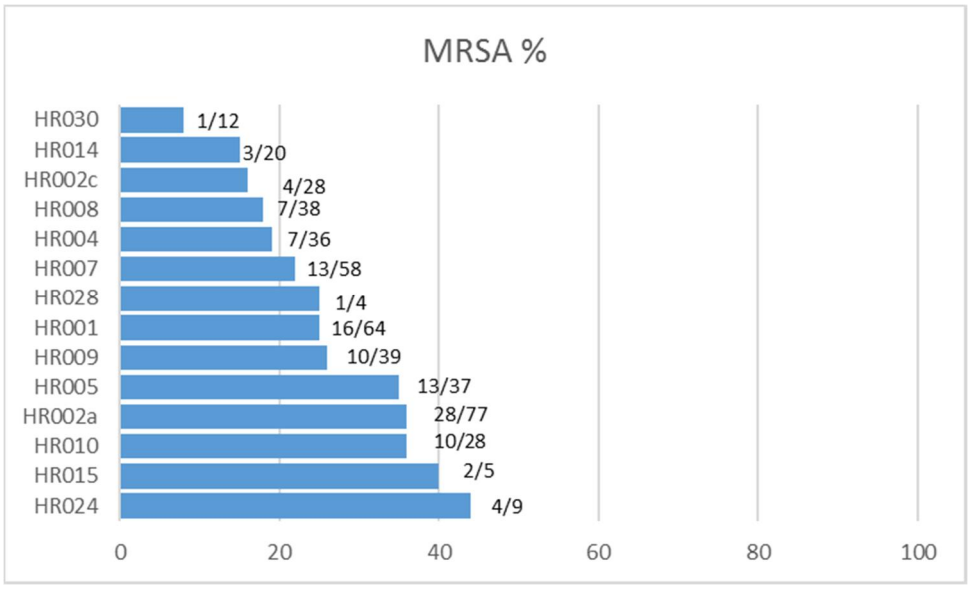
	E.coli			*Acinetobacter* spp.		*K.pneumoniae*		*P.aeuroginosa*	
	n=1078			n=188		n=339		n=269	
	% tot	% FREC	% CREC	% tot	% CRA	% tot	% CRKP	% tot	% CRPA
UZORAK ***SAMPLE***									
Krv / Blood	100	28	12	99	95	99	47	98	38
Likvor / CSF	0	0	0	1	50	1	0	2	60
SPOL ***GENDER***									
M	40	66	17	61	95	54	53	57	36
Ç / F	57	21	9	35	94	43	38	41	40
Nepoznato / Unknown	3	31	6	4	86	3	55	1	50
DOB ***AGE***									
0-4	3	15	15	3	67	11	76	5	40
5-19	<1	0	0	3	100	1	20	1	67
20-64	33	28	10	46	93	32	46	41	40
>65	63	29	14	47	94	54	41	51	35
Nepoznato / Unknown	>1	11	0	4	0	2	33	1	0
ODJEL ***DEPARTMENT***									
Intenzivna / ICU	6	36	16	36	98	17	50	18	24
Interna / Medical	75	26	11	38	92	55	39	45	34
Kirurgija / Surgery	8	47	14	8	100	12	44	14	42
Ostalo/ Other	11	25	16	18	91	16	69	35	51

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 *Acinetobacter* spp.

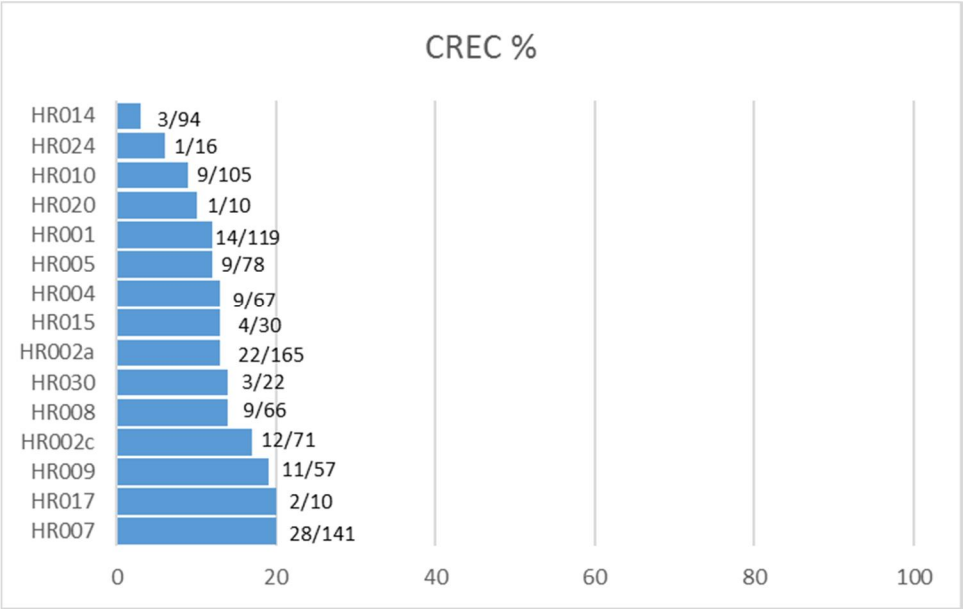
Slika 1. / *Figure 1.*
Udio (%) izolata *S. pneumoniae* smanjene osjetljivosti na penicilin (PNSP) po centrima /
Proportion (%) of penicillin non-susceptible S. pneumoniae (PNSP) by center



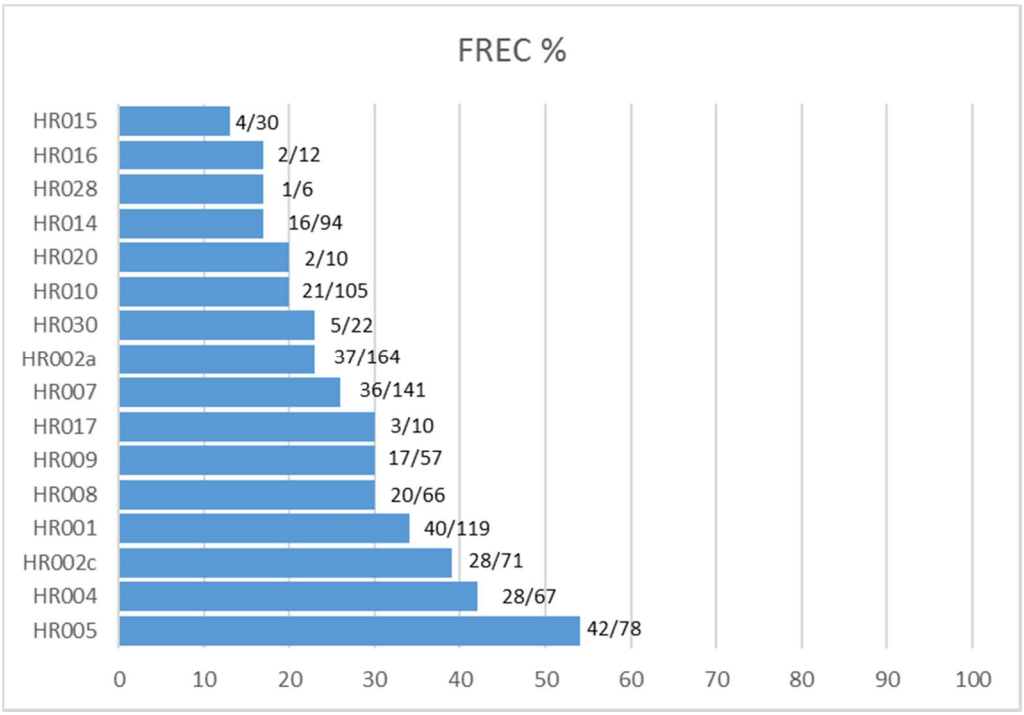
Slika 2. / *Figure 2.*
Udio (%) MRSA izolata po centrima /
Proportion (%) of MRSA isolates by center



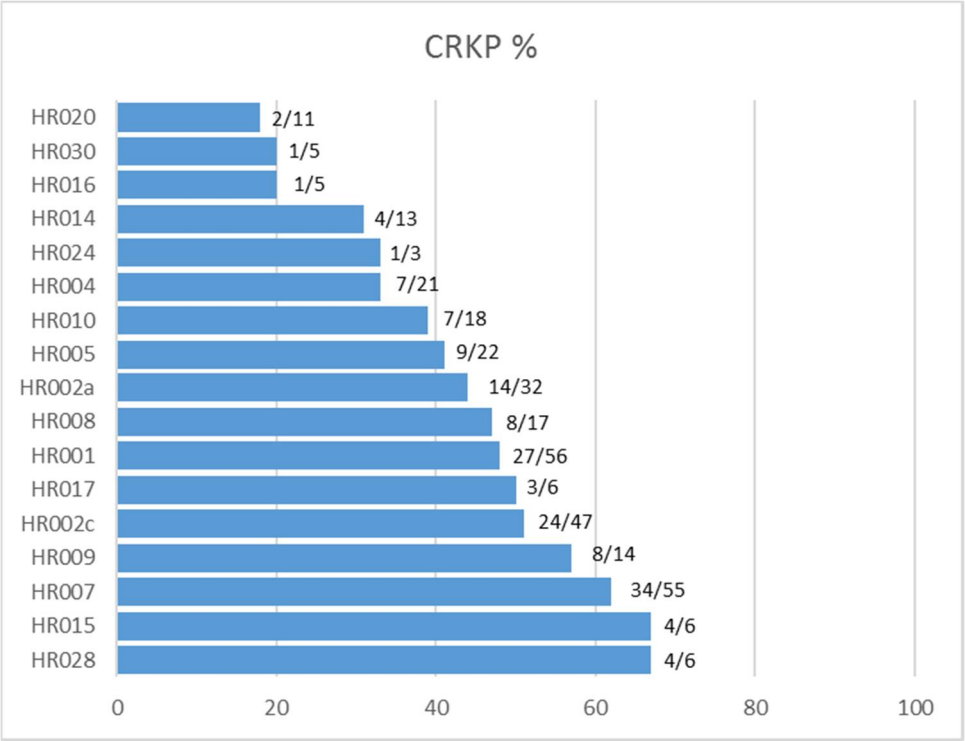
Slika 3. / *Figure 3.*
Udio (%) ceftazidim rezistentnih izolata *E. coli* (CREC) po centrima /
Proportion (%) of ceftazidime resistant E. coli isolates (CREC) by center



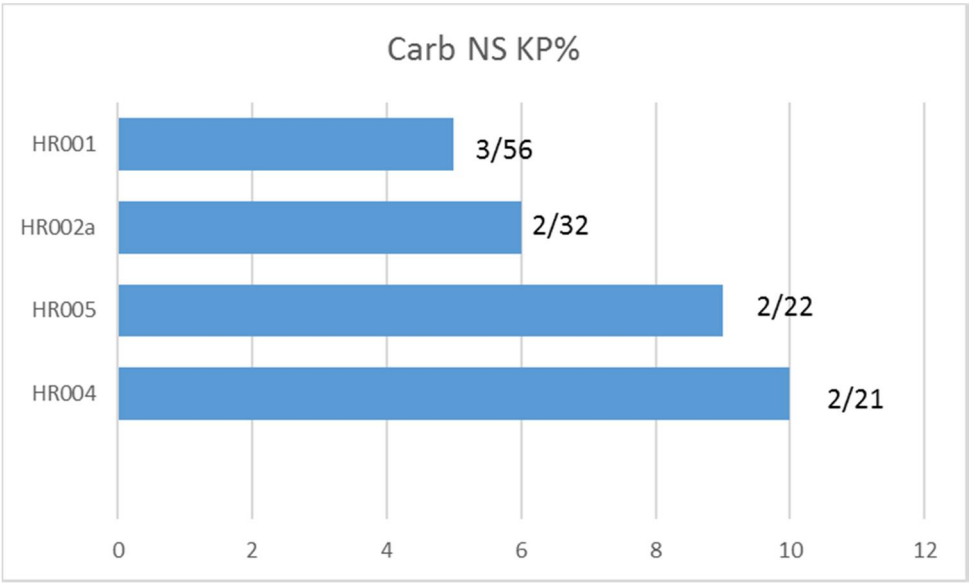
Slika 4. / *Figure 4.*
Udio (%) fluorokinolon rezistentnih izolata *E. coli* (FREC) po centrima /
Proportion (%) of fluoroquinolone resistant E.coli isolates (FREC) by center



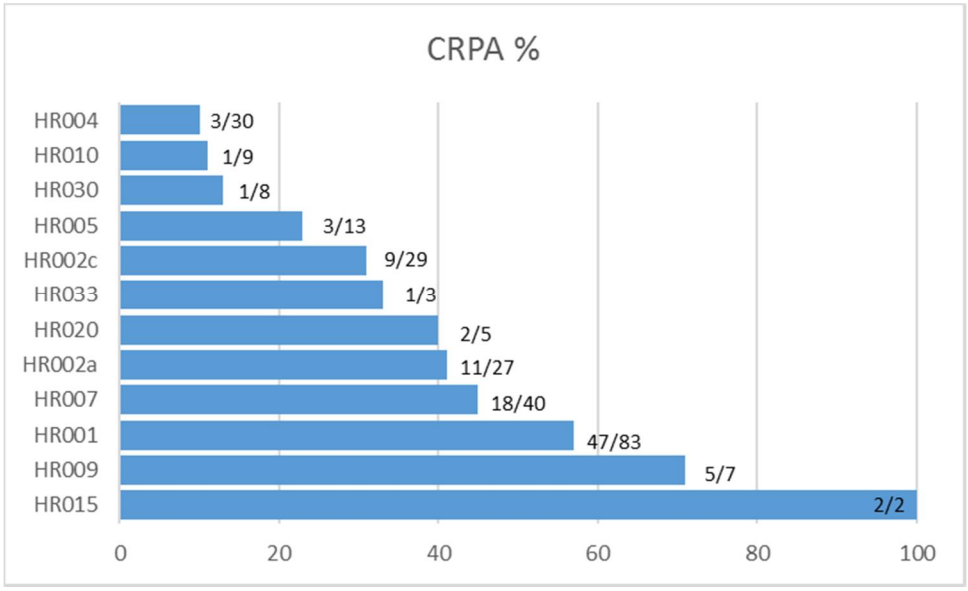
Slika 5. / *Figure 5.*
Udio (%) ceftazidim rezistentnih izolata *K. pneumoniae* (CRKP) po centrima /
Proportion (%) of ceftazidime resistant K. pneumoniae (CRKP) by center



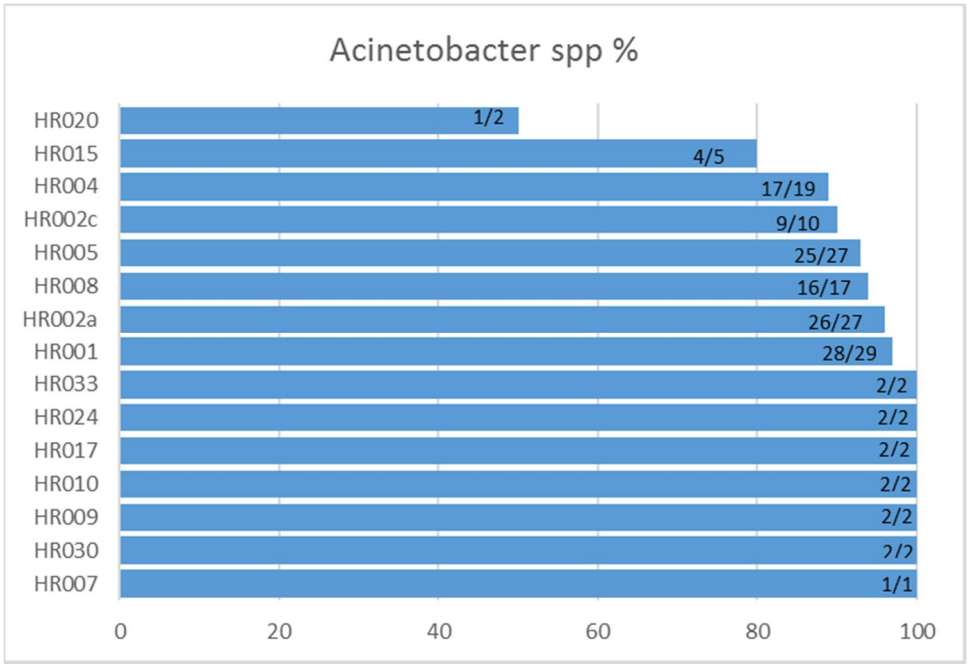
Slika 6. / *Figure 6.*
Udio (%) karbapenem neosjetljivih izolata *K. pneumoniae* (Carb NS KP) po centrima /
Proportion (%) of carbapenem non-susceptible K. pneumoniae (Carb NS KP) by center



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.

POTROŠNJA ANTIBIOTIKA U HRVATSKOJ
ANTIBIOTIC CONSUMPTION IN CROATIA

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Izvanbolnička potrošnja antibiotika

Praćenje potrošnje antibiotika u Hrvatskoj započelo je 2001. godine u okviru European Surveillance of Antibiotic Consumption (ESAC) propisanom metodologijom za sve zemlje koje su se uključile u praćenje. Podaci o potrošnji antibiotika (J01) prikupljeni su u skladu s anatomsko-terapijsko-kemijskom klasifikacijom (ATK) na petoj razini, a objavljuju se na četvrtoj i trećoj razini, odvojeno za bolnice i ambulantnu (izvanbolničku) potrošnju.

Do 2013. godine prikupljeni podaci su uneseni u ABC kalkulator, koji se redovito, svake godine usklađivao s hrvatskim tržištem. Za 2014. godinu prirađena je Excel tablica-predložak u koju su unijeti podaci o potrošnji antibiotika, a koja je usklađena sa predloškom za ESAC-Net u okviru The European Surveillance System (TESSY) praćenja potrošnje antibiotika. Potrošnja antibiotika se izražava u definiranim dnevnim dozama na 1000 stanovnika po danu (DDD/TID).

Od 2012. godine u Hrvatskoj pratimo ambulantnu potrošnju iz dva izvora, veledrogerija i Hrvatskog zavoda za zdravstveno osiguranje (HZZO). Podatke dobivene od HZZO-a, koji se temelje na propisanim i izdanim receptima koristimo kao službene podatke o potrošnji antibiotika (Tablica 1, Slika 1).

U 2016. godini kao denominator je korišten broj stanovnika prema popisu stanovništva iz 2011. godine (4 284 889), kao i u prethodne tri godine, dok je do 2012. denominator iznosio (4 555 219) prema popisu stanovništva iz 2001. godine.

Uočava se razlika u potrošnji antibiotika ovisno o izvoru podataka, tako je i u 2016. godini veća potrošnja, kada se računa prema podacima iz veledrogerija (21,57 DDD/TID), u odnosu na podatke dobivene od HZZO-a (20,73 DDD/TID) (tablica 3; slika 2). Najveća razlika se uočava kod klase penicilna J01C (za 0,45 DDD/TID) te klase makrolid-linkozamid J01F (0,18 DDD/TID) (tablica 4; slika 3), što je znatno manje nego prethodne godine, kada je razlika iznosila 1,27 DDD/TID. Mogući razlozi mogu biti direktna kupovina antibiotika putem privatnog recepta ili opskrba ambulanti primarne zdravstvene zaštite antibioticima preko veledrogerija.

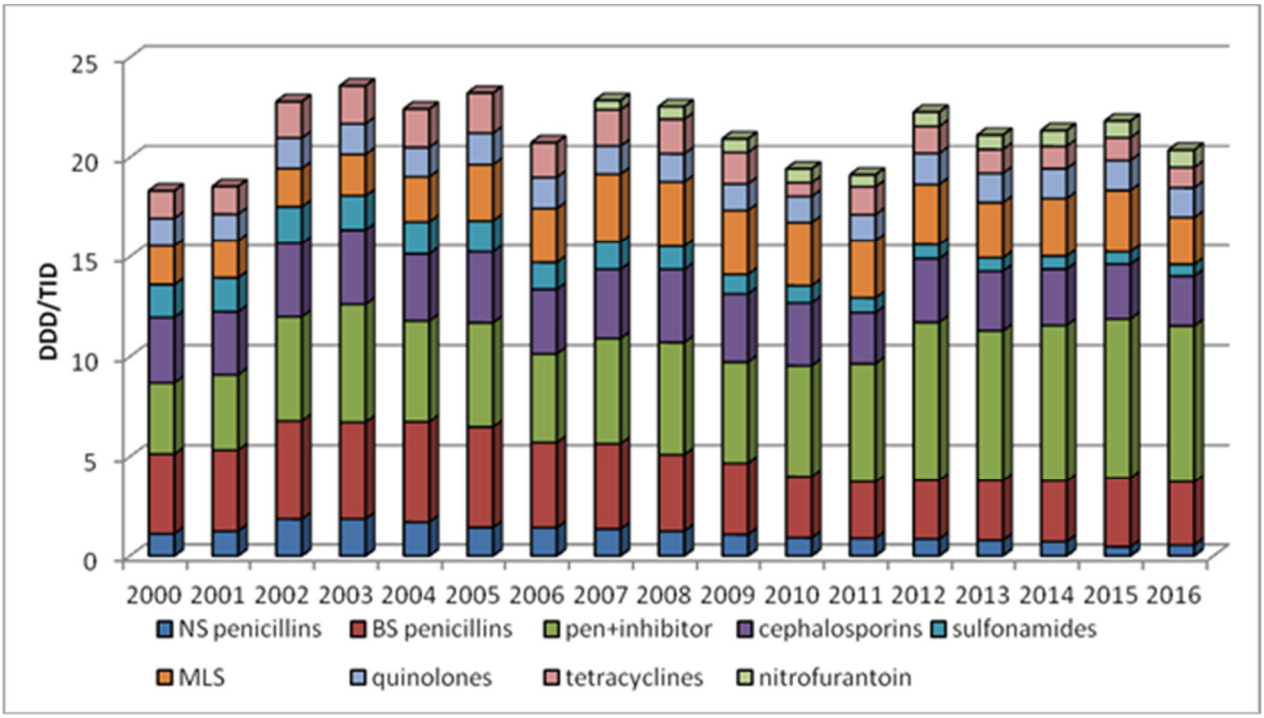
Širokospektralni penicilinski antibiotici (J01CA; J01CR) pokazuju pad u potrošnji, dok je zabilježen porast penicilina uskog spektra (J01CE) (Tablica 1, Slika 1). I kod ostalih klasa se uočava pad u potrošnji, najviše u klasi makrolid-linkozamid (0,72 DDD/TID). Potrošnja klase tetraciklina je najniža do sada (1,02 DDD/TID), dok jedino nitrofurantoin (J01XE) bilježi trend porasta u zadnjih pet godina (0,72; 0,72; 0,79; 0,83; 0,87). Nadamo se da oba indikatora, tj. smanjenje potrošnje široko spektralnih penicilina uz porast potrošnje penicilina uskog spektra te porast potrošnje nitrofurantoina ukazuju na bolje pridržavanje ISKRA smjernica za liječenje urinarnih infekcija i grlobolje.

I u 2016. godini ambulantna potrošnja u Hrvatskoj prelazi 90% ukupne potrošnje antibiotika, odnosno čini 92% od ukupne potrošnje. Od 2012. godine, od kada koristimo isti denominator, prema popisu stanovništva iz 2011. godine (4 284 889 stanovnika) bilježimo najnižu ambulantnu potrošnju antibiotika (20,73 DDD/TID). U tumačenju pada ambulantne potrošnje treba, ipak, biti oprezan i svjestan da se broj stanovnika nakon popisa 2011.g. prema podacima EURO STATA nastavio smanjivati te da denominator koji koristimo može biti podcijenjen.

Kontinuirana edukacija o pravilnoj upotrebi antibiotika koja uključuje sve sudionike zdravstvenog sustava, a započinje u dodiplomskoj nastavi studenata medicine, zatim liječnika primarne zdravstvene zaštite i bolničkih liječnika različitih profila neophodna je za postizanje racionalne primjene antibiotika.

Istovremeno kontinuiran rad na podizanju svjesnosti javnosti o važnosti antibiotika i njihovoj pravilnoj upotrebi važan je cilj u kontroli nepotrebne i neprimjerene potrošnje antibiotika, kao najjače poticajne sile za razvoj rezistencije bakterija na antibiotike.

Slika 1. */ Figure 1.*
Ambulantna potrošnja antibiotika (DDD/TID) u Hrvatskoj, 2000 - 2016.
Ambulant antibiotic consumption (DDD/TID) in Croatia, 2000 - 2016



Outpatient Antibiotic Consumption

Surveillance of antibiotic consumption in Croatia started in 2001 within the European Surveillance of Antibiotic Consumption (ESAC) project in a standardized way for all countries included in surveillance. Data on antibiotic consumption (J01) are collected in accordance with the Anatomical Therapeutic Chemical (ATC) classification on the fifth level, and are published on the fourth and third level, separately for hospitals and outpatient consumption.

Up until 2013, collected data were entered into ABC calculator, which was routinely and annually harmonised with the Croatian market. For 2014, data on antibiotic consumption were entered into Excel template table, which has been harmonised with the template for ESAC-Net under The European Surveillance System (TESSy) for the surveillance of antibiotic consumption. Data on consumption are expressed in defined daily doses per 1,000 inhabitans per day (DDD/TID).

Since 2012, data for outpatient consumption are collected from two sources (wholesales and Croatian Health Insurance Fund- CHIF). CHIF data are based on prescriptions and are considered as an official national data (Table 1, Figure 1).

In 2016, the Census of 2011 is used as a denominator (4 284 889) like in the previous three years, while up until 2012 the denominator was the Census of 2001 (4 555 219).

There is a difference in antibiotic consumption depending on the source of the data. According to the data obtained from wholesales, the consumption is higher (21,57 DDD/TID for wholesales data and 20,73 for CHIF data) (Table 3 and Figure 2). The biggest difference is observed in the penicillin class J01C, where the difference is 0,45 DDD/TID, and in macrolides-lincosamides class J01F (Table 4 and Figure 3). The difference in macrolides-lincosamides class is 0,18 DDD/TID and in comparison with the consumption in last year is significantly smaller (1,27 DDD/TID). The reason for difference in registered consumption might be due to the antibiotic purchase with private prescriptions, and direct ordering of antibiotic from wholesale pharmacies for primary health care.

There is a decrease in broad spectrum penicillins consumption (J01CA; J01CR), and increase in narrow spectrum penicillins consumption (J01CE) (Table 1, Figure 1). A decrease in other antibiotic classes was also recorded. The biggest difference is observed in the macrolides-lincosamides class (0,72 DDD/TID). Consumption of tetracyclines is the lowest ever (1,02 DDD/TID). Only nitrofurantoin has an increasing trend in antibiotic consumption in the last 5 years (0,72; 0,72; 0,79; 0,83; 0,87). We hope that both indicators, decrease in the use of broad spectrum penicillins with simultaneous increase in consumption of narrow spectrum penicillins and increase in the use of nitrofurantoin, may indicate better compliance with ISKRA guidelines on the antimicrobial treatment of urinary tract infections and sore throat.

In 2016, the outpatient antibiotic consumption makes over 90% of total antibiotic consumption (92%). Since 2012, since we are using the Census of 2011 as a denominator (4 284 889 residents), the outpatient antibiotic consumption rate is the lowest ever (20,73 DDD/TID). However, a decrease in consumption data should be interpreted with caution because according to the EURO STAT data the number of inhabitants in Croatia is decreasing so the 2011 Census data might be underestimating the number of inhabitants.

To calculate the antibiotic consumption we are using the official data of the Croatia Bureau of Statistics (the data according to the Census of 2011), so the final calculation of consumption is based on the same denominator and does not follow the current dynamics of changes in the number of inhabitants in Croatia.

Much desired decrease and rationalization in antibiotic consumption can only be achieved through continuous education of all participants in the health system, starting with medical students, then the primary health care physician and hospital doctors of different profiles.

Also, continuous education of general public about proper use and importance of antibiotics is an important goal in controlling of the unnecessary use of antibiotics. Unnecessary use of antibiotics is the strongest stimulating force for the development of bacterial resistance.

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

ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2006	2007	2008	2009	2010	2011	2012 *	2013 *	2014 *	2015 *	2016 *
JO1AA	Tetraciklini Tetracylines	1.74	1,81	1,73	1,57	1,46	1,39	1,35	1,19	1,12	1,14	1,02
JO1CA	Penicilini širokog spektra Broad spectrum penicillins	4.30	4,31	3,86	3,60	3,09	2,84	2,96	3,00	3,05	3,47	3,17
JO1CE	Penicilini uskog spektra Narrow spectrum penicillins	1.41	1,34	1,24	1,07	0,91	0,88	0,85	0,79	0,72	0,46	0,55
JO1CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0.05	0,05	0,04	0,00	0,00	0,00	0,00	0,00	0,00	0,01	0,00
JO1CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	4.43	5,26	5,61	5,06	5,55	5,93	7,91	7,50	7,80	7,96	7,82
JO1DB	Cefalosporini I gen. cephalosporins	1.66	1,88	1,56	1,21	1,05	0,84	0,82	0,77	0,72	0,66	0,60
J01DC	Cefalosporini II gen. cephalosporins	1.15	1,02	1,55	1,59	1,50	1,19	1,80	1,77	1,85	1,85	1,69
J01DD	Cefalosporini III gen. cephalosporins	0.42	0,56	0,55	0,61	0,59	0,53	0,57	0,45	0,24	0,23	0,20
JO1EE	Sulfonamides + trimethoprim	1.35	1,4	1,17	0,98	0,87	0,73	0,72	0,67	0,66	0,63	0,59
JO1F	Macrolides, lincosamides	2.73	3,40	3,24	3,24	3,19	2,89	3,03	2,80	2,91	3,10	2,38
JO1G	Aminoglikozidi Aminoglycosides	0.01	0,01	0,01	0,01	0,01	0,01	0,01	0,00	0,05	0,01	0,00
JO1MA	Fluorokinoloni Fluoroquinolones	1.56	1,41	1,41	1,33	1,31	1,32	1,55	1,47	1,50	1,50	1,49
JO1XE	Nitrofurantoin		0,47	0,63	0,68	0,69	0,60	0,72	0,72	0,79	0,83	0,87
UKUPNO TOTAL		**20,81**	**22,92**	**22,60**	**20,95**	**20,22**	**19,16**	**21,72**	**21,10**	**21,40**	**21,84**	**20,73**

∗ Izvor podataka Hrvatski zavod za zdravstveno osiguranje / sourse of data Croatian Health Insurance Fund
Popis stanovništva 2011/ The Croatian Bureau of Statistics, Census 2011

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

ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2006	2007	2008	2009	2010	2011	2012 *	2013 *	2014 *	2015 *	2016 *
JO1AA	Tetraciklini Tetracylines	0.07	0,06	0,06	0,06	0,05	0,07	0,06	0,05	0,04	0,04	0,04
JO1CA	Penicilini ğrokog spektra Broad spectrum penicillins	0.12	0,09	0,08	0,05	0,04	0,06	0,06	0,09	0,04	0,05	0,06
JO1CE	Penicilini uskog spektra Narrow spectrum penicillins	0.12	0,10	0,06	0,01	0,01	0,04	0,03	0,03	0,02	0,02	0,02
JO1CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0.03	0,04	0,02	0,00	0,00	0,03	0,04	0,03	0,03	0,03	0,03
JO1CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	0.27	0,22	0,25	0,23	0,22	0,51	0,52	0,45	0,48	0,49	0,49
JO1DB	Cefalosporini I gen. cephalosporins	0.10	0,11	0,09	0,10	0,09	0,11	0,10	0,08	0,09	0,10	0,10
J01DC	Cefalosporini II gen. cephalosporins	0.22	0,22	0,19	0,15	0,21	0,23	0,23	0,21	0,20	0,20	0,19
J01DD	Cefalosporini III + IV gen. cephalosporins	0.11	0,13	0,14	0,16	0,16	0,16	0,15	0,16	0,19	0,20	0,17
JO1DH	Carbapenems	0.02	0,04	0,04	0,04	0,04	0,07	0,07	0,06	0,07	0,08	0,08
JO1EE	Sulfonamides + trimethoprim	0.07	0,07	0,06	0,06	0,05	0,05	0,06	0,04	0,05	0,04	0,04
JO1F	Macrolides, lincosamides	0.10	0,11	0,11	0,12	0,11	0,15	0,16	0,15	0,14	0,15	0,15
JO1G	Aminoglikozidi Aminoglycosides	0.10	0,09	0,10	0,10	0,09	0,12	0,11	0,10	0,11	0,10	0,09
JO1MA	Fluorokinoloni Fluoroquinolones	0.17	0,19	0,19	0,21	0,21	0,23	0,22	0,22	0,23	0,24	0,25
JO1XA	Glycopeptides	0.02	0,03	0,03	0,03	0,03	0,04	0,03	0,03	0,03	0,04	0,03
JO1XD	Metronidazole	0.05	0,06	0,06	0,07	0,07	0,07	0,07	0,08	0,09	0,10	0,10
JO1XE	Nitrofurantoin		0,01	0,01	0,01	0,01	0,01	0,02	0,01	0,02	0,01	0,01
UKUPNO TOTAL		**1.57**	**1,57**	**1,49**	**1,40**	**1,39**	**1,96**	**1,98**	**1,80**	**1,87**	**1,91**	**1,88**

∗ Popis stanovniğtva 2011/ The Croatian Bureau of Statistics, Census 2011

Potrošnja antibiotika u hrvatskim bolnicama

Od 2001. godine, od kada se prati potrošnja antibiotika u Hrvatskoj, prati se odvojeno bolničko i ambulantna potrošnja. Do 2009. godine za bolničku potrošnju antibiotika su korišteni podaci samo od veledrogerija, dok se od 2010. godine podaci prikupljaju od bolničkih ljekarni i putem veledrogerija, tako da se zadnjih šest godina kontinuirano prati potrošnja iz dva izvora.

Uz podatke o potrošnji antibiotika, bolnice dostavljaju neophodno potrebne administrativne podatke, o broju bolničkih dana, broju primitaka pacijenata te broju bolničkih kreveta. Podaci se prikupljaju za ličitavu bolnicu i odvojeno za JIL-ove, prema vrstama (mješoviti, kirurški, internistički, pedijatrijski, i dr.). Temeljem dobivenih podataka potrošnja antibiotika se može izraziti u definiranim dnevnim dozama (DDD) na 100 bolničkih koopskrbnih dana (DDD/100 BOD), što znatno povećava mogućnost detaljnijeg i preciznijeg praćenja potrošnje kako na nivou pojedinačne bolnice, tako i na nacionalnom nivou. Od 2011. godine u praćenje bolničke potrošnje uključena je i dnevna bolnica te broj terapijskih dana.

Bolnička potrošnja antibiotika u 2016. godini prikazana je na tablici 2, za što je korišten denominator prema popisu stanovništva iz 2011. godine. Na tablici 5 i slici 4 je prikazana usporedba bolničke potrošnje antibiotika prema podacima dobivenim od veledrogerija i podacima iz bolničkih ljekarni. Niti jedne godine ne postoji potpuna podudarnost, a za prošlu godinu razlika, ovisno o izvoru podataka, iznosi 0,16 DDD/TID u korist podataka dobivenih iz bolničkih ljekarni.

Kao i prethodne godine, i u 2016. godini podatke o bolničkoj potrošnji su poslale sve bolnice elektronskim putem na adresu iskra.antibiotici@gmail.com. Nakon zaprimanja podataka i njihove obrade, svakoj bolnici su elektronskim putem vraćeni podaci na kontrolu i provjeru te usporedbu s potrošnjom u prethodnim godinama. Svim bolnicama smo omogućili i potakli ih da dostave podatke o potrošnji elektronskim putem direktno iz LIS-a bolničkih ljekarni, što su u 2016. godini učinile četiri bolnice. Radi se o jednostavnom i sigurnom načinu dostave podataka s minimalnom mogućnošću pogreške tijekom daljnje obrade.

Bolnička potrošnja antibiotika u 2016. godini iznosi 1,88 DDD/TID (tablica 2), što je niža potrošnja u odnosu na prethodne dvije godine. Međutim, ako se bolnička potrošnja antibiotika izračuna na način da se kao denominator koriste bolnički koopskrbni dani (BOD), tada je potrošnja u 2016. godini u porast (tablica 6; slika 5). Nažalost, od 2013. godine se prati trend porasta bolničke potrošnje antibiotika (40,10; 41,00; 41,67; 42,59) prema podacima dobivenim iz bolničkih ljekarni uz korištenje podatka o bolničkoj koopskrbnim danima kao denimonatoru (DDD/100BOD). Takav način praćenja je precizniji i pouzdaniji u usporedbi s podacima o potrošnji antibiotika koji se izračunavaju prema broju stanovnika (DDD/TID).

Porast potrošnje se bilježi za klasu penicilna (J01C), klasu makrolid/linkozamid (J01F), klasu kinolona (J01M) i klasu ostali (J01X). Tri klase bilježe pad potrošnje: klasa tetraciklina (J01A), klasa cefalosporina (J01D) po prvi puta te klasa sulfonamida i trimetoprim (J01E). Klasa aminoglikozida (J01G) bilježi istu potrošnju kao i godinu prije, kada je zabilježena najniža potrošnja u razdoblju praćenja od 2010. godine (tablica 7, slika 6).

Potrošnja klase penicilina i klase cefalosporina zajedno čini preko 60% ukupne bolničke potrošnje antibiotika. Potrošnja klase penicilina je najveća, osobito kombinacije (J01CR). Potrošnja uskospektralnih penicilina je zadnje tri godine ista. Druga i treća generacija cefalosporina najzastupljenije su u potrošnji te klase antibiotika. Potrošnja karbapenema se u zadnje dvije godine ne mijenja. Skupina kinolona (J01M) je treća najzastupljenija klasa antibiotika koja u bolničkoj potrošnji pokazuje daljnji trend porasta. Uočljiv je porast potrošnje skupine ostali antibiotici (J01 X), u kojoj su zastupljeni glikopeptidi, imidazoli i polimiksin. (tablica 7, slika 6).

Podatke o potrošnji antibiotika dostavilo je 13 **kliničkih ustanova** (tablica 8). Raspon potrošnje se kretao od 27,0 do 143,2 DDD/100 BOD, ovisno o profilu klinička ustanove. Najniža i najviša potrošnja vrlo su slični prošlogodišnjim vrijednostima istih ustanova (25,2 DDD/BOD i 144,7DDD/BOD). Kod

6 klinič kih ustanova K 05, K 06, K 08, K 11, K 13, K 15 uoč ava se porast potrošnje. Za klinič ku ustanovu K 15, kontinuirano se bilježi trend porasta potrošnje, u zadnjoj godini č ak za 11,2 DDD/BOD, što je najviša potrošnja u desetogodišnjem periodu prać enja. Č etiri klinike bilježe pad potrošnje (K 01; K 02; K 03; K 07), dok se kod tri klinike ne uoč avaju razlike u potrošnji u zadnje dvije godine (K 04; K 09; K 14). Na slici 6 prikazani su trendovi u potrošnji antibiotika za svaku klinič ku ustanovu.

Najhomogeniju skupinu bolnica č ine **opće bolnice**, njih 21, koje se meĐusobno mogu usporeĐivati po potrošnji antibiotika. Potrošnja antibiotika u opć im bolnicama se kreć e u rasponu od 44,1 do 84,5 DDD/100 BOD, što odražava velike razlike u propisivanju antibiotika u ovoj skupini bolnica (tablica 9). Tri bolnice kreć u se u rasponu potrošnje izmeĐu 41-50 DDD/100 BOD (O 02; O 12; O 14). Opć im bolnicama O 01, O 04, O 11, O 17, O 22 potrošnja se kretala u rasponu od 51 ï 60 DDD/BOD. Najveć i broj opć ih bolnica potroši o je antibiotika izmeĐu 61 i 70 DDD/BOD (O 03; O 05; O 13; O 15; O 18; O 19; O 23; O 24). Č ak č etiri bolnice bilježe potrošnju iznad 71 DDD/100BOD (O 07; O 08; O 20; O 21), a jedna opć a bolnica iznad 80, odnosno 84,5 DDD/100BOD, što je gotovo dvostruko više od bolnice s najniš om potrošnjom (tablica 9, slika 8). Deset opć ih bolnica poveć alo je potrošnju antibiotika u 2016. godini. Posebno se izdvaja bolnica 7, koja izrazito oscilira u potrošnji, koja je u 2016. godini dvostruko porasla u odnosu na prethodnu godinu.

Potrošnja antibiotika u **psihijatrijskim bolnicama** kreć e se od 2,9 do 31,9 DDD/100 BOD (tablica 10). To je, do sada, najviša potrošnja antibiotika u psihijatrijskim ustanovama od kada se prati potrošnja. U 2016. godini u šest psihijatrijskih bolnica (P 01; P 04; P 06; P 07; P 09) uoč ava se porast potrošnje, dok je u č etiri bolnice u padu (P 02; P03; P05; P 08). Najveć i skok u potrošnji antibiotika bilježi psihijatrijska ustanova P 07 (slika 9).

Specijalne bolnice su podijeljene u dvije velike grupe s obzirom na njihov profil rada i kao takve bilježe veliki raspon u potrošnji antibiotika. U prvoj skupini nalazi se 10 bolnica, koje su namijenjene liječ enju (akutnom/kronič nom), dok je u drugoj skupini 14 ustanova namijenjeno rehabilitaciji. U prvoj skupini ustanova raspon potrošnje se kreć e od 8,6 do 61,5 DDD/100 BOD. U drugoj skupini kretanje potrošnje antibiotika je od 0,6 do 12,5 DDD/100 BOD (tablica 11, slika 10).

Koristeć i podatke o potrošnji antibiotika od bolnič kih ljekarni i izražavajuć i potrošnju na 100 bolnič koopskrbnih dana dobivamo precizne i pouzdane podatke. Nažalost, od 2013. godine se uoč ava porast bolnič ke potrošnje iz godine u u godinu. Neke bolnice su uspjele zaustaviti trend porasta i oč igledno uspješno kontroliraju potrošnju, dok se kod nekih uoč ava trend porasta. Najveć e razlike u potrošnji se uoč avaju u skupini opć ih bolnica, koje se mogu usporeĐivati, što govori u prilog još uvijek vrlo neracionalnog propisivanja antibiotika u nekim bolnicama.

Oč ita je potreba za implementiranjem rukovoĐenog nač ina propisivanja antibiotika u bolnicama (ñantibiotic stewardshipò), kako bi primjena antibiotika bila usklaĐena sa struč nim preporukama, stvarnim indikacijama/potrebama i koriš tena na pravilan nač in.

Antibiotic consumption in Croatian hospitals

Since 2001 antibiotic consumption in Croatian hospitals has been monitored separately from outpatient consumption. Until 2009 only wholesales data have been used for monitoring, but since 2010 all hospital pharmacies are also delivering information about antibiotic consumption, so in the last six years, antibiotic consumption is continuously monitored from two sources.

To express the antibiotic consumption, it is necessary to obtain the administrative data (number of bed days, number of admissions, number of hospital beds). Data are collected separately for the whole hospital and Intensive Care Units (mixed, surgical, intern, pediatric and otheré). The data on consumption can be expressed in defined daily doses (DDD) per 100 bed days, what is more reliable indicator, and enable more detailed and precisely surveillance of antibiotic consumption, not only for each hospital but also on the national level. Since 2011 the surveillance of hospital antibiotic consumption also includes collecting data for the day hospital and number of therapy days.

The overview of the hospital consumption is shown in Table 2. The data from Census 2011 have been used as the denominator. Table 5 and Figure 4 show parallel monitoring of antibiotic consumption from wholesales data and data from hospital pharmacies. In the last year there is a difference in consumption between these sources (0,16 DDD/TID). Results from hospital pharmacies are higher.

As well as the previous year, in 2016, all hospitals sent their data on antibiotic consumption electronically to iskra.antibiotici@gmail.com. After processing, each hospital received the processed data to check and compare with results in previous years. All hospitals had an opportunity for sending data directly from LIS program, and 4 hospitals sent us data on that way. That is a simple and secure way of delivering data and possible error during further processing is minimum.

The hospital consumption in 2016 amounted to 1,88 DDD/TID (Table 2), which is less than in a two previous years. The consumption in 2016 is higher then previous year if bed days are used as a denominator (Table 6, Figure 5). Unfortunately, since 2013, there is a negative trend of increasing hospital antibiotic consumption (40,10; 41,00; 41,67; 42,59) if we use the data from hospital pharmacies and defined daily doses per 100 bed days as a denominator. We can get more reliable and precise data if we use defined daily doses per 100 bed days as a denominator.

There was an increase in the consumption of penicillins (J01C), macrolide/lincosamides (J01F), quinolones (J01M) and other antibiotics (J01X).There was a decrease in the consumption of three classes of antibiotics: tetracyclins (J01A), cephalosporins (J01D) and, for the first time, sulphonamides trimethoprim (J01E). Consumption of aminoglycosides class is the same as in the previous year when was the lowest since 2010. (Table 7, Figure 6).

The consumption of penicillins and cephalosporins makes over 60% of total hospital antibiotic consumption. The consumption of penicillins is the highest, especially combination (J01CR). Consumption of narrow-spectrum penicillins is equal in the last three years. The consumption of the second and the third generation of cephalosporins is the highest in that class of antibiotics. There was an increase in the consumption of carbapenems. The class of quinolones (J01M) is the third most common class of antibiotic, with increase in consumption in the last few years. There was an increase in the consumption in other antibiotics (J01X) (glycopeptides, imidazole and polymyxn) (Table 7, Figure 6).

The data on antibiotic consumption was submitted by 13 clinical institutions (Table 8). Their consumption ranged between 27,0 and 143,2 DDD/100 BD. The differences in consumption reflect different hospital institution profiles. The lowest and the highest leap in consumption are similar as in the last year in the same hospitals (25,2 and 144,7 DDD/100 BD). In six clinics (K 05; K 06; K 08; K 11; K 13; K 15) there has been an increase in antibiotic consumption. In one clinic (K 15), there is a positive trend of increasing consumption in the last few years. Last year an increase was 11,2 DDD/100 BD, and that is the highest rate of consumption in the last ten years. In four clinics there is a decrease in

consumption (K 01; K 02; K 03; K 07). In three clinics there is no difference in consumption in the last two years (K 04; K 09; K 14). Figure 7 shows the consumption for each clinical institution.

The group consisting of 21 general hospitals is the most homogeneous group, so the data about antibiotic consumption can be easily compared. Antibiotic consumption in general hospitals ranges between 44,1 and 84,5 DDD/100 BD, which reflects quite different approaches in antibiotic prescribing (Table 9). There are three hospitals with consumption range between 41-50 DDD/100 BD (O 02; O 12; O 14). Hospitals O 01; O 04; O 11; O 17; O 22 have consumption range between 51-60 DDD/100 BD. The most number of general hospitals have consumption between 61 and 70 DDD/100 BD (O 03; O 05; O 13; O 15; O 18; O 19; O 23; O 24). Even four hospitals have consumption range more than 71 DDD/100 BD (O 07; O 08; O 20; O 21), while only one hospital has consumption range more than 80 (84,5 DDD/100 BD), which is almost twice as much as in the hospital with the lowest consumption in this hospital group. (Table 9, Figure 8). In ten general hospitals there is an increase in antibiotic consumption in 2016. Only hospital O 07 has a lot oscillations in consumption. In 2016, consumption is almost twice as much as in the last year.

Antibiotic consumption in psychiatric hospitals ranges between 2,9 and 31,9 DDD/100 BD (Table 10). We registered the highest increase in consumption since surveillance started. In 2016, five psychiatric hospitals registered an increase in consumption (P 01; P 04; P 06; P 07; P 09), while four hospitals registered a decrease trend in consumption (P 02; P 03; P 05; P 08). Hospital P 07 has the highest positive trend of increasing antibiotic consumption.

Special hospitals are divided into two large groups with regard to their working profile, and they are characterised by wide range of antibiotic consumption. In the first group there are 10 hospitals which are intended for treatment (acute/chronic), while in other there are 14 institutions intendend for rehabilitation. The first group has the consumption range between 8,6 and 61,5 DDD/100 BD. In the other group, the range is between 0,6 and 12,5 DDD/100 BD (Table 11, Figure 10).

We can get more reliable and precise data about antibiotic consumption if we use the data from hospital pharmacies and express them in defined daily doses per 100 bed days.

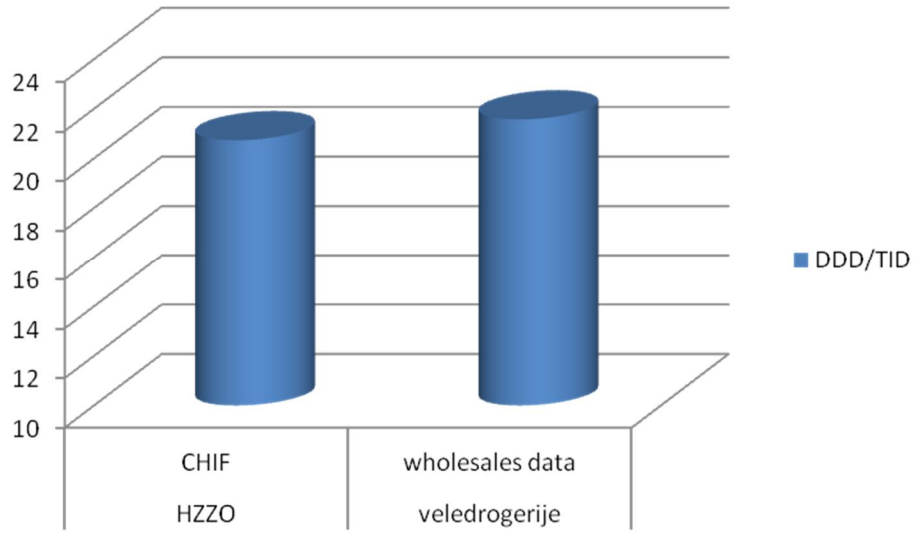
Unfortunately, since 2013, there is an increase trend in hospital antibiotic consumption. Some hospitals have a positive trend of decreasing antibiotic consumption, but some of them have a trend of increasing antibiotic consumption. The biggest difference in consumption is in the group of general hospitals, which are similar so we can compare them. That clearly points to improper use of antibiotics in some of these hospitals.

Responsible practice of prescribing antibiotics and antibiotic stewardship need to be implemented in all hospitals so antibiotic use can be in accordance with guidelines and actual indications.

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

	HZZO CHIF	veledrogerije wholesales data
DDD	32422817,86	33737591,65
DDD/TID	20,73	21,57

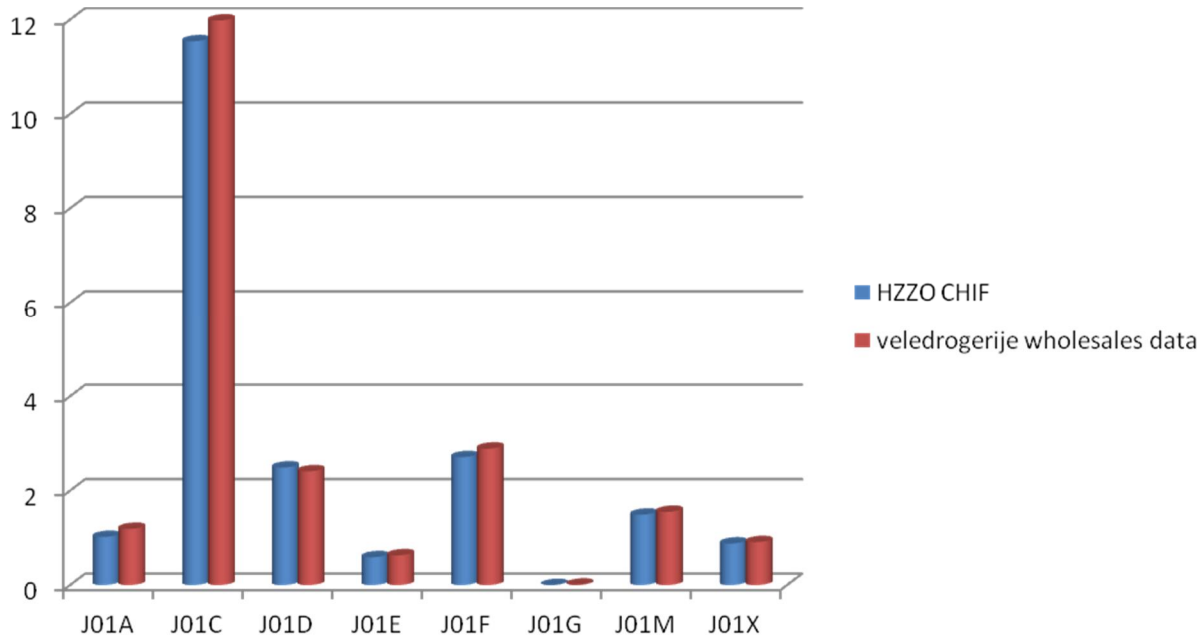
Slika 2. */ Figure 2.*
Ambulantna potrošnja antibiotika (DDD/TID) usporedba podataka HZZO i veledrogerija /
Ambulant antibiotic consumption (DDD/TID) comparison between CHIF data and wholesales dana



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

DDD/TID	HZZO CHIF	veledrogerije wholesales data
J01A	1,02	1,19
J01C	11,54	11,98
J01D	2,49	2,41
J01E	0,59	0,63
J01F	2,71	2,89
J01G	0,00	0,01
J01M	1,49	1,55
J01X	0,88	0,91

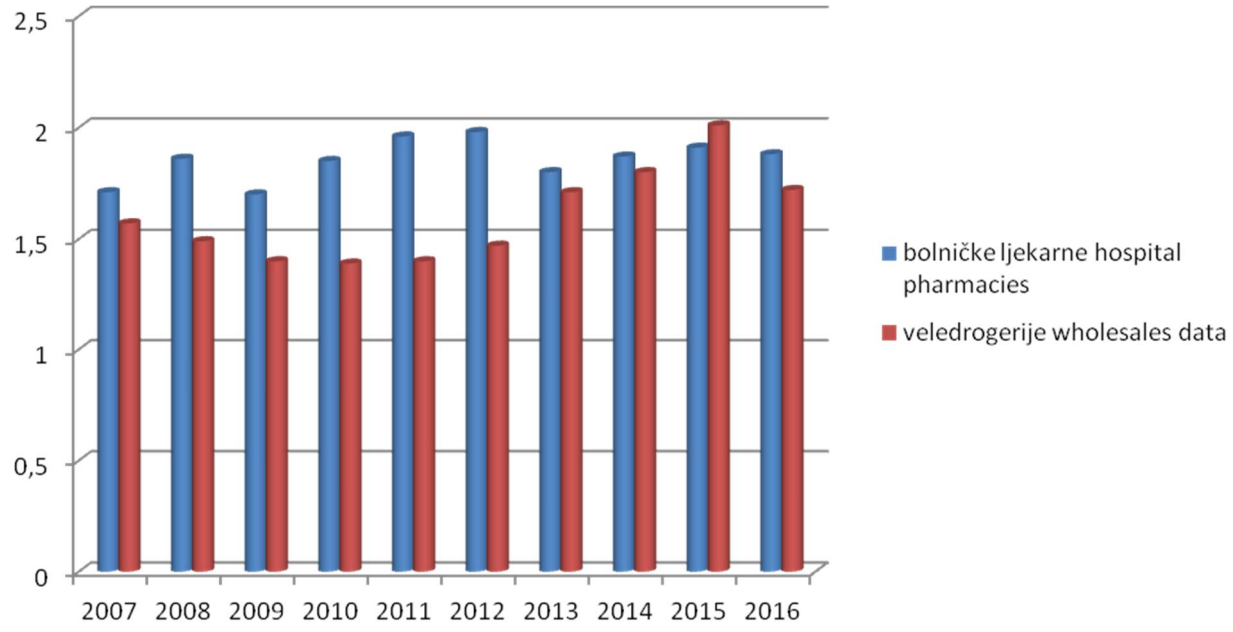
Slika 3. / *Figure 3.*
Ambulantna potrošnja antibiotika (DDD/TID) po klasama, usporedba podataka HZZO i veledrogerija /
Ambulant antibiotic consumption (DDD/TID) *by class, comparison between CHIF data and wholesales data*



Tablica 5. / *Table 5.*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija / *Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales dana*

godina year	bolniļke ljekarne hospital pharmacies	veledrogerije wholesales data
2007	1,71	1,57
2008	1,86	1,49
2009	1,70	1,40
2010	1,85	1,39
2011	1,96	1,40
2012	1,98	1,47
2013	1,80	1,71
2014	1,87	1,80
2015	1,91	2,01
2016	1,88	1,72

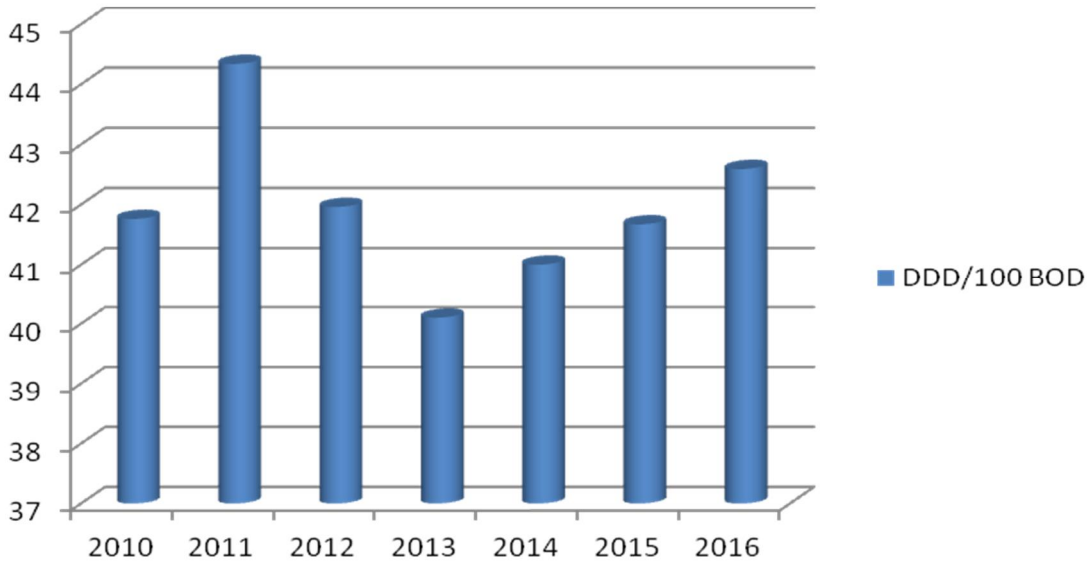
Slika 4. / *Figure 4.*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija /
Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales dana



Tablica 6. */ Table 6.*
Bolnička potrošnja antibiotika (DDD/100 BOD) /
Hospital antibiotic consumption (DDD/100 BD)

Godina / *year*	DDD/100 BOD / *DDD/100 BD*
2010	41,76
2011	44,34
2012	41,96
2013	40,10
2014	41,00
2015	41,67
2016	42,59

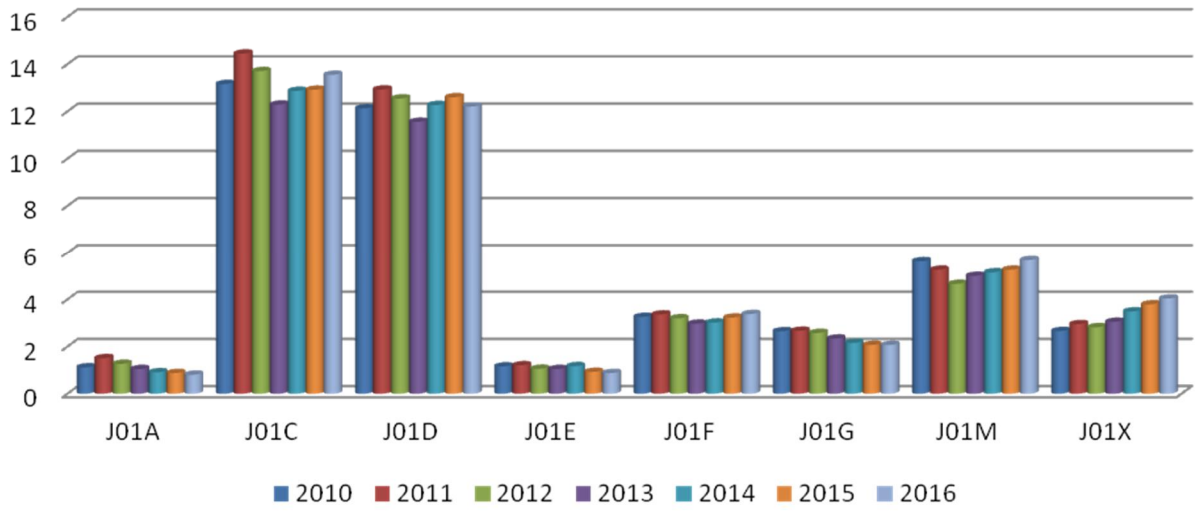
Slika 5. */ Figure 5.*
Bolnička potrošnja antibiotika (DDD/100BOD) /
Hospital antibiotic consumption (DDD/100 BD)



Tablica 7. */ Table 7.*
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*						
	2010	2011	2012	2013	2014	2015	2016
J01A	1,12	1,51	1,27	1,05	0,91	0,88	0,81
J01C	13,16	14,45	13,71	12,29	12,87	12,92	13,55
J01D	12,13	12,93	12,55	11,56	12,27	12,6	12,21
J01E	1,16	1,21	1,06	1,05	1,17	0,93	0,88
J01F	3,26	3,36	3,2	2,97	3,02	3,23	3,38
J01G	2,65	2,67	2,58	2,34	2,16	2,07	2,07
J01M	5,62	5,26	4,66	5,00	5,15	5,26	5,67
J01X	2,66	2,95	2,82	3,05	3,49	3,79	4,04

Slika 6. */ Figure 6.*
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

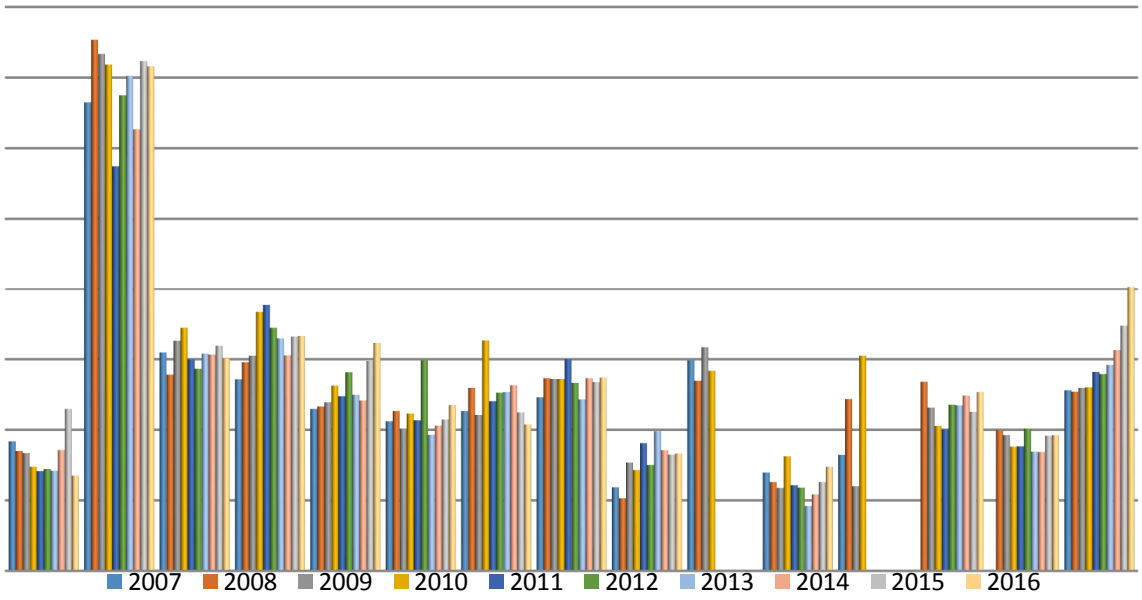


Tablica 8. */ Table 8.*
KLINIČKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2016. /
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2016

	DDD/100 BOD, DDD/100BD								
USTANOVA INSTITUTION	UKUPNO TOTAL	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
K 01	27,0	0,1	7,1	9,6	0	4,0	3,8	0,5	1,9
K 02	143,2	2,3	53,7	46,2	3,1	11,9	3,0	8,0	15,0
K 03	60,2	0,2	16,7	16,0	2,0	4,0	2,5	11,1	7,6
K 04	66,6	1,0	23,5	16,1	1,6	4,2	1,7	11,4	7,1
K 05	64,6	1,5	21,1	16,0	1,0	4,5	3,8	9,8	6,9
K 06	47,0	0,4	7,5	21,1	1,3	3,1	2,6	4,4	6,6
K 07	41,5	0,6	8,9	13,1	1,1	4,4	2,4	6,3	4,7
K 08	54,8	1,6	13,5	18,2	1,3	2,4	1,5	9,3	7,0
K 09	33,3	0,0	10,6	12,1	0,3	0,4	0,4	8,4	1,0
K 10*									
K 11	29,5	1,8	6,5	13,4	0,4	1,6	1,4	1,0	3,5
K 12*									
K 13	50,7	0,2	18,1	13,1	2,9	5,1	2,2	3,0	6,0
K 14	38,5	0,2	12,0	15,9	1,0	3,2	2,0	1,2	3,1
K 15	80,7	0,5	38,8	15,5	0,0	5,5	2,2	12,3	5,8

* bolnice koje su uģle u sastav drugih klinič kih ustanova / these hospitals merged in other clinical hospitals

Slika 7 / *Figure 7.*
KLINIČKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2007.-2016. /
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2007-2016

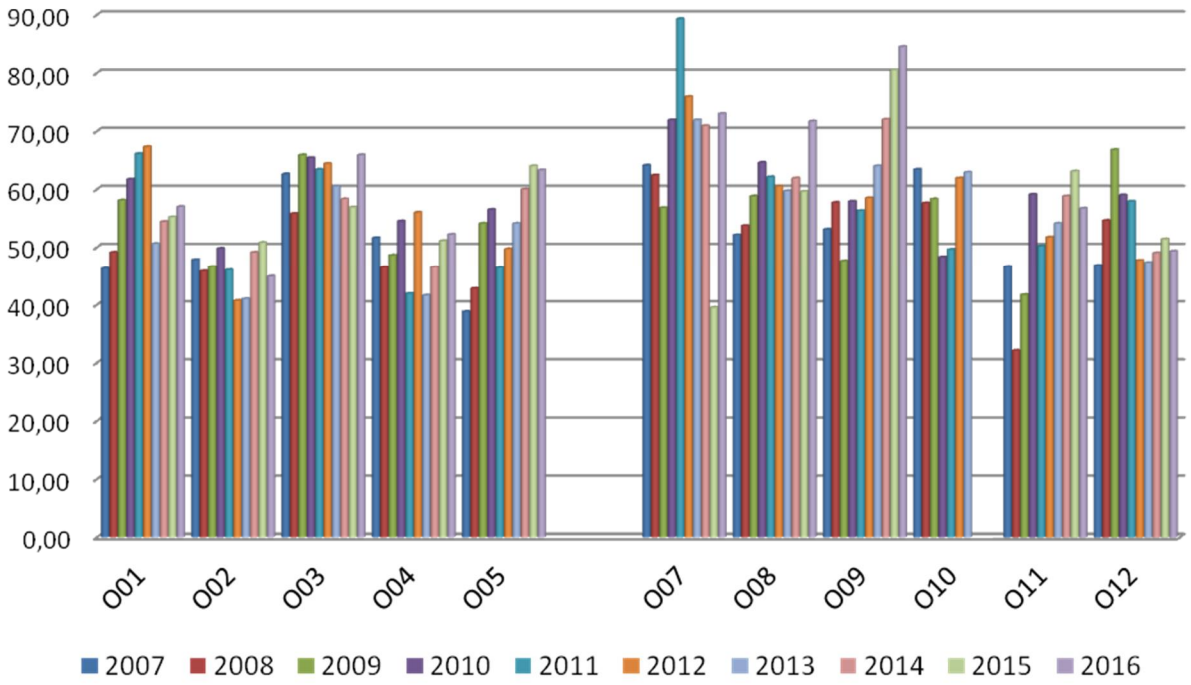


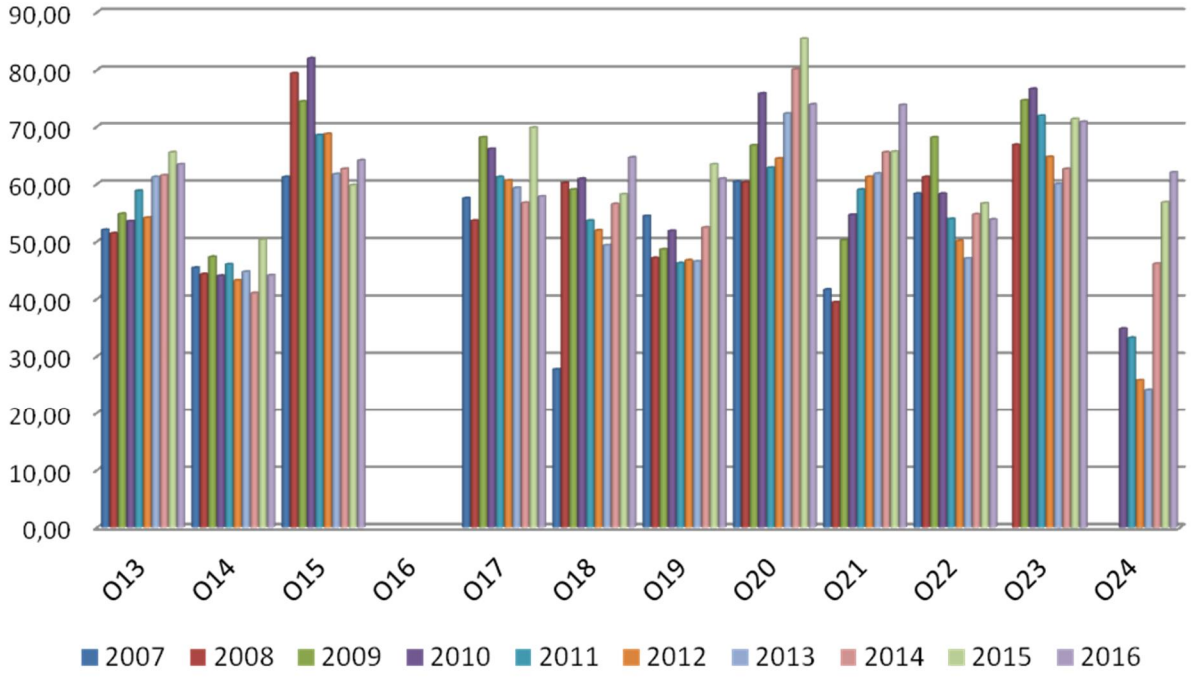
Tablica 9. */ Table 9.*
OPĆE BOLNICE - POTROŠNJA ANTIBIOTIKA 2016. /
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2016

USTANOVA INSTITUTION	UKUPNO TOTAL	DDD/100 BOD, DDD/100 BD							
		JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
O 01	57,0	2,5	20,3	15,6	0,7	4,9	4,0	3,7	5,3
O 02	44,9	0,5	22,0	11,3	0,4	2,4	1,9	3,0	3,5
O 03	65,9	4,6	16,3	20,9	1,0	9,6	2,8	5,8	5,1
O 04	52,2	1,9	10,0	10,4	0,5	6,7	6,4	11,6	4,6
O 05	63,3	3,3	22,5	13,7	0,7	6,4	5,0	6,3	5,5
O 06*									
O 07	73,0	0,7	19,9	25,2	1,2	7,8	7,3	7,8	3,1
O 08	71,7	1,3	25,3	17,9	1,6	4,9	2,9	9,0	8,8
O 09	84,5	1,6	25,8	30,9	0,9	6,8	5,3	7,7	5,4
O 10									
O 11	56,7	0,9	15,7	20,9	0,6	2,6	2,5	8,3	5,3
O 12	49,3	1,6	16,3	13,3	0,8	4,6	1,4	8,0	3,4
O 13	63,4	0,6	21,5	24,3	0,9	5,3	1,8	4,5	4,4
O 14	44,1	1,0	15,1	12,4	0,7	3,7	2,5	4,5	4,1
O 15	64,1	2,2	24,7	17,9	0,4	3,2	5,8	2,9	7,0
O 16**									
O 17	57,8	0,4	18,4	18,1	0,5	6,2	2,7	5,2	6,2
O 18	64,6	1,4	27,1	15,8	0,3	3,1	1,7	10,6	4,8
O 19	60,9	0,2	23,2	13,2	0,5	5,1	3,9	10,1	4,8
O 20	74,0	2,7	17,3	28,8	0,4	4,3	2,8	13,7	4,0
O 21	73,9	0,6	25,5	15,9	1,0	7,8	5,1	10,2	7,9
O 22	53,8	0,5	15,3	13,2	0,6	3,2	3,7	14,1	3,1
O 23	70,8	1,1	28,7	15,0	0,7	8,8	5,7	5,6	5,4
O 24	62,0	1,0	25,8	10,6	3,0	3,2	2,1	12,2	4,1

*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 8. */ Figure 8.*
OPĆE BOLNICE - POTROŠNJA ANTIBIOTIKA 2007.-2016. /
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION 2007-2016

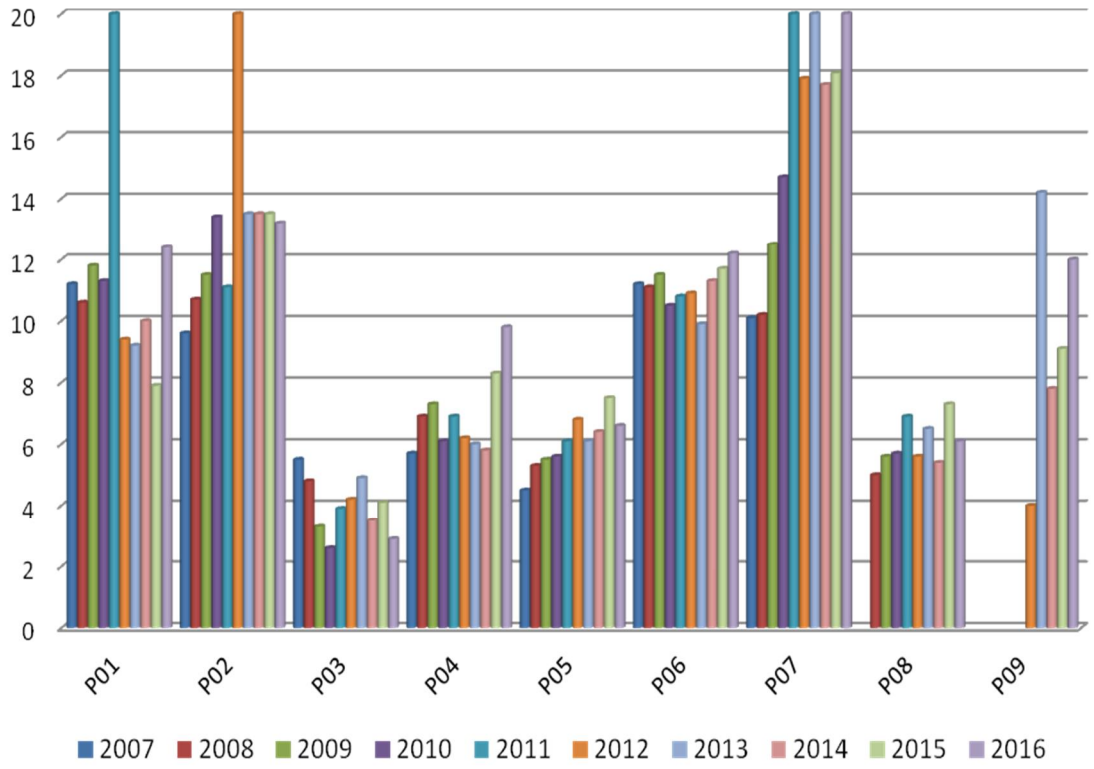




Tablica 10. */ Table 10*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2016. /
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION IN 2016

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100BD								
	UKUPNO / TOTAL	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
P 01	12,4	0,2	6,8	1,7	0,9	1,0	0,2	1,0	0,6
P 02	13,2	0,2	6,3	2,0	0,5	1,2	0,1	2,5	0,5
P 03	2,9	0	2,4	0,3	0	0,2	0	0	0,1
P 04	9,8	0,6	3,7	1,6	0,1	1,7	0	1,7	0,2
P 05	6,6	0,1	4,7	0,5	0,1	0,4	0	0,9	0,1
P 06	12,2	0,1	6,3	1,5	0,2	1,1	0,1	2,4	0,5
P 07	31,9	0	7,8	8,6	0,8	0,4	3,5	2,1	8,7
P 08	6,1	0,3	3,4	1,0	0,2	0,2	0	0,2	0,7
P 09	12,0	0,4	4,7	2,6	0,2	0,8	0,9	0,9	1,6

Slika 9. / *Figure 9.*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2007.-2016. /
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION 2007-2016



Tablica 11. */ Table 11.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2016. /
SPECIALISED HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2016

	DDD/100 BOD, DDD/100 BD								
USTANOVA IINSTITUTION	UKUPNO TOTAL	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
S 01	61,5	1,4	14,9	8,6	3,4	8,6	7,0	13,3	4,3
S 02	45,4	0,3	16,1	12,2	0,3	14,8	0,9	0,6	0,2
S 03	48,6	0,4	18,3	6,8	1,5	6,6	3,8	9,5	1,7
S 04	26,4	0,1	13,1	2,7	2,1	1,2	1,8	3,7	1,6
S 13	19,9	2,3	3,1	5,9	2,2	0,3	1,2	2,4	2,5
S 18	34,5	0,9	18,2	9,4	0,5	1,3	0,2	3,4	0,7
S 19	20,1	0	3,5	7,0	4,4	0,9	0,4	3,1	0,7
S 20									
S 21	43,7	0	19,7	11,3	0,1	1,8	0,4	7,4	3,0
S 22	8,6	0,2	1,7	4,8	0	0,5	1,3	0	0
S 23	45,4	0	0,9	42,4	0	1,5	0	0,2	0,4
S 05	9,0	0,1	4,6	1,3	0,4	0,7	0,5	0,9	0,5
S 06	5,2	0	1,9	0,7	0,3	0,1	0	2,0	0
S 07	12,5	0	3,8	2,8	0,5	0,9	0,3	3,3	0,9
S 08	3,2	0,1	2,0	0,3	0,2	0,2	0	0,5	0
S 09	1,3	0	0,6	0	0	0,2	0,1	0,2	0,1
S10	2,8	0,3	0,7	0,4	0,4	0,1	0	0,6	0,2
S11	9,2	0,1	4,7	1,1	0,6	1,0	0,1	0,9	0,6
S12	3,6	0,5	2,0	0	0,1	0,6	0	0,3	0
S14	5,3	0	1,2	2,5	0,3	0,6	0	0,7	0
S15	1,2	0	0,5	0,5	0	0,1	0	0,2	0
S16	4,9	0,5	2,1	0,5	0	0,4	0	0,6	0,7
S17	0,6	0	0,4	0,1	0	0	0	0	0,1
S24	1,3	0	0,3	0	0,2	0,1	0	0,4	0,3
S25	2,9	0	2,0	0,4	0	0,5	0	0	0

Slika 10. / *Figure 10.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2007.-2016. /
SPECIALISED HOSPITALS – ANTIBIOTIC CONSUMPTION 2007-2016

ATK KLASIFIKACIJA ANTIBIOTIKA:
ATC CLASSIFICATION OF ANTIBIOTICS

J01A ï TETRACIKLINI / *TETRACYCLINES*

J01B ï AMFENIKOLI / *AMPHENICOLS*

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

J01D ï ß LAKTAMI ï CEFALOSPORINI / *ß LACTAM-CEPHALOSPORINS*

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

J01G ï AMINOGLIKOZIDI / *AMINOGLYCOSIDES*

J01M ï KINOLONI /*QUINOLONES*
J01X ï OSTALI (GLIKOPEPTIDI, POLIMIKSIN, METRONIDAZOL, NITROFURANTOIN) / *OTHERS (GLYCOPEPTIDES, POLYMYXIN, METRONIDASOLE, NITROFURANTOIN*

POGLAVLJE / CHAPTER 6.

ZNAČAJKE MRSA IZOLATA U HRVATSKOJ U 2014. GODINI

CHARACTERISTICS OF CROATIAN MRSA ISOLATES IN 2014

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Značajke MRSA izolata u Hrvatskoj u 2014. godini

Staphylococcus aureus rezistentan na meticilin (MRSA)još uvijek predstavlja vrlo znaajnu prijetnju u obliku multirezistentne bakterije, koja je pristuna globalno, a u veći ini slučajeva izaziva infekcije povezane sa zdravstvenom skrbi.

MRSA može izazvati široki spektar infekcija u svakom organskom sustavu ljudskog tijela. Također je poznato i njegovo širenje u zajednicu, prepoznavši ga kao patogena u osoba koje nisu imale nikakve tipične rizične čimbenike za MRSA kolonizaciju/infekciju.

Jedno od područja u kojima se MRSA udomaćio su i farme za uzgoj životinja za preradu mesa, osobito farme svinja, kojim putem dalje dospijeva u industriju hrane, a MRSA koja se povezuje sa stočnim uzgojem naziva se LA (engl. Livestock associated) MRSA.

Klinički bolnički centar Zagreb, Klinički zavod za kliničku i molekularnu mikrobiologiju, koordinirao je MRSA studiju s ciljem prikupljanja izolata iz Hrvatske, analizirajući genetske profile, kao i osjetljivost na antimikrobne lijekove prikupljenih izolata. ,

Cilj ove studije je bio prikupljanje MRSA izolata iz raznih, reprezentativnih dijelova prevalenciju izvanbolničkih MRSA, kao i njihove fenotipske i genotipske karakteristike.

Stotinu i šezdeset sedam izolata je zaprimljeno u KMM KBC-a, izolata prikupljenih u razdoblju od 1.11. do 31.12. 2014. godine.

Uzorci iz kojih su sojevi izolirani potječu iz različitih sustava: 57-iz respiratornog sustava (trahealni aspirat, bronhoalveolarni lavat, nos, šrijelo..), 60 uzoraka iz rana, 6 hemokultura, i 39 ostalih, među kojima 16 iz uzoraka urina.

Popis laboratorija i broja izolata koje su dostavili u KMM, KBC Zagreb

Laboratorij u HR	Broj dostavljenih MRSA izolata
ZAGREB-SVETI DUH	38
ZAGREB-KBC ZAGREB	20
ZAGREB-KB DUBRAVA	16
ZAGREB -ZZJZ ANDRIJA ŠTAMPAR	3
SISAK	12
OSIJEK	10
DUBROVNIK	10
PULA	8
ČAKOVEC	6
GOSPIĆ	3
SPLIT	4
ZABOK	2
VINKOVCI	2
VARAŽDIN	15
KIB F. MIHALJEVIĆ ZAGREB	7
KB MERKUR ZAGREB	6

Identifikacija izolata kao SA je potvrđena korištenjem MALDI Tof MS uređaja tvrtke Bruker Daltonics, i analizom je nađeno da su 2 od 167 dostavljenih izolata pogrešno identificirana te su izbačeni iz daljnje analize.

Testiranje osjetljivosti na antimikrobne lijekove provedeno je preme EUCAST standardima, testiranje je provedeno na sljedeće antibiotike: penicilin, cefoksitin, klindamicin, eritrocimin,gentamicin, amikacin, ciprofloksacin, ko-trimoksazol, tetraciklin, rifampicin, linezolid, mupirocin i vankomicin. Testiranje na ceftarolin je provedeno određivanjem minimalne inhibitorne koncentracije putem E-testa. Nakon utvrđivanja osjetljivosti na cefoksitin, daljnja 3 izolata su odbačena zbog osjetljivosti na cefoksitin a provedeno je molekularno testiranje prisutnosti mecA gena, koji je bio negativan u ta 3 izolata.

Osim fenotipkih i metoda masene spektrometrije, provedena je i molekuarna tipizacija izolata : SCCmec tipizacija, prema ranijim publikacijama, kao i detekcija Pantone Valentine toksina (PVL).

Tipizacija temeljem sekvencioniranja-Spa tipizacija provedena je korištenjem SeqNet protokola i Ridom StaphType softvera.

Rezultati:
Testiranje osjetljivosti na antimikrobne lijekove: svi sojevi osjetljivi su na linezolid, vankomicin, i teikoplanin, a MIK-ovi ceftarolina varirali su od 0,125 mg/L do 1 mg/L za sve osim jedan izolat koji je pokazivato MIK ceftarolina od 2mg/L (0,61% rezistencije na ceftarolin).
MeĽu testiranim sojevima, samo 3 izolata bila su rezistentna na ko-trimoksazol (1,85% rezistencija na ko-trimoksazol).
Rezistencija na ciprofloksacin zabilježena je u 87,4 % izolata.
Profili rezistencije za 12 izolata ukazivali su na tipiļne izvanbolniļke MRSA. Nisu bili multirezistentni, osjetljivi, dakle, na sve testirane antibiotike, osim cefoksitina, pa i eritromicin i klindamicin. Od nih 12 ļak 7 ih je bilo osjetljivo i na ciprofloksacin.
Ne-multirezistentni MRSA sojevi su tipizirani kao SCCmec IV i V, predominantno spa t008, te t005, t1139, t011 i t355.
PVL-pozitivnima je okarakterizirano 5 izolata od njih 12 ne-multirezistentnih, a PVL-pozitivni izolati su imali spa tip t008 , osim jednoga koji je bio t355.
AnalizirajuĺI demografske karakteristike, srednja dob bolesnika kod kojih je izolira ñbolniļ kih ñ MRSA je bila 63,73 godine, dok je u izvanbolniļ koj skupini srednja vrijednost 35,66 godina, ģto je, zapravo, I oļ ekivano.
38% pacijenata iz studije ģivjelo je u vlastitom domu, a njih 22,2% je smjeģteno u neku od ustanova za umirovljene ili za dugotrajnu skrb. ObraĽujuĺI podatke o faktorima rizika z astejcanje MRSA, kod 9 bolesnika, osim onih koji su bili hospitalizirani, netko od obitelji radio je u zdravstvenom sustavu. Za 53 bolesnika nismo imali podatke u prethodno uporabi antibiotika, dok je njih 60,7% od ukupnog broja bolesnika u studiji upotrebljavalo antibiotike u godini koja je prethodila MRSA izolataciji.
Osim razlike u godinama, nije zamijeĺena druga bitna razlika u skupinama HA MRSA bolesnika u odnosu na CA MRSA, jednaki je postotak hospitaliziranih I ambulantnih pacijentat. TakoĽer, zamijeĺeni su sliļni riziļni ļimbenici u ove dvije skupine. U jedne osobe je zabilježena dodatna povezanost s bolniļkim sustavom. Epidemiološki podaci dobiveni su iz iscrpnog upitnika koji je uglavnom bio samo djelomiļno popunjen.
Prevalencija CA-MRSA, temeljem ovih kombiniranih genotipskih i fenotipskih, s epidemiološkim kriterijima, je 7,4% u 2014. godini, ģto je znaļajno više u usporedbi s 2004. godinom, kad smo imali 1,61% CA MRSA u Hrvatskoj, ukazujuĺI na ļinjenicu da je moguĺe da je došlo ido transera CA MRSA iz zajednice u bolniļku sredinu, u tipiļne skupine bolesnika koji su se uglavnom povezivali s HA MRSA. Dominantni SCCmec tipovi su tip II i I kao i SCC mec IV . Zabilježen je i SCCmec tip V, ali 10 % izolata nije moglo biti tipizirano korištenjem metodologije uveden u naģem laboratoriju.
Spa tipizacija

Spa tip	Podrijetlo izolata	Broj MRSA istog spa tipa
t003	Zagreb, Sisak, GospiĺI , Pula	28
t014	Zagreb, Osijek, Ļ.akovec, Vinkovci, Sisak	24
t022	Zagreb, Sisak, Ļ.akovec	22
t041	Osijek, Zagreb	12
t001	Split, Dubrovnik, Zagreb	8
t005	Zagreb, Ļ.akovec, Sisak	6
t008	Zagreb, DUbrovnik	5

U zakljuļku: 2014. godine, prisutan je znaļajno veĺi broj CA MRSA, kao i znaļajna promjena u distribuciji MRSA spa tpova, u uspredbi s 2004. godinom, kad je dominantan bio tip t041, SCCmec I, a nakon njega , t001 i t003 koji je još uvijek brojļano snaģno zastupljen, kao i poveĺan broj spa tipova t008, tipiļno prisutnih u CA MRSA, koji posjeduju i vaģnu karakteristiku viruencije, PVL-toksin.

Characteristics of Croatian MRSA isolates in 2014

Methicillin-resistant Staphylococcus aureus is still one of the most important multi-resistant global pathogens, causing mainly hospital-acquired infections.

MRSA can cause wide spectrum of infections in literarilly every part of the human body. It is also known as a community-associated pathogen, isolated in patients which did not have typical risk factors for HA-MRSA.

One of the niches where MRSA spread is one in animal farms, food industry, especially pif farms, and MRSA connected to animals is so-called livestock-assocated (LA) MRSA.

University hospital centre Zagreb coordinated Croatian-wide MRSA study, investigating susceptibility profiles, and genotypic characteristics of collected strains. The aim of this study was to collect all different MRSA in Croatia and to establish the prevalence of Community-associated MRSA, based on phenotypic and genotypic features.

One hundered and sixty seven (167) isolates were received in laboratory of Department of clinical and molecular microbiology, University hospital center Zagreb, collected from 1st of November until 31st of December 2014.

57-respiratory samples: TA, BA, nose, throaté ,60-wound samples, 6 blood culture samples 39-other, among which 16 urine samples.

List of laboratories with number of isolates sent to UHC Micro lab

Laboratory in HR	Number of MRSA isolates
ZAGREB-SVETI DUH	38
ZAGREB-KBC ZAGREB	20
ZAGREB-KB DUBRAVA	16
ZAGREB -ZZJZ ANDRIJA ĠTAMPAR	3
SISAK	12
OSIJEK	10
DUBROVNIK	10
PULA	8
ĻAKOVEC	6
GOSPIĹ	3
SPLIT	4
ZABOK	2
VINKOVCI	2
VARAĢDIN	15
KIB F. MIHALJEVIĹ ZAGREB	7
KB MERKUR ZAGREB	6

Identification of strains was confirmed by MALDI-TOF showing that 2 out of 167 strains were not Staph. aureus.

Susceptibility testing was performed according to EUCAST standards: 3 strains showed susceptibility to cefoxitin, and were methicillin susceptible, mecA negative, were excluded from further analysis.

Susceptibility testing was performed to following antimicrobials: penicillin, cefoxitine, clindamycin, erithromycin, gentamicin, amikacin, ciprofloxacin, sulfamethoxazole-trimethoprim, tetracycline, rifampicin, linezolid, mupirocin, vancomycin, and ceftaroline.

SCCmec typing was performed as previously described, as well as PVL detection.

Spa typing was performed by using the SeqNet protocol and Ridom StaphType software.

Results:

All strains were susceptible to linezolid, vancomycin and teicoplanin, and MIC to ceftaroline varied from 0,125 to 1 mg/L, only one strain had MIC of 2 mg/L to ceftaroline (0,006% resistance to ceftaroline).

Among tested strains, only 3 isolates were resistant o trimethoprim -sulfamethoxazole (0,02% resistance rate).

Inducible clindamycin resistance was present in 27 strains, resistance to ciprofloxacin is 87,4 %.

Susceptibility profiles for 12 strains showed typical CA (community associated)-like pattern. These strains were not multi-resistant , resistant only to cefoxitin, and all were susceptible to clindamycin and erithromycin, 7 out of 12 were susceptible to ciprofloxacin as well.
Non-mulitresistant MRSA strains were typed as SCCmec IV, mainly, and SCCmec V, and predominant spa type was t008, followed by t005, t1139, t011 and t355. PVL-positivity was recorded in 5 out of 12 non-multiresistant strains, and all PVL-positive strains had spa type t008, except one, which was typed as t355.
Mean age value in typical Ămultiresistant groupñ was 63,73 years, where in CA group, this value was 35,66 years, as expected. 38% patients live in their own homes and 22,2% of patients from the study live in nursing homes. Regarding risk factors for MRSA, 9 patients had some from the family working in the health care system, for 53 patients there are no data on previous antibiotic use and 60,7% patients (were using atb in the year preceding isolation of MRSA.
Except for the difference in age, we did not observe any absence of ñtypicalò risk factors for CA MRSA, within epidemiological questionnaire. There were no MRSA ï positive patients observed living with pets, and only one person had a connection to healthcare system. The drawback of these conclusion is that we do not know many facts about MRSA-positive patients, since not all questions were answered in the questionnaire.
Prevalence of CA-MRSA, based on combined phenotypic and genotypic definition, is 7,4% in 2014, which is signifficanlty higher in comparison to 2004 (1,61%) in Croatia, indicating that even strains wiht genetic characteristics of CA MRSA can be found in hospitals and in typical HA-MRSA patient groups.
Prevalent SCCmec types amog the rest of MRSA are type II and I and SCC mec IV (typical for CA-MRSA). There also were some type V strains, but 10% of strains were not typeable by methods applied in our laboratory.

Spa typing

Spa type	City of origin	Number of isolates with same spa type
t003	Zagreb, Sisak, GospiĹ, Pula	28
t014	Zagreb, Osijek, Ļakovec, Vinkovci, Sisak	24
t022	Zagreb, Sisak, Ļakovec	22
t041	Osijek, Zagreb	12
t001	Split, Dubrovnik, Zagreb	8
t005	Zagreb, Ļakovec, Sisak	6
t008	Zagreb, DUbrovnik	5

Conclusion: in 2014, there is a signifficant shift in MRSA spa types, in comparison to year 2004, when the predominant type was t041, followed by t001, and we still have t03 present, together with the increased number of t008, typically presenting CA MRSA and harbouring PVL toxin genes.

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