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

KLINIKA ZA INFEKTIVNE BOLESTI "DR. 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

HRVATSKO DRUŠTVO ZA KLINIČKU MIKROBIOLOGIJU HRVATSKOG LIJEČNIČKOG ZBORA
CROATIAN SOCIETY FOR CLINICAL MICROBIOLOGY OF THE CROATIAN MEDICAL ASSOCIATION

Osjetljivost i rezistencija bakterija na antibiotike u Republici Hrvatskoj u 2017. g.

Izdavač
Akademija medicinskih znanosti Hrvatske

Antibiotic resistance in Croatia, 2017

Published by
The Croatian Academy of Medical Sciences

AUTORI / *AUTHORS*

Prof. prim. dr. sc. Arjana Tambić Andrağević, prim. dr. med. FESCMID
Prim. dr. sc. Tera Tambić, dr. med.
Vera Katalinić-Janković, prim. dr. med.
Dr. sc. Ljiljana Čamak, dr. med.
Dr. sc. Mihaela Obrovac, dr. med.
Prim. Marina Payerl Pal, dr. med.
Damjan Debelec, prvostupnik medicinsko laboratorijske dijagnostike
Prim. doc. dr. sc. Suzana Bukovski, dr. med.
Prim. dr. sc. Blaženka Hunjak, dr.med.
Prim. dr. sc. Andrea Babić-Erceg, dr.med.
Tatjana Unukić, prvostupnik medicinsko laboratorijske dijagnostike
Iva Butić, dr. med.
Silvija Čoprek, dr. med.
Irina Pristaš, dr. med.
Sandra Lucić, mag. MLD

UREDNICI / *EDITORS*

Prof. prim. dr. sc. Arjana Tambić Andrağević, dr. med.
Prim. dr. sc. Tera Tambić, dr. med.

Izdavač / *Publisher*

Akademija medicinskih znanosti Hrvatske
The Croatian Academy of Medical Sciences

Kompjutorska obrada teksta / *Computer typesetting*
Jasminka Blaha
Sandra Lucić, mag. MLD

Tisak / *Printed by*
INTERGRAF-BI

Zagreb, 2017

ISSN 1846-1654

Za izdavanje ove monografije zahvaljujemo na potpori Ministarstvu zdravstva Republike Hrvatske
We thank the Croatian Ministry of Health for supporting the publication of this monograph

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

Prof. prim. dr. sc. **Arjana Tambić Andrašević**, dr. med. (predsjednica / *president*)
Prim. dr. sc. **Tera Tambić**, dr. med. (poļasna predsjednica / *honorary president*)
Prim. **Marina Payerl Pal**, dr. med. (tajnica / *secretary*)
Dunja Skoko Poljak, dr. med. (predstavnik Ministarstva zdravstva / *Ministry of health delegate*)
Prof. dr. sc. **Maja Abram**, dr. med.
Saša Baranjec, dr. med.
Prim. dr. sc. **Danijela Bejuk**, dr. med.
Prim. mr. sc. **Ljiljana Betica Radić**, dr. med.
Maja Bogdan, dr.med.
Prof.dr.sc. **Ana Budimir**, dr.med.
Sabina Cviljević, dr.med.
Irena Franolić, dr. med.
Sonja Hejtmanek, dr. med.
Dr.sc. **Blaženka Hunjak,** dr.med.
Prim. dr. sc. **Ines Jajić**, dr. med.
Vlatka Janeš Poje, dr. med.
Doc.dr.sc. **Vanja Kaliterna,** dr.med.
Prim. **Vera Katalinić-Janković**, dr. med.
Iva Košćak, dr. med.
Sanja Krešić, dr. med.
Ivanka Lerotić, dr. med.
Prof. dr. sc. **Amarela Lukić-Grlić**, dr. med.
Mr. sc. **Vesna Mađarić**, dr. med.
Prof.dr.sc. **Ivana Mareković**, dr.med.
Tamara Marković, dr. med.
Mr. sc. **Biserka Matica**, dr. med.
Zdravko Matić, dr. med.
Mr. sc. **Ana Mlinarić Džepina**, dr. med.
Prof.dr.sc. **Emilija Mlinarić Missoni**, dr.med.
Snježana Nad, dr. med.
Khalil Nemer, dr. med**.**
Alma Raljević Baradić, dr. med**.**
Dr. sc. **Sanda Sardelić**, dr. med.
Ivan Stepinac, dr. med.
Marijana Stipetić, dr. med.
Mr. sc. **Edita Sušić**, dr. med.
Sandra Šestan Crnek, dr. med.
Prof. dr. sc. **Jasenka Šubić Škrlin**, dr. med.
Prim. dr. sc. **Tera Tambić**, dr. med.
Prof. dr. sc. **Brigita Tićac**, dr. med.
Prof.dr.sc. **Marija Tonkić**, dr.med.
Mr. sc. **Maja Tomić Paradžik**, dr. med.
Prof. dr. sc. **Vera Vlahović Palčevski**, dr. med.
Marina Vodnica Martucci, dr. med.
Prof. dr. sc. **Jasmina Vraneš**, dr. med.
Dr. sc. **Mirna Vranić-Ladavac**, dr. med.
Marijana Zadravec, dr.med.

SADRŽAJ / *TABLE OF CONTENTS*

PREDGOVOR:

Prema analizama Europskog centra za prevenciju i kontrolu bolesti (European Center for Disease Prevention and Control, ECDC) rezistencija bakterija na antibiotike ima pogibeljniji uļinak na zdravlje europskih graĽana negoli gripa, tuberkuloza i AIDS zajedno. Ipak, niti nakon 10 godina javne kampanje o podizanju svijesti o ovom problemu ģira javnost, a i dobar dio zdravstvenih djelatnika joģuvijek ne prepoznaje problem rezistencije i ne ģele se odreĺi komfora propisivanja ģirokospektralnih antibiotika u bilo kojoj indikaciji. Naģalost, bakterije ne ļekaju spori odgovor ljudske vrste veĺ se lako prilagoĽavaju okoliģu punom antibiotika i zadnjih godina pratimo uspješno ģirenje poglavito gram-negativnih bakterija otpornih na veĺinu antibiotika. Hrvatska raspolaģe podacima o rezistenciji na nacionalnoj i lokalnoj razini veĺ više od 20 godina, od kada je 1996. g. osnovan Odbor za praĺenje rezistencije bakterija na antibiotike pri Akademiji medicinskih znanosti Hrvatske. Mreģa mikrobioloģkih laboratorija okupljena unutar Odbora lako se priključ ila europskom projektu za praĺenje rezistencije u invazivnih izolata (European Antimicrobial Resistance Surveillance System, EARSS) na samom poļetku njegovog rada 1998.g., a kad je 2001.g. zapoļeo europski projekt za praĺenje potroģnje antibiotika (European Surveillance of Antimicrobial Consumption, ESAC), Odbor je potaknuo prikupljanje podataka o potroģnji antibiotika sukladno meĽunarodno priznatim ESAC standardima. Ovi projekti su 2010. i 2011. g. prerasli u kontinuirane programe ECDC-a u kojima Hrvatska kao zemlja ļlanica ima i ģelju i obvezu sudjelovati. U okviru Odbora osnovana je 2003.g. i hrvatska podruģnica internacionalne organizacije The Alliance for the Prudent Use of Antibiotics (APUA) ģto je daljnje produbilo meĽunarodnu izmjenu informacija. Od ranih 2000-tih Svjetska zdravstvena organizacija istiļe da problem rezistencije nadilazi pitanje struke i potiļe uključ ivanje vlada u rješģavanje tog problema na nacionalnoj i meĽunarodnoj razini. Ministarstvo zdravstva (MZ) RH je od samog poļetka rada Odbora imalo svog predstavnika u Odboru, a suradnja s MZ je produbljena 2003.g. osnivanjem Referentnog centra MZ za praĺenje rezistencije na antibiotike pri Klinici za infektivne bolesti „Dr. Fran Mihaljevića", koji je preuzeo tehniļku podrģku praĺenju rezistencije. MZ je osnivanjem Interdisciplinarne sekcije za kontrolu rezistencije na antibiotike (ISKRA) 2006.g. omoguĺilo daljnje jaļanje mreģe praĺenja rezistencije i potroģnje antibiotika, a rezultati praĺenja objavljeni u ovoj publikaciji su postali sluģbeni nacionalni podaci i sastavni dio nacionalnog programa za kontrolu ģirenja rezistencije, prvi put donesenog 2009.g. te revidiranog 2017.g. Standardizacija rada mikrobioloģkih laboratorija prepoznata je kao prioritet od samog poļetka rada Odbora i hrvatski laboratoriji su spremno prihvatili standarde europskog odbora The European Committee for Antimicrobial Sensitivity Testing (EUCAST) ļim su objavljeni. Kako bi se osiguralo redovito aģuriranje EUCAST standarada u svim hrvatskim laboratorijima, unutar Odbora osnovano je 2011.g. Povjerenstvo za metodologiju odreĽivanja osjetljivosti na antibiotike (hrvatski „National Antibiotic Committee, NAC"). Zahvaljujuĺi dobroj povezanosti mikrobioloģkih laboratorija u stanju smo pravovremeno uočavati i pojavu sojeva s novim mehanizmima rezistencije te dobro suraĽivati s timovima za kontrolu bolniļkih infekcija. Ipak, uz sve te pozitivne preduvijete, stope rezistencije, kao indikatori racionalnog propisivanja antibiotika i uspješne kontrole bolniļkih infekcija uglavnom ne pokazuju trend opadanja. Da bismo očuvali djelotvornost antibiotika potreban je kritiļniji pristup interpretaciji mikrobioloģkih nalaza i primjeni antibiotika. Nadamo se da ĺe se to ostvariti kroz formiranje timova za rukovoĽenje antimikrobnom terapijom, tzv. A-timova, koji ĺe pomagati liječ nicima drugih struka u dijagnostici i liječ nju infekcija kod bolesnika, danas sve ļeģće opteręenih brojnim ko-morbiditetima.

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

PREFACE

According to the European Center for Disease Prevention and Control (ECDC) estimates antimicrobial resistance (AMR) has more dangerous effect on human health than influenza, tuberculosis and AIDS together. And yet, not even after 10 years of public campaign on raising antibiotic resistance awarenes general public and large part of health care professionals still do not recognize AMR as one of the major issues worth renouncing convenineces that the use of broad spectrum antibiotics in any indication provide. Unfortunatelly, bacteria are not waiting for the slow response from the human side but are easily adapting to the enviroment full of antibiotics and we are recently witnessing successful spread of principally gram-negative bacteria resistant to almost all antibiotics. Croatia has data on national and regional AMR rates for the period of more than 20 years ever since 1996 when the Croatian Committee for Antibiotic Resistance Surveillance (CARS) was founded at the Croatian Academy of Medical Sciences. The Croatian CARS microbiology laboratory network readily joined the European Antimicrobial Resistance Surveillance System (EARSS) at the very beginning of its functioning in 1998. When the European Surveillance of Antimicrobial Consumption (ESAC) project started in 2001 the Croatian CARS initiated collection of antibiotic consumption data using standardized ESAC methodology. These projects evolved into continuous ECDC programs in 2010 and 2011 in which Croatia as an EU Member State was invited to take part. In 2003 the Croatian Chapter of The Alliance for the Prudent Use of Antibiotics (APUA) was established within the Croatian CARS to further promote international collaboration. Since the early 2000s the World Health Organization emphasize that the AMR problem exceeds the problem of one profession only and that governments should get strongly involved at solving this problem at national and international level. The Croatian Ministry of Health (MoH) has its representative in the CARS ever since this Committee was founded and collaboration with MoH was further enhanced in 2003 when the Reference Centre (RC) for Antibiotic Resistance Surveillance was established at the University Hospital for Infectious Diseases. The RC provides technical support for AMR surveillance activities. MoH also founded the Croatian Intersectoral Coordination Mechanism (ICM), the Interdisciplinary Section for Antimicrobial Resistance Control (ISKRA) in 2006 which strengthened the national AMR and antimicrobial consumption surveillance networks and results reported in this publication are official national data integrated in the national AMR control program which was first issued in 2009 and updated in 2017. Laboratory standardization was recognized as a priority since the beginning of the national surveillance network and Croatian laboratories readily adopted the European Committee for Antimicrobial Sensitivity Testing (EUCAST) standards the same year when they were first issued. To ensure compliance with updates of the EUCAST standards the National Antibiotic Committee (NAC) was founded within CARS in 2011. Thanks to the good collaboration among the microbiology laboratories we are able to timely note emergence of strains with novel resistance mechanisms and to collaborate well with the network of infection control teams. However, in spite of many good initiatives national AMR rates as the indicators of rational antimicrobial prescribing and effective infection control are generally not decreasing. To preserve the efficacy of antibiotics a more rational approach to antibiotic therapy and interpretation of microbiology findings is needed. We hope that this will be achieved through establishing antimicrobial stewardship teams, the A-teams, who will help physicians in rational diagnosing and treating of infections in patients who are increasingly burdened with multiple comorbidities.

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

POGLAVLJE / CHAPTER 1.

REZISTENCIJA BAKTERIJSKIH IZOLATA U 2017. GODINI

ANTIBIOTIC RESISTANCE IN 2017

Arjana Tambić Andrašević
Sandra Lucić
Klinika za infektivne bolesti "Dr. F. Mihaljević"
University Hospital for Infectious Diseases "Dr. F. Mihaljević"

Tera Tambić
Akademija medicinskih znanosti Hrvatske
Croatian Academy of Medical Sciences

UVOD

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. ănational antibiotic committeeò, NAC) je tijelo pri Odboru za praćenje rezistencije koje prati novosti u standardima European Committee for Antimicrobial Sensitivity Testing (EUCAST) i na zimskom sastanku Odbora donosi preporuke o standardima važećim za narednu godinu. Zahvaljujući redovitim sastancima Odbora i djelovanju nacionalnog povjerenstva za antibiotike postignut je visok stupanj standardizacije u međulaboratorijskom testiranju, a rezultati vanjske kontrole rada laboratorija ukazuju na visoku pouzdanost prijavljenih rezultata. Iako se u ovom poglavlju prikazuju agregirani nacionalni podaci, oni zapravo predstavljaju skup podataka koji se na lokalnoj razini obrađuju po izolatu uz veliku pažnju da se uključi samo jedan izolat po pacijentu te da se u razdoblju ispitivanja svi izolati testiraju na sve zadane antibiotike. Manjak ovakve organizacije praćenja je da na nacionalnoj razini, nije moguće analizirati podatke prema demografskim osobinama pacijenata, ali uključivanje velikog broja izolata iz različitih uzoraka omogućuje dosljedno praćenje stopa rezistencije i pravodobno otkrivanje sojeva s rijetkim mehanizmima rezistencije.

INTRODUCTION

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

MATERIJALI I METODE

Globalno praćenje rezistencije

U praćenje su uključeni svi izolati dogovorenih bakterijskih vrsta izolirani iz kliničkih materijala u razdoblju od 1.10. do 31.12.2017.g. Od 2016.g. u ispitivanje osjetljivosti 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 31.12.2017. Podatke za 2017.g. podnijelo je 37 centara (popis u legendi za tablice), što obuhvaća >90% populacije u Hrvatskoj.

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

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

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

c. u ispitivanom razdoblju s dogovorenom paletom antibiotika testiraju se svi izolati iz kliničkih materijala ili 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 2017.g. korišteni su za testiranje i interpretaciju nalaza standardi europskog odbora, European Committee for Antimicrobial Sensitivity Testing (EUCAST) standardi (Breakpoint Table 7.1 za bakterije i Antifungal Clinical Breakpoint Table 8.0 za *Candida* spp.). U testiranju osjetljivosti na antibiotike većina laboratorija koristi disk difuzijsku metodu, a određivanje minimalnih inhibitornih koncentracija (MIK) se koristi za određivanje osjetljivosti anaerobnih bakterija, osjetljivosti na penicilin i ampicilin kod pneumokoka smanjene osjetljivosti na penicilin, osjetljivosti stafilokoka na glikopeptide te pseudomonasa i acinetobaktera na kolistin. Preporuka Odbora je da se izolati *A. baumannii* i *P. aeruginosa* rezistentni na jedan, ali ne i oba karbapenema retestiraju određujući i MIK za imipenem i meropenem.

Minimalne inhibitorne koncentracije se određuju korištenjem gradijent testova (Etest, bioMérieux; MIC Test Strip, Liofilchem). Za određivanje MIK kolistina od 2017.g. usvojen

je naputak EUCAST-a da se koristi mikrodilucija u bujonu i tu svrhu NAC je osigurao dostupnost komercijalnih testova (MICRONAUT MIC-Strip, Merlin Diagnostika; MIKROLATEST MIC, Erba Lachema) na hrvatskom trġiġtu.

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

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.

Od 2016.g. su u praĺenje rezistencije uključ eni i klinič ki izolati gonokoka. Rezultati praĺenja 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 praĺenje rezistencije prikuplja i obraĽuje demografske podatke pacijenata, a u svrhu detaljnije analize invazivni izolati enterokoka, stafilokoka i *P. aeruginosa* ġalju 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. Mihaljeviĺ ò. RC za praĺenje rezistencije ġalje 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 poļetka praĺenja do 2017.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 potroġnju antibiotika izraġenu u definiranim dnevnim dozama na 1000 stanovnika dnevno (DDD/TID). Podaci o bolnič koj i izvanbolnič koj potroġnji antimikrobnih lijekova se takoĽer ġalju u Tessy sustav ECDC-a. Podaci o potroġnji antibiotika u Hrvatskoj u 2017.g. su objavljeni kao posebno poglavlje ove publikacije, a uključ uju i detaljniju analizu bolnič ke potroġnje antibiotika koja se detaljnije poļela 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 praĺenje rezistencije. Iz ovog poglavlja bolje se moġe uoļiti problem multiplorezistentnih bakterija u Hrvatskoj s obzirom da se rijetki izolati s novim mehanizmima rezistencije ļesto ne prikazuju kao znaļajan postotak u velikom broju izolata obraĽenih u masovnom praĺenju.

MATERIALS AND METHODS

Global surveillance

Global antibiotic resistance surveillance includes all clinical isolates of designated bacterial species isolated from 1 October till 31 December, 2017. Since 2016 clinical isolates of *Candida* spp. are also 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, 2017 due to the small number of isolates. In 2017 thirty-seven centers took part in antibiotic resistance surveillance (names of the centers are listed in the legend to the tables) which makes a catchment population of >90%.

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

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

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

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

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

Laboratories send their data for analysis to the Croatian Reference Centre for Antibiotic Resistance Surveillance, University Hospital for Infectious Diseases ñDr. F. MihaljeviÍ 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 2017 all laboratories used EUCAST standards for susceptibility testing (Breakpoint Table 7.1 for bacteria and Antifungal Clinical Breakpoint Table 8.0 for *Candida* spp.). Disk diffusion method is the most widely used sensitivity testing method in Croatian laboratories and minimal inhibitory concentration (MIC) testing is used for testing susceptibility in anaerobic bacteria and for detection of penicillin and ampicillin resistance in penicillin non-susceptible pneumococci, glycopeptide resistance in staphylococci and colistin resistance in pseudomonas and acinetobacter. The NAC 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.

Minimal inhibitory concentrations are determined by gradient tests (Etest, bioMérieux; MIC Test Strip, Liofilchem). In 2017 the EUCAST recommendation to use microbroth dilution for testing colistin MIC was adopted and NAC took care that comercial tests (MICRONAUT MIC-Strip, Merlin Diagnostika; MIKROLATEST MIC, Erba Lachema) are available at the Croatian market.

Bacterial species and antibiotics tested are listed in tables.

Focused studies

Data on *M. tuberculosis* were processed in the National Laboratory for Tuberculosis at the Croatian Public Health Institute. Resistance in *Mycobacterium tuberculosis* is described in a separate chapter of this publication.

Gonococci are included in antibiotic resistance surveillance since 2016. Data are analyzed at the Department of Bacteriology of the Croatian Public Health Institute and are described in a separate chapter of this publication.

Data on invasive isolates (isolates from blood and cerebrospinal fluid) of *S. pneumoniae*, *S. aureus, E. faecalis, E. faecium, E. coli*, *K. pneumoniae, P. aeruginosa* and *Acinetobacter baumannii* were first collected within the European Antimicrobial Resistance Surveillance System (EARSS) project and afterwards within the EARS-Net program. For these isolates Reference center (RC) for resistance surveillance collects and analyses patient demographic data and for the purpose of more detailed analysis 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. MihaljeviĹ 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 2017 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 2017 are presented in a separate chapter of this publication and they also include a more detailed analysis of antibiotic consumption in hospitals which was initiated by the APUA Croatia Chapter in 2006 and is in line with ISKRA requirements.

A special chapter deals with the isolates sent for retesting to the Reference Center for Antibiotic Resistance Surveillance. This detailed report provides a better insight in the spread of multiply resistant bacteria in Croatia as the presence of some strains with novel resistance mechanisms may still not be seen as a significant increase in resistance rates.

REZULTATI

U praćenju rezistencije u 2017.g. sudjelovalo je 37 centara u Hrvatskoj. Prosječni rezultati za Hrvatsku i rezultati za pojedinačne centre prikazani su u tablicama i grafovima u daljnjem tekstu. Rezultati laboratorija koji su prijavili manje od 30 izolata pojedine bakterijske vrste smatraju se nepouzdanim podacima za taj centar, ali su 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 vaţećima.

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

- ĐK 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 *Enterococcus faecalis* i *A. baumannii* je prikazao rezultate za cijelu godinu
- KA ZZJZ je za *E. faecium* i *A. baumannii* prikazao rezultate za cijelu godinu
- PU ZZJZ je za *H.influenzae* i *A. baumannii* prikazao rezultate za cijelu godinu
- PĐ ZZJZ je za *E. coli* 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)
- VT ZZJZ je za *H. influenzae* i *E. faecium* prikazao rezultate za cijelu godinu, a za BHS ï A od 1.10. do 31.12.2017.
- ZD ZZJZ je za *S. pneumoniae* prikazao rezultate za cijelu godinu
- SB ZZJZ je za *S. pneumoniae* i *H.influenzae* prikazao rezultate za cijelu godinu

Tri laboratorija su prijavila izolaciju ğigela: RI KBC *Sh.flexneri* (2); RI NZZJZ *Sh.flexneri* (2) i ZG KIB *Sh.flexneri* (1), *Sh.sonnei* (2); . Ukupno je tijekom 2017.g. izolirano sedam ğigela.

U 2017.g. ukupno je obrađeno 911 anaerobnih bakterija, 508 gram-pozitivnih i 403 gram-negativna anaeroba iz 20 centara : ĐK ZZJZ gram-pozitivni anaerobi (37), gram-negativni anaerobi (56); KA ZZJZ gram-pozitivni anaerobi (3), gram-negativni anaerobi (9); KC ZZJZ gram-negativni anaerobi (3); KT MAGD. gram-pozitivni anaerobi (2), gram-negativni anaerobi (1); OG OB gram-pozitivni anaerobi (5), gram-negativni anaerobi (8); OS ZZJZ gram-pozitivni anaerobi (15), gram-negativni anaerobi (15); PU ZZJZ gram-negativni anaerobi (7); RI KBC gram-pozitivni anaerobi (41), gram-negativni anaerobi (33); SB ZZJZ gram-pozitivni anaerobi (11), gram-negativni anaerobi (14); SK ZZJZ gram-pozitivni anaerobi (4); ST KBC gram-pozitivni anaerobi (103), gram-negativni anaerobi (40); ĠI ZZJZ gram-pozitivni anaerobi (12), gram-negativni anaerobi (14); VK ZZJZ gram-pozitivni anaerobi (2), gram-negativni anaerobi (5); VT ZZJZ gram-pozitivni anaerobi (1), gram-negativni anaerobi (12); VĐ ZZJZ gram pozitivni anaerobi (120), gram-negativni anaerobi (67); ZD ZZJZ gram-pozitivni anaerobi (4), gram-negativni anaerobi (3); ZG KBM gram-pozitivni anaerobi (23), gram-negativni anaerobi (35); ZG KIB gram-pozitivni anaerobi (12), gram-negativni anaerobi (9); ZG KDB gram-pozitivni anaerobi (15), gram-negativni anaerobi (31); ZG KBSD gram-pozitivni anaerobi (98), gram-negativni anaerobi (41).

Ġesnaest laboratorija je prijavilo izolaciju *Candida* spp.: ĻK ZZJZ *C. glabrata* (3), *C. utilis* (1); OS ZZJZ *C. glabrata* (2), *C. parapsilosis* (6), *C. rugosa* (1); PU ZZJZ *C. glabrata* (1); RI KBC *C. glabrata* (69), *C. tropicalis* (14); SB ZZJZ *C. glabrata* (2), *C. parapsilosis* (4); SK *ZZJZ C. glabrata (1), C. parapsilosis* (2); ST KBC *C. glabrata* (3), *C. parapsilosis* (11); ĠI ZZJZ *C. glabrata* (2), *C. parapsilosis* (4); VK ZZJZ *C. glabrata* (1), *C. parapsilosis* (5); VĢ ZZJZ *C. parapsilosis* (1), *C. utilis* (1); ZG KBC *C. glabrata* (18), *C. parapsilosis* (24); ZG KBD *C. glabrata* (2), *C. parapsilosis* (2), *C. krusei* (1), *C. kefyr* (1); ZG KBM *C. glabrata* (3); ZG KBCSM *C. glabrata* (1), *C. parapsilosis* (4), *C. tropicalis* (1); ZG KZT *C. glabrata* (1), *C. parapsilosis* (2); ZG KIB *C. glabrata* (7), *C. parapsilosis* (3). Ukupno je tijekom 2017.g. izolirano 204 *Candida* spp.

RESULTS

Thirty-seven centers took part in antibiotic resistance surveillance in Croatia in 2017. 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 *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 *E. coli* 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

Three laboratories reported shigella isolates: RI KBC *Sh. flexneri* (2); RI NZZJZ *Sh. flexneri* (2) i ZG KIB *Sh. flexneri* (1), *Sh.sonnei* (1). Altogether seven shigella isolates were reported in 2017.

In 2017 altogether 911 anaerobic bacteria were isolated, 508 gram-positives and 403 gram-negatives. They were isolated in 20 centers: ĻK ZZJZ gram-positive anaerobes (37), gram-negative anaerobes (56); KA ZZJZ gram-positive anaerobes (3), gram-negative anaerobes (9); KC ZZJZ gram-negative anaerobes (3); KT MAGD gram-positive anaerobes (2), gram-negative anaerobes (1); OG OB gram-positive anaerobes (5), gram-negative anaerobes (8); OS ZZJZ gram-positive anaerobes (15), gram-negative anaerobes (15); PU ZZJZ gram-positive anaerobes (1), gram-negative anaerobes (8); RI KBC gram-positive anaerobes (55), gram-negative anaerobes (7); RI KBC gram-positive anaerobes (41), gram-negative anaerobes (33);SB ZZJZ gram-positive anaerobes (11), gram-negative anaerobes (14); 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 (4); ST KBC gram-positive anaerobes (103), gram-negative anaerobes (40); VK ZZJZ gram-positive anaerobes (2), gram-negative anaerobes (5); VT ZZJZ gram-positive anaerobes (1), gram-negative anaerobes (12); VĢ ZZJZ gram-positive anaerobes (120), gram-negative anaerobes (67); ZD ZZJZ gram-positive anaerobes (4), gram-negative anaerobes (3); ZG KBM gram-positive anaerobes (23), gram-negative anaerobes (35); ZG KIB gram-positive anaerobes (12), gram-negative anaerobes (9); ZG KDB gram-positive anaerobes (15), gram-negative anaerobes (31); ZG KBSD gram-positive anaerobes (98), gram-negative anaerobes (41).

Sixteen laboratories reported *Candida* spp. isolates: ĻK ZZJZ *C. glabrata* (3), *C. utilis* (1); OS ZZJZ *C. glabrata* (2), *C. parapsilosis* (6), *C. rugosa* (1); PU ZZJZ *C. glabratai* (1); RI KBC *C. glabrata* (69), *C. tropicalis* (14); SB ZZJZ *C. glabrata* (2), *C. parapsilosis* (4); SK *ZZJZ C. glabrata* (1), *C. parapsilosis* (2); ST KBC *C. glabrata* (3), *C. parapsilosis* (11); ĠI ZZJZ *C. glabrata* (5), *C. krusei* (1), *C. dubliniensis* (1), *C. tropicalis* (1); VK ZZJZ *C. glabrata* (1), *C. parapsilosis* (5); VÇ ZZJZ *C. parapsilosis* (1), *C. utilis* (1); ZG KBC *C. glabrata* (18), *C. parapsilosis* (24); ZG KBD *C. glabrata* (2), *C. parapsilosis* (2), *C. krusei* (1), *C. kefyr* (1); ZG KBM *C. glabrata* (3); ZG KBCSM *C. glabrata* (1), *C. parapsilosis* (4), *C. parapsilosis* (4); *C.tropicalis* (1); ZG KZT *C. glabrata* (1), *C. parapsilosis* (2); ZG KIB *C. glabrata* (7), *C. parapsilosis* (3).Altogether 204 *Candida* spp. isolates were reported in 2017.

DISKUSIJA

Beta-hemolitički streptokok grupe A (BHS-A) je glavni uzročnik bakterijskih upala grla, no može i asimptomatski kolonizirati sluznicu gornjeg dijela. 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 2017.g. (7%) je identična prošlogodišnjoj stopi i zadnjih godina nisu uočena značajnija kretanja rezistencije na makrolide (7% u 2016.g., 9% u 2015.g. i 2014.g, 10% u 2013.g., 9% u 2012. g., 7% u 2011.g., 8% u 2010.g., 9% u 2009.g., 13% u 2008.g.). Rezistencija na klindamicin je također identična prošlogodišnjim stopama (konstitutivna 3%, inducibilna 3%). Prema EUCAST standardima izolati s inducibilnom rezistencijom su se do 2014.g. izdavali kao osjetljivi na klindamicin uz upozorenje da se izbjegava dugotrajnija terapija težkih infekcija klindamicinom, a od 2014.g. se takvi izolati interpretiraju kao rezistentni na klindamicin uz opasku da se klindamicin još uvijek može primijeniti u kratkotrajnom liječenju ili u liječenju blažih infekcija kože i mekih tkiva. Klindamicin se preporuča i u kombiniranoj terapiji s penicilinom kod težkih 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.

Najčešći uzročnici infekcija dišnih puteva su virusi, no upalu pluća, srednjeg uha i sinusa osim virusa mogu uzrokovati i bakterije, najčešće pneumokoki, *Haemophilus influenzae* i *Moraxella catarrhalis*. Ove bakterije se smatraju respiratornim patogenima, no često se nalaze i kao dio fiziološke mikrobiote gornjih dišnih puteva u zdravih ljudi ili tijekom virusne infekcije gornjih dišnih puteva. Brisevi nazofarinksa, stoga, pokazuju nisku specifičnost i osjetljivost, često zavode u kliničkom rasuđivanju i ne preporučuju se kao uzorci za dijagnosticiranje etiologije infekcija gornjih dišnih puteva. U Hrvatskoj se brisevi nazofarinksa sve manje uzimaju, čemu doprinose i smjernice Hrvatskog društva za kliničku mikrobiologiju, te se broj prijavljenih pneumokoka i hemofilusa sve više smanjuje. Izolati pneumokoka i hemofilusa opisani u ovom poglavlju potječu, ipak, još uvijek pretežno iz briseva nazofarinksa i predstavljaju pretežno kolonizirajuću mikrobiotu. Neinvazivni pneumokoki često pokazuju veće stope rezistencije negoli invazivni izolati. Rezistencija invazivnih pneumokoka opisana je u poglavlju o invazivnim izolatima i mjerodavnija je kao putokaz za primjenu antimikrobne terapije. Stope rezistencije ukupnih pneumokoka imaju, međutim, epidemiološko značenje jer ukazuju na trendove u širenju rezistencije. U Hrvatskoj, parenteralni penicilin je još uvijek lijek izbora u liječenju pneumokoknih pneumonija jer visoka rezistencija na penicilin iznosi 2%. 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 2017.g. iznosi 23% i u razini je stopa neosjetljivosti zadnjih godina (23% u 2016.g., 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 srednji 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 2017.g. 98% svih pneumokoka ima MIK penicilina ≤2.0 mg/L i reagirat će na dozu od 6x2.4g (6x4MIU), 95% pneumokoka ima MIK penicilina ≤1.0 mg/L i reagirat će na dozu od 4x2.4g (4x4MIU) ili 6x1.2g (6x2MIU), a 90% 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 počeli registrirati već i postotak na ampicilin visoko (2% u 2017.g., 3% u 2016.g., 2015.g. i 2014.g.) i intermedijarno (10% u 2017.g., 9% u 2016.g. i 2015.g. i 11% u 2014.g.) rezistentih pneumokoka, što se vjerojatno može nadvladati primjenom viših doza ampicilina. Iako je u Hrvatskoj već duže vremena u pedijatrijskoj populaciji uobičajeno primjenjivati više doze amoksicilina (80mg/kg), kod odraslih pacijenata je još uvijek uobičajeno propisivati niske doze amoksicilina (3x500mg) koje pokrivaju samo dobro osjetljive sojeve pneumokoka (u 2017.g. 88% izolata). Više doze od 3x750mg ili 3x1g amoksicilina mogu biti djelotvorne i na intermedijarne izolate (u 2017.g. 98% izolata je dobro i intermedijarno osjetljivo na amoksicilin). Prelaskom na EUCAST počeli 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. i 2017.g.). Zabrinjava, ipak, rezistencija od Ó20% u zadnje tri godine. Rezistencija pneumokoka na makrolide (32%), ko-trimoksazol (22%) i tetraciklin (19%) je slična prošlogodišnjim stopama (35%, 23% i 20%). 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., 22% u 2017.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 i najnižih stopa 2013. i 2014.g. (12%) stopa MRSA je od 2015.g. opet počela rasti, ali se trend porasta u 2017.g. zaustavio (25% u 2007. g., 26% u 2008. g., 21% u 2009. g., 16% u 2010. g., 14% u 2011. g., 13% u 2012. g., 12% u 2013.g. i 2014.g., 14% u 2015.g., 16% u 2016.g., 15% u 2017.g.). Udio MRSA sojeva s inducibilnom rezistencijom na klindamicin (16% u 2014.g., 21% u 2015.g., 28% u 2016.g., 32% u 2017.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., 23% u 2017.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 9% u 2017.g., 8% u 2016.g., 7% u 2015.g., 16% u 2014.g. i 20% u 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 u svrhu postizanja sinergističkog učinka. Kod sojeva visoko rezistentnih na aminoglikozide, ovi se antibiotici ne mogu upotrebljavati niti u kombiniranoj terapiji. Udio sojeva s visokom rezistencijom na aminoglikozide iznosi 26% za *E.faecalis* i 59% za *E.faecium*, što je podjednako prošlogodišnjim stopama. Rezistencija na vankomicin je još uvijek rijetka u *E.faecalis* (<1%). Porast rezistencije na vankomicin u *E. faecium* uočen posljednjih godina nije se nastavio u 2017.g. (1% u 2012.g., 5% u 2013.g., 7% u 2014.g., 15% u 2015.g., 17% u 2016.g., 16% u 2017.g.). 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. Kinoloni su namijenjeni liječenju enterokoknih infekcija, samo

ako se radi o nekompliciranim infekcijama mokraćnog sustava. Rezistencija na kinolone u *E. faecalis* (22%) i *E. faecium* (69%) podjednaka je prošlogodišnjim stopama (19% i 80%).

Escherichia coli je najčešći uzročnik infekcija mokraćnog sustava (IMS), a ostale enterobakterije češće 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 uočiti i kontrolirati. Od početka praćenja *E. coli* pokazuje visoku rezistenciju na ampicilin (50% u 2017.g.), ali amoksicilin s dodatkom klavulanske kiseline pokazuje dobru djelotvornost jer klavulanska kiselina uspješno blokira beta-laktamaze širokog spektra i veći inu beta-laktamaza proširenog spektra (engl. ñextended spectrum beta-lactamases, ESBLò). Kombinacija s klavulanskom kiselinom, međutim, ograničava primjenu amoksicilina u visokim dozama, kakve su često potrebne kod ozbiljnih sistemnih infekcija. U 2014.g. EUCAST je po prvi puta razdvojio interpretaciju osjetljivosti na amoksicilin s klavulanskom kiselinom ovisno o tome radi li se o nekompliciranoj IMS ili drugim oblicima infekcije. Nakon te podjele, stope rezistencije su ostale podjednake ako se interpretiraju za primjenu kod nekompliciranih IMS (7% u 2013.g. i 2014.g., 9% u 2015.g., 10% u 2016. i 2017.g.) no znatno su se povisile ako se interpretiraju za primjenu kod ostalih infekcija (16% u 2014. i 2015.g., 15% u 2016. i 2017.g.). Rezistencija na cefalosporine treće generacije (6% do 9%) je istovjetna prošlogodišnjim stopama, a rezistencija na karbapeneme je i dalje izuzetno rijetka i ne odražava se u stopama rezistencije. Zabrinjava što je rezistencija na kinolone u daljnjem porastu i dosegla 20% (14% u 2012. i 2013.g., 17% u 2014.g., 18% u 2015.g., 19% u 2016.g., 20% u 2017.g.). Stope rezistencije na ko-trimoksazol (27%), gentamicin (9%), amikacin (1%) i nitrofurantoin (3%) su jednake prošlogodišnjim stopama.

Proteus mirabilis još uvijek izaziva pretežno izvanbolničke infekcije i prirodno bi trebao biti bakterijska vrsta dobro osjetljiva na sve beta-laktamske antibiotike usmjerene na gram-negativne bakterije. Nažalost, rezistencija na beta-laktamske antibiotike je već dosegla visoke stope i u 2017.g. iznosi za ampicilin 50%, za ko-amoksiklav 23%, za piperacilin/tazobaktam 2%, za cefalosporine 3.generacije od 18% do 19% i za cefepim 5%. Stope rezistencije na ciprofloksacin (28%), gentamicin (23%), amikacin (11%) i ko-trimoksazol (40%) su podjednake prošlogodišnjima. Zbog svoje urođene otpornosti na kolistin, tigeciklin te niže osjetljivosti na imipenem *Proteus mirabilis* i drugi *Proteus* spp. bi u budućnosti mogli predstavljati sve veći problem, naročito kod uroloških bolesnika i infekcija povezanih s bolničkom skrbi.

Klepsijele i enterobakteri često uzrokuju infekcije povezane s bolničkom skrbi te već dugi niz godina pokazuju visoke stope rezistencije. *Klebsiella pneumoniae* je prirodno rezistentna na ampicilin no rezistencija na ostale beta-laktame je stečena uslijed dugotrajnog izlagnja antibioticima. Stope rezistencije na cefalosporine treće i četvrte generacije (26% za cefepim do 32% za ceftriakson i cefiksim) i ko-amoksiklav (34%) su slične prošlogodišnjima. Nakon što 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 zadržale i u 2017.g. (1% rezistentnih i 1% intermedijarnih izolata).

Enterobakteri, citrobakteri i seracije čine grupu enterobakterija koje prirodno posjeduju inducibilne cefalosporinaze i s izuzetkom *Citrobacter koseri* pokazuju rezistenciju ne samo na ampicilin već i na ko-amoksiklav i cefalosporine prve generacije. Cefuroksim samo marginalno djeluje na ovu grupu enterobakterija i prema EUCAST standardima ne postoji klinička interpretacija osjetljivosti na cefuroksim za ovu grupu bakterija. Divlji sojevi su osjetljivi na treću generaciju cefalosporina, no u tijeku terapije cefalosporinima može doći i do probira derepresiranih mutanti koji stabilno hiperproduciraju AmpC cefalosporinaze i time uvjetuju rezistenciju i na cefalosporine treće generacije. Udio mutanti rezistentnih na cefalosporine treće i četvrte generacije (16% za cefepim do 32% za cefiksim) je nešto veći u

odnosu na prošlu godinu (8% do 28%). Stopa rezistencije enterobaktera na imipenem i meropenem postala je vidljiva 2013.g. (1%), u 2015.g. i 2016.g. je bila <1, a u 2017.g. je ponovno 1%. Stope rezistencije na ciprofloksacin (13%), gentamicin (12%) i ko-trimoksazol (16%) se nisu znaļajnije promijenile u odnosu na prethodnu godinu.

Multiplorezistentni *Pseudomonas aeruginosa* već i dugi niz godina predstavlja veliki problem u Hrvatskoj. Neosjetljivost (visoka i umjerena rezistencija) *P.aeruginosa* na imipenem (19%) i meropenem (21%) se nije bitno promijenila u odnosu na prethodnu godinu (20% i 21%). Rezistencija na piperacilin/tazobaktam (9%), ceftazidim (16%), cefepim (9%), gentamicin (20%), amikacin (9%) i ciprofloksacin (26%) se takoĽer nije znaļajnije mijenjala. S obzirom da se u 2017.g. osjetljivost na ceftolozan + tazobaktam mogla odrediti samo testiranjem MIK vrijednosti, osjetljivost na ovaj novi antibiotik nije rutinski testirana već se procjena osjetljivosti na taj antibiotik i dalje oslanja na pilot studiju iz 2016.g. u kojoj je osjetljivost *P.aeruginosa* na ceftolozan + tazobaktam iznosila 94%.

Rezistencija na karbapeneme kod *Acinetobacter baumannii* se u Hrvatskoj naglo proširila od 2008.g. i u 2016.g. su se zadržale visoke stope neosjetljivosti na imipenem (88%) i meropenem (87%), podjednake prošlogodišnjima. Prema EUCAST standardima ne postoje jasni dokazi o uļinkovitosti ampicilin/sulbaktama na acinetobaktere, no kako je to jedan od rijetkih antibiotika koji još pokazuju djelotvornost *in vitro*, ovaj antibiotik se u Hrvatskoj testira i interpretira prema ameriļkim standardima. Neosjetljivost (visoka i umjerena rezistencija) na ampicilin/sulbaktam se zadržala na visokim vrijednostima (33% u 2013.g., 43% u 2014.g., 55% u 2015.g., 49% u 2016.g., 48% u 2017.g.). Osjetljivost na kolistin se može ispitati samo odreĽivanjem minimalnih inhibitornih koncentracija te se osjetljivost na kolistin zasada odreĽuje samo kod pseudomonasa i acinetobaktera rezistentnih na karbapeneme. Iako su registrirani pojedinaļni izolati acinetobaktera i pseudomonasa rezistentni na kolistin, to se još ne prikazuje kao postotak rezistencije.

Rezistencija salmonela na ampicilin dugo nije prelazila 10%, no u 2014., 2015., 2016. i 2017.g. iznosi 14%, 16%, 14% i 13%. ESBL sojevi su i dalje rijetki meĽu salmonelama, ali se od 2015.g. prikazuju kao postotak rezistencije na cefalosporine 3. generacije (1%). Rezistencija na ko-amoksiklav (3%), ko-trimoksazol (2%) i ciprofloksacin (4%) je niska i identiļna ili sliļna prošlogodišnjim stopama. Do 2013.g. osjetljivost salmonela na ciprofloksacin na razini Hrvatske je bila 100%, a na nalidiksiļnu kiselinu, koja je bolji pokazatelj niske razine rezistencije na kinolne, do 2%. Od 2014.g. EUCAST je uveo testiranje osjetljivosti na kinolone (ciprofloksacin) preko pefloksacinskog diska što je vjerojatno utjecalo na registriranje stopa rezistencije na ciprofloksacin od 2% u 2014.g., 4% u 2015.g., 3% u 2016.g. i 4% u 2017.g.

Osjetljivost u *Campylobacter coli* i *Campylobacter jejuni* se prati od 2013.g. Rezistencija na ciprofloksacin (69% i 66%) u 2017.g. i dalje raste (u 2015.g. 52% i 50%, u 2016.g. 60% obje vrste). Rezistencija na eritromicin iznosi 3% i 2%, a na tetraciklin 35% i 30% što je sliļno prošlogodišnjim stopama.

Tijekom 2017.g. registrirano je sedam izolata šigela, dva izolata *Shigella sonnei* i pet izolata *Shigella flexneri*. Iako je zbog malog broja izolata teško govoriti o stopama rezistencije, rezistencija je visoka na ampicilin (100%), ko-amoksiklav (57%), ciprofloksacin (43%) i kotrimoksazol (43%), a ni ove godine rezistencija na cefalosporine treće generacije nije zabiljeđena.

Stope rezistencije se kod anaerobnih bakterija nisu znaļajnije mijenjale. MeĽu gram-negativnim anaerobima rezistencija je visoka na penicilin (76%) i klindamicin (27%), a kod gram-pozitivnih anaeroba rezistencija je visoka na metronidazol (58%). Rezistencija na ko-amoksiklav, piperacilin/tazobaktam i ertapenem je niska (Ò2%).

Osjetljivost se u *Candida* spp. poļela pratiti u 2016.g. Kako se smatra da je *Candida albicans* dobro osjetljiva na antifungike, ova vrsta nije uključena u praćenje rezistencije. I ove godine najčešći su bili izolati *Candida glabrata* (116) i *Candida parapsilosis* (68). Divlji tip *C. glabrata* pokazuje osjetljivost na flukonazol samo uz više doze, a rezistencija je zabilježena u 6% izolata. *C. parapsilosis* je bila rezistentna na flukonazol (46%) i vorikonazol (40%), ali ne i na amfotericin B i anidulafungin. Visoka stopa rezistencije *C. parapsilosis* na vorikonazol je neuobičajena te bi se takvi izolati trebali retestirati u referentnom laboratoriju. Kako je testiranje osjetljivosti na kaspofungin nepouzdano, osjetljivost na kaspofungin se može predvidjeti prema osjetljivosti na anidulafungin.

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 organism 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 2017 is 7%, the same as in the previous year demonstrating no 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, and 13% in 2008). Resistance to clindamycin is also identical to the previous year rates (both constitutive and inducible 3%). 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 most commonly caused by viruses but acute otitis media, sinusitis and pneumonia may also be caused by bacteria such as pneumococci, *Haemophilus influenzae* and *Moraxella catarrhalis*. These bacteria are classified as respiratory pathogens but are frequently found as part of the normal microbiota of the upper respiratory tract in healthy individuals or during a viral upper respiratory tract infection. Nasopharyngeal swabs have, therefore, low sensitivity and specificity, they can be misleading in clinical judgement and they are not recommended as samples for diagnosing aetiology of upper respiratory tract infections. In Croatia nasopharyngeal swabs are becoming less popular as diagnostic tool and their use is discouraged in guidelines of the Croatian Society of Clinical Microbiology so the number of reported pneumococcal and haemophilus isolates is decreasing. Most of the pneumococcal and haemophilus isolates reported in this chapter are still from nasopharyngeal swabs and aspirates and therefore mostly represent colonizing 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 2%. 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 2017 is 23% which is similar to the rates recorded in previous years (23% in 2016, 22% in 2015, 23% in 2014, 31% in 2013%, 30% in 2012, 29% in 2011, 24% in 2010, 29% in 2009, 30% in 2008, and 26% in 2007). 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, 98% of pneumococci have penicillin MIC Ò2.0 mg/L and will be covered by 6x2.4g (6x4MIU) dosing, 95% have penicillin MIC Ò1.0 mg/L and will be covered by 4x2.4g (4x4MIU) or 6x1.2g (6x2MIU) dosing and 90% 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 (2% in 2017, 3% in 2016, 2015 and 2014) and intermediate (10% in 2017, 9% in 2016 and 2015 and 11% in 2014) pneumococci which can probably be overcome by higher ampicillin dosing. Although in Croatia higher ampicillin dosing (80mg/kg) is common in paediatrics, usual ampicillin dosing in adult patients includes lower doses (3x500mg) which cover only completely sensitive pneumococcal isolates (88% of pneumococci in 2017). Higher dosing includes 3x750mg or 3x1g of amoxicillin and this is efficient for intermediately sensitive isolates as well (98% of isolates in 2017 were completely or intermediately sensitive to amoxicillin). 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 and 2017). However, resistance rates over 20% in the past three years are alarming. Pneumococcal resistance rates to macrolides (32%), co-trimoxazole (22%) and tetracycline (19%) are similar to the last year rates (35%, 23% and 20%). Resistance to co-trimoxazole is showing decreasing trend (43% in 2010, 35% in 2011, 29% in 2012, 27% in 2013, 29% in 2014, 26% in 2015, 23% in 2016, 22% in 2017). 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. After a decrease in MRSA rates that reached 12% in 2013 and 2014, MRSA rates started to increase in 2015 but this increase did not continue in 2017 (25% in 2007, 26% in 2008, 21% in 2009, 16% in 2010, 14% in 2011, 13% in 2012, 12% in 2013 and 2014, 14% in 2015, 16% in 2016, 15% in 2017). The rate of MRSA isolates with inducible clindamycin resistance (16% in 2014, 21% in 2015, 28% in 2016, 32% in 2017) 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, and 23% in 2017). 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 9% in 2017, 8% in 2016, 7% in 2015, 16% in 2014 and 20% in 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 but a combination of aminoglycosides with ampicillin or glycopeptides is considered to have synergistic effect in treating infections caused by wild type enterococci. Aminoglycosides should not be used in isolates with high level aminoglycoside resistance, not even in combination with other antibiotics. High level aminoglycoside resistance rate in 2017 is 26% in *E.faecalis* and 59% in *E.faecium* which is similar to the previous year results. Resistance to vancomycin is still rare in *E.faecalis* (<1%). The increase of vancomycin resistance in *E.faecium* did not continue in 2017 (1% in 2012, 5% in 2013, 7% in 2014, 15% in 2015, 17% in 2016, and 16% in 2017). Since 2015 vancomycin resistant *E. faecium* (VRE) strains became more prevalent in many regions outside Zagreb as well. In 2014 EUCAST introduced testing susceptibility to fluoroquinolones in enterococci and using norloxacin disk as an indicator of susceptibility to ciprofloxacin and levofloxacin. Quinolones are to be used to treat enterococci only in case of uncomplicated urinary tract infections (UTI). Quinolone

resistance in *E.faecalis* (22%) and *E.faecium* (69%) is similar to previous year rates (19% and 80%).

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 2017) 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 and 2017) but did change significantly if using breakpoints for other infections (16% in 2014 and 2015, 15% in 2016 and 2017). Resistance to 3rd generation cephalosporins (6% to 9%) is the same as in the previous year and resistance to carbapenems is still rare and bellow the rate of detection. It is worrisome that quinolone resistance is constantly increasing and has reached 20% (14% in 2012 and 2013, 17% in 2014, 18% in 2015, 19% in 2016, and 20% in 2017). Resistance rates to co-trimoxazole (27%), gentamicin (9%), amikacin (1%) and nitrofurantoin (3%) are identical to the 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 2017 resistance to ampicillin is 50%, co-amoxiclav 23%, piperacillin/tazobactam 2%, 3rd generation cephalosporins 18% to 19% and cefepime 5%. Resistance rates to ciprofloxacin (28%), gentamicin (23%), amikacin (11%) and co-trimoxazole (40%) are 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 (26% cefepime to 32% ceftriaxone and cefixime) and co-amoxiclav (34%) 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 2017 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 (16% cefepime to 328% cefixime) increased compared to the previous year (8% and 28%). Resistance to imipenem and meropenem first became visible in 2013 (1%), in 2015 and 2016 it was <1%

and in 2017 it is 1% again. Resistance to ciprofloxacin (13%), gentamicin (12%) and co-trimoxazole (16%) 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 (19%) and meropenem (21%) did not change significantly as compared with the previous year (20% and 21%). Resistance to piperacillin/tazobactam (9%), ceftazidime (16%), cefepime (9%), gentamicin (20%), amikacin (9%) and ciprofloxacin (26%) did not change significantly either. In 2017 only MIC breakpoints were available for testing susceptibility to ceftolozane + tazobactam and susceptibility to this antibiotic was not tested routinely. Susceptibility to ceftolozane + tazobactam is still estimated according to the results of the pilot study done in 2016 in which 94% of *P.aeruginosa* isolates were susceptible to ceftolozane + tazobactam.

Carbapenem resistance in *A. baumannii* has rapidly spread throughout Croatia since 2008 and in 2016 non-susceptibility to imipenem (88%) and meropenem (87%) 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, and 48% in 2017). 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, 2016 and 2017 it reached 14%, 15%, 14 and 13%. ESBL isolates are still rare among salmonellae but since 2015 this is already visible as a resistance rate of 1% to 3rd generation cephalosporins. Resistance to co-amoxiclav (3%), co-trimoxazole (2%) and ciprofloxacin (4%) 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, 3% in 2016 and 4% in 2017.

Susceptibility rates in *Campylobacter coli* and *Campylobacter jejuni* were first reported in 2013. In 2017 resistance to ciprofloxacin (69% and 66%) still demonstrates an increasing trend (52% and 50% in 2015, 60% for both species in 2016). Resistance to erythromycin is 3% and 1% and to tetracycline 35% and 30% which is similar to the rates recorded previously.

During 2017 seven shigella isolates were reported, two *Shigella sonnei* and five *Shigella flexneri* isolates. Due to the low number of isolates it is difficult to estimate resistance rates but resistance to ampicillin (100%), co-amoxiclav (57%), ciprofloxacin (43%) and co-trimoxazole (43%) is high and again this year no resistance to 3rd generation cephalosporins was recorded.

Resistance rates in anaerobic bacteria did not change significantly. Among gram-negative anaerobes resistance is high to penicillin (76%) and clindamycin (27%), and in gram-positive anaerobes high resistance is recorded for metronidazole (58%). Low rates of resistance (Ò2%) were recorded for co-amoxiclav, piperacillin/tazobactam and ertapenem.

Susceptibility rates in *Candida* spp. were first reported in 2016. As *Candida albicans* is generally well sensitive to antifungals this species is not included in resistance surveillance.

Again this year the most common isolates were *Candida glabrata* (116) and *Candida parapsilosis* (68). Wild type *C. glabrata* has dose dependent susceptibility to fluconazole and resistance was recorded in 6% of isolates. *C. parapsilosis* was resistant to fluconazole (46%) and voriconazole (40%) but not to amphotericin B or anidulafungin. High rate of resistance to voriconazole in *C. parapsilosis* is unusual suggesting that such isolates should be retested in a reference laboratory. Susceptibility testing to caspofungin is unreliable and is derived from the susceptibility to anidulafungin.

LEGENDA ZA TABLICE */ LEGEND TO TABLES*

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

* uključuje podatke i za: Opću bolnicu Zabok
** uključuje podatke i za: Opću županijsku bolnicu, Pakrac
*** uključuje podatke i za: Bolnicu za plućne bolesti i TBC, Klenovnik
**** uključuje podatke i za: Kliniku za plućne bolesti „Jordanovac“, Zagreb
***** uključuje podatke i za: Sveučilišnu Kliniku za dijabetes, endokrinologiju i bolesti metabolizma „Vuk Vrhovac“, Zagreb
****** uključuje podatke i za: Institut za tumore, Zagreb

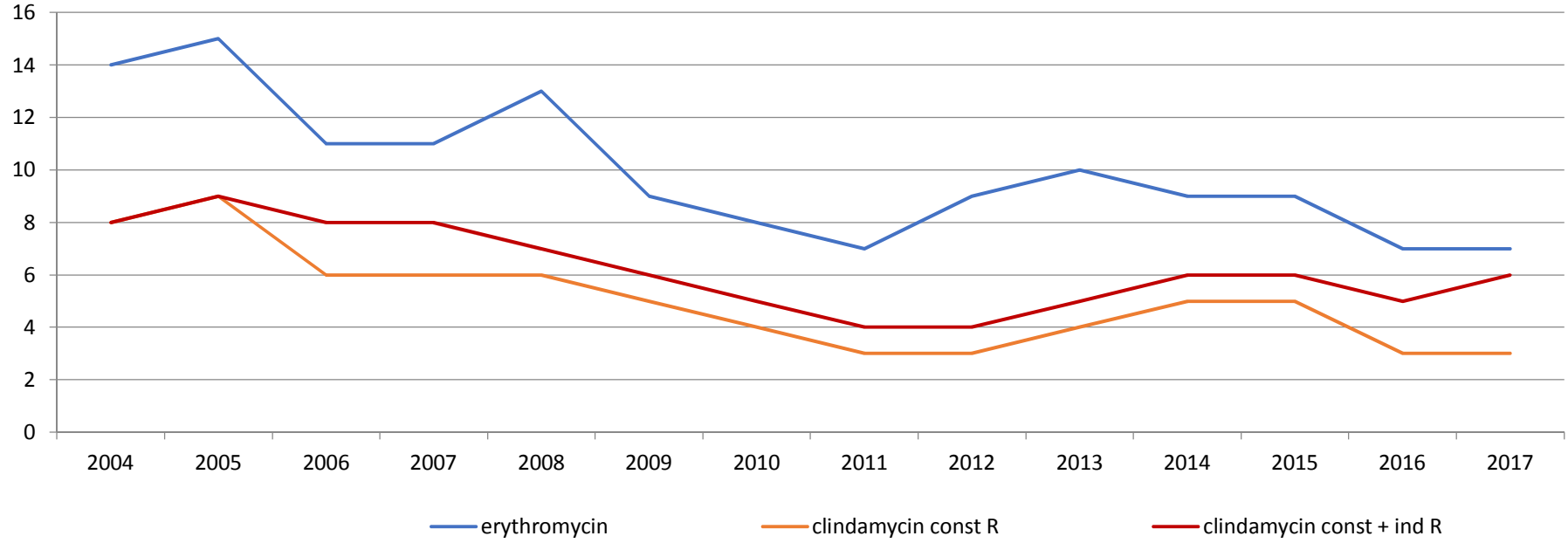
ANTIBIOTICI / *ANTIBIOTICS*

P $_{\textbf{parenteral}}$	*penicillin parenteral*
P $_{\textbf{oral}}$	*penicillin oral*
AMP	*ampicillin*
AMC	*amoxicillin + clavulanic acid*
AMC $_{\textbf{u}}$	*amoxicillin + clavulanic acid* $_{\textbf{uncomplicated urinary tract infection}}$
SAM	*ampicillin + sulbactam*
FOX $_{\textbf{screen}}$	*cefoxitin* (screening disk)*
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 $_{\textbf{screen}}$	*norfloxacin* (screening disk)*
GM	*gentamicin*
GM30	*gentamicin "high level resistance"*
NT	*netilmicin*
AN	*amikacin*
MUP	*mupirocin*
MTZ	*metronidazole*
MOX	*moxifloxacin*
LZD	*linezolid*
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*
*antibiotici koji se sami ne upotrebljavaju u terapijske svrhe već služe kao indikatori rezistencije na svoju klasu antibiotika / antibiotics with no therapeutic use that serve as resistance indicators for their antibiotic class

Beta-hemolitički streptokok grupe A /
Group A streptococcus

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 2004. - 2017.



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*

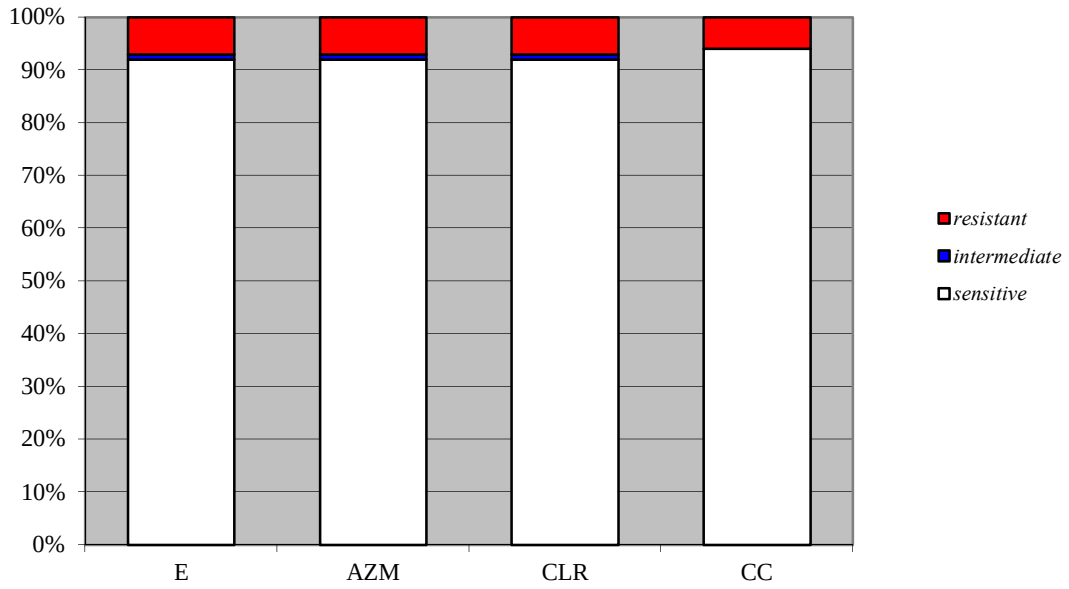
Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Beta-hemolitički streptokok grupe A /
Group A streptococcus

rezistencija na antibiotike u razdoblju od 1.01.- 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.01. - 31.12. 2017,
summary results for the isolates from 37 centers in Croatia

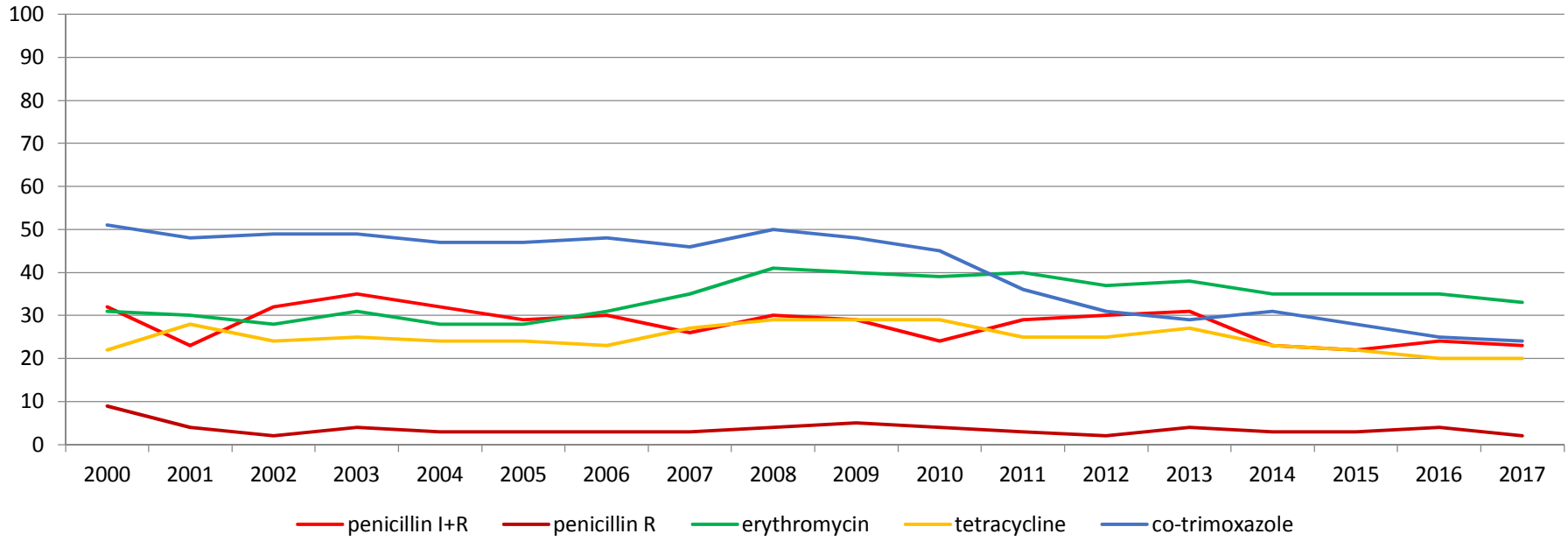
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Erythromycin	12 513	7 (1)	0 (0) - 27 (0)
Azithromycin	12 513	7 (1)	0 (0) - 27 (0)
Clarythromycin	12 513	7 (1)	0 (0) - 27 (0)
Clindamycin	12 513	6 (0)	
constitutive		3	0 - 18
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. - 2017.



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

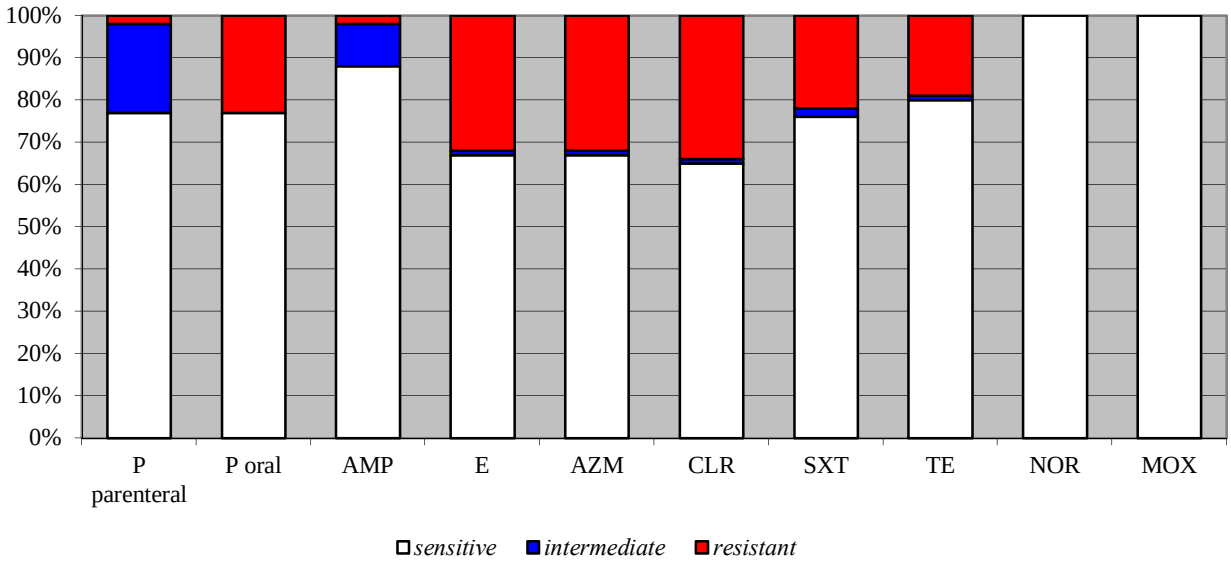
Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo,
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Streptococcus pneumoniae

rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the isolates from 37 centers in Croatia

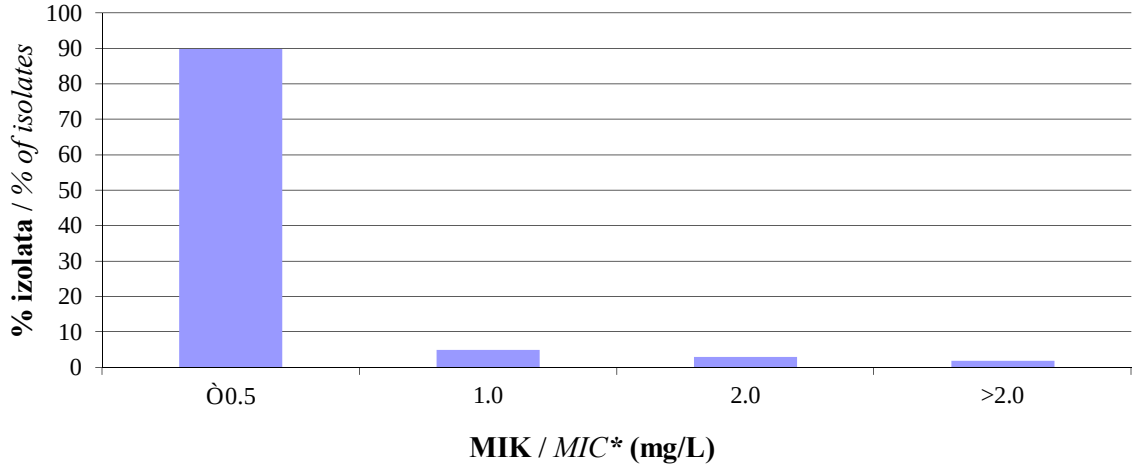
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Penicillin parenteral	1 838	2 (21)	0 (0) ï 10 (26)
Penicilin oral	1 838	23 (0)	0 (0) - 56 (0)
Ampicillin	1 689	2 (10)	0 (0) - 13 (6)
Erythromycin	1 842	32 (1)	0 (0) - 75 (0)
Azithromycin	1 842	32 (1)	0 (0) - 75 (0)
Clarythromycin	1 842	32 (1)	0 (0) - 75 (0)
Co-trimoxazole	1 846	22 (2)	0 (0) - 43 (4)
Tetracycline	1 577	19 (1)	0 (0) - 44 (0)
Norfloxacin	1 821	0 (0)	0 (0) - 4 (0)
Moxifloxacin	1 742	0 (0)	0 (0) ï 2 (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, (1 813 *S. pneumoniae* izolata) /
Penicillin MIC distribution, (1 813 S. pneumoniae isolates), 1.10. ï 31.12. 2017.



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

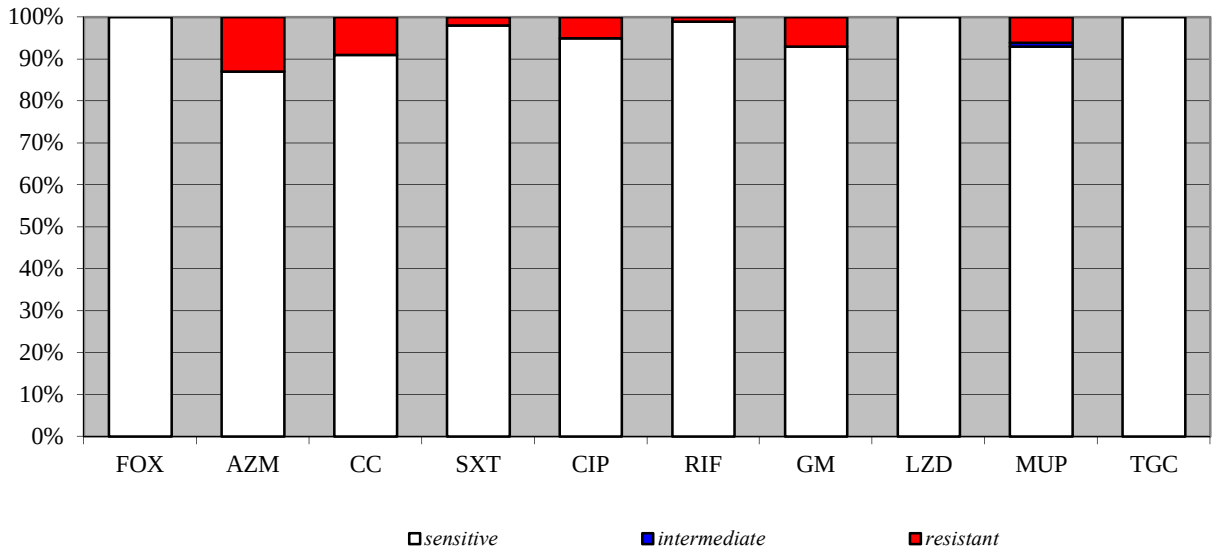
Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Staphylococcus aureus / MSSA

rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the isolates from 37 centers in Croatia

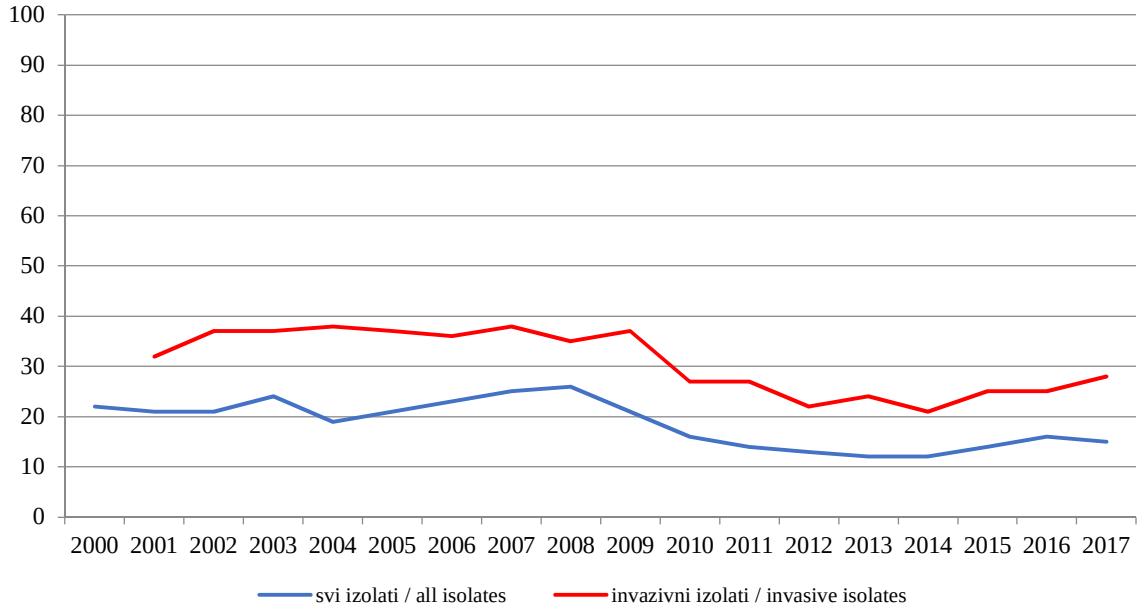
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Cefoxitin/ Methicillin	3 524	0 (0)	0 (0) - 0 (0)
Azithromycin	3 448	13 (0)	3 (0) - 28 (0)
Clindamycin	3 446	9 (0)	
constitutive		5	0 - 13
inducible		4	0 - 17
Co-trimoxazole	3 454	2 (0)	0 (0) - 11 (0)
Ciprofloxacin	3 422	5 (0)	0 (0) - 13 (0)
Rifampicin	3 398	1 (0)	0 (0) - 4 (0)
Gentamicin	3 446	7 (0)	0 (0) - 15 (0)
Linezolid	3 279	0 (0)	0 (0) - 0 (0)
Mupirocin	3 005	6 (1)	0 (0) - 16 (0)
Tigecycline	2 785	0 (0)	0 (0) - 2 (0)

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

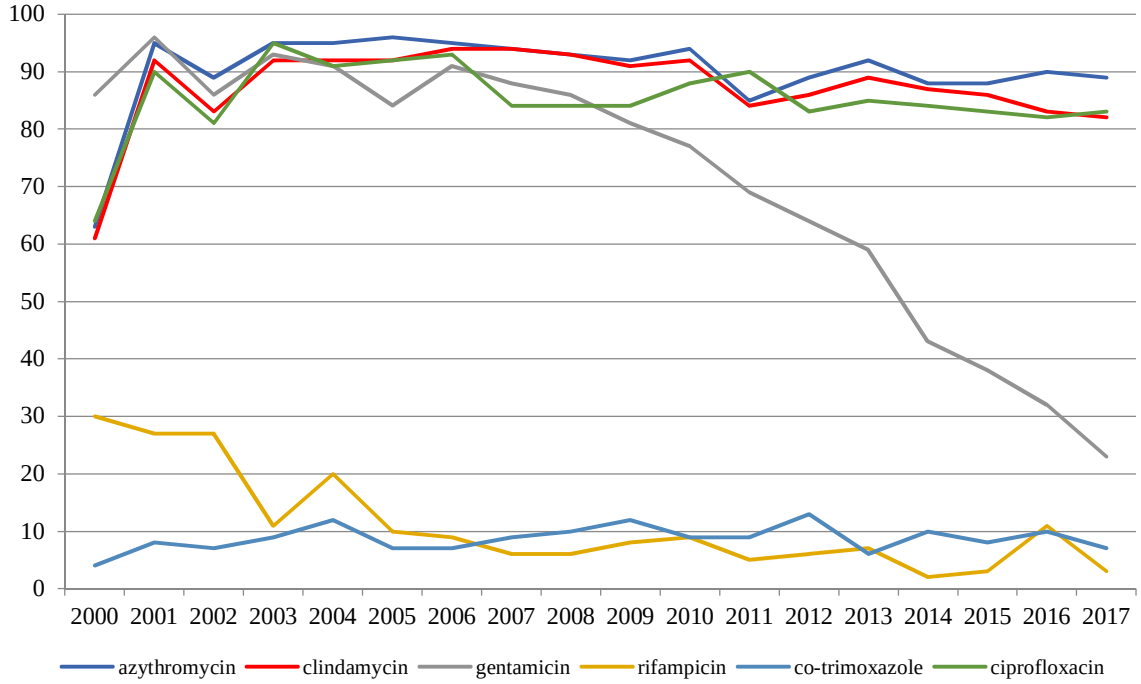


Staphylococcus aureus / MRSA

Methicillin resistant *Staphylococcus aureus* (MRSA) – stope / *rates*, 2000. - 2017.



neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2017.



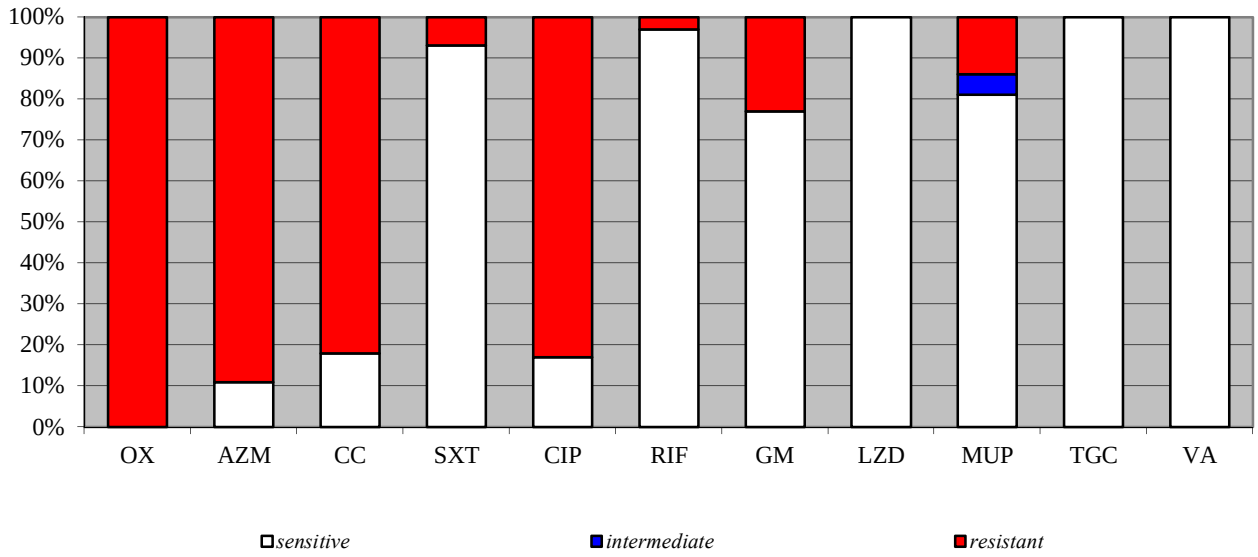
Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Staphylococcus aureus / MRSA

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the isolates from 37 centers in Croatia

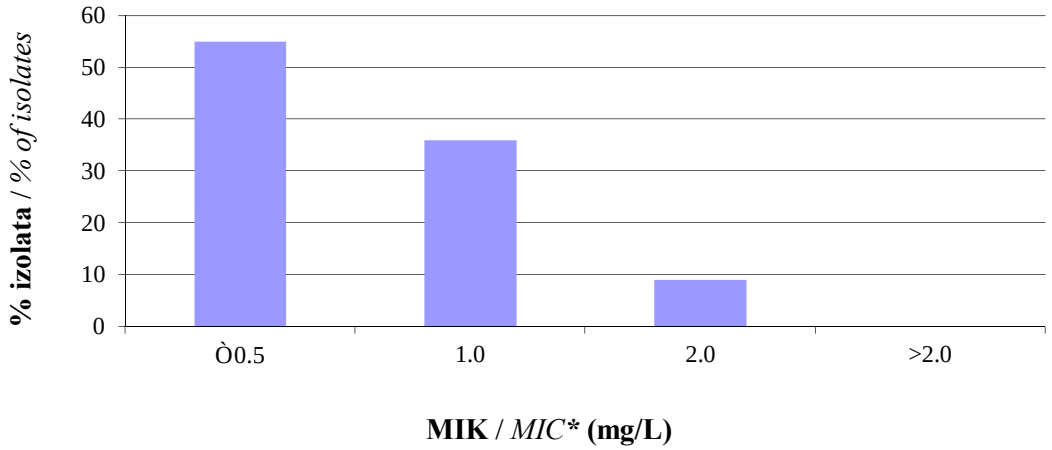
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Cefoxitin/ Methicillin	620	100 (0)	100 (0) - 100 (0)
Azithromycin	614	89 (0)	94 (0) - 100 (0)
Co-trimoxazole	617	7 (0)	0 (0) - 11 (6)
Clindamycin	613	82 (0)	83 (0) - 100 (0)
constitutive		50	29 - 78
inducible		32	6 - 67
Ciprofloxacin	612	83 (0)	77 (0) - 97 (0)
Rifampicin	618	3 (0)	0 (0) - 6 (0)
Gentamicin	619	23 (0)	2 (0) - 61 (0)
Linezolid	609	0 (0)	0 (0) - 0 (0)
Mupirocin	518	14 (5)	5 (0) - 28 (0)
Tigecycline	504	0 (0)	0 (0) - 0 (0)
Vankomicin	580	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, (580 MRSA izolata) /
Vancomycin MIC distribution, (580 MRSA isolates), 1.10. ï 31.12. 2017.



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

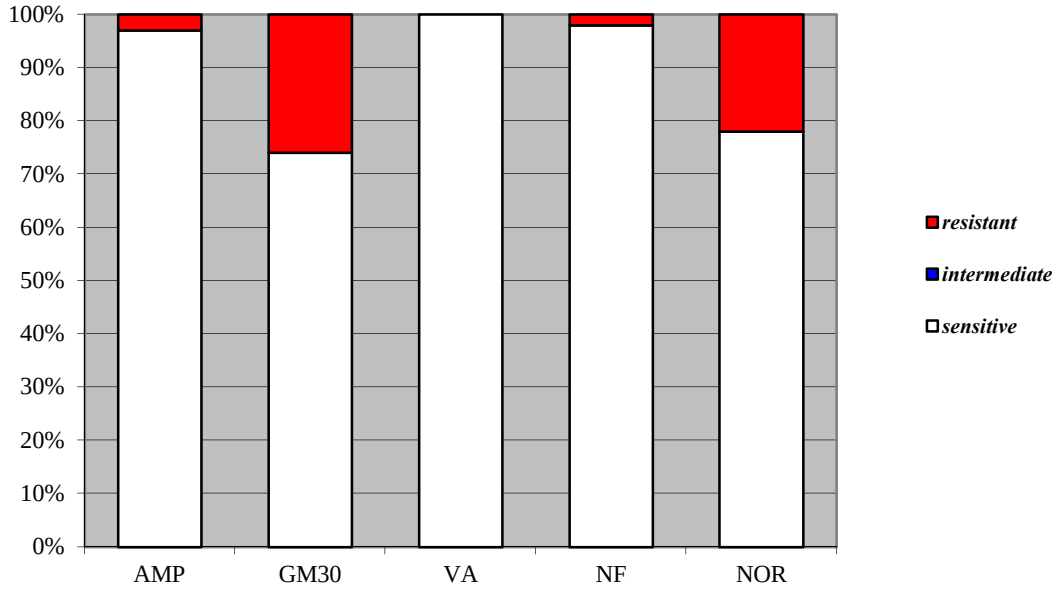
Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Committee for Antibiotic Resistance Surveillance

Enterococcus faecalis

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the isolates from 37 centers in Croatia

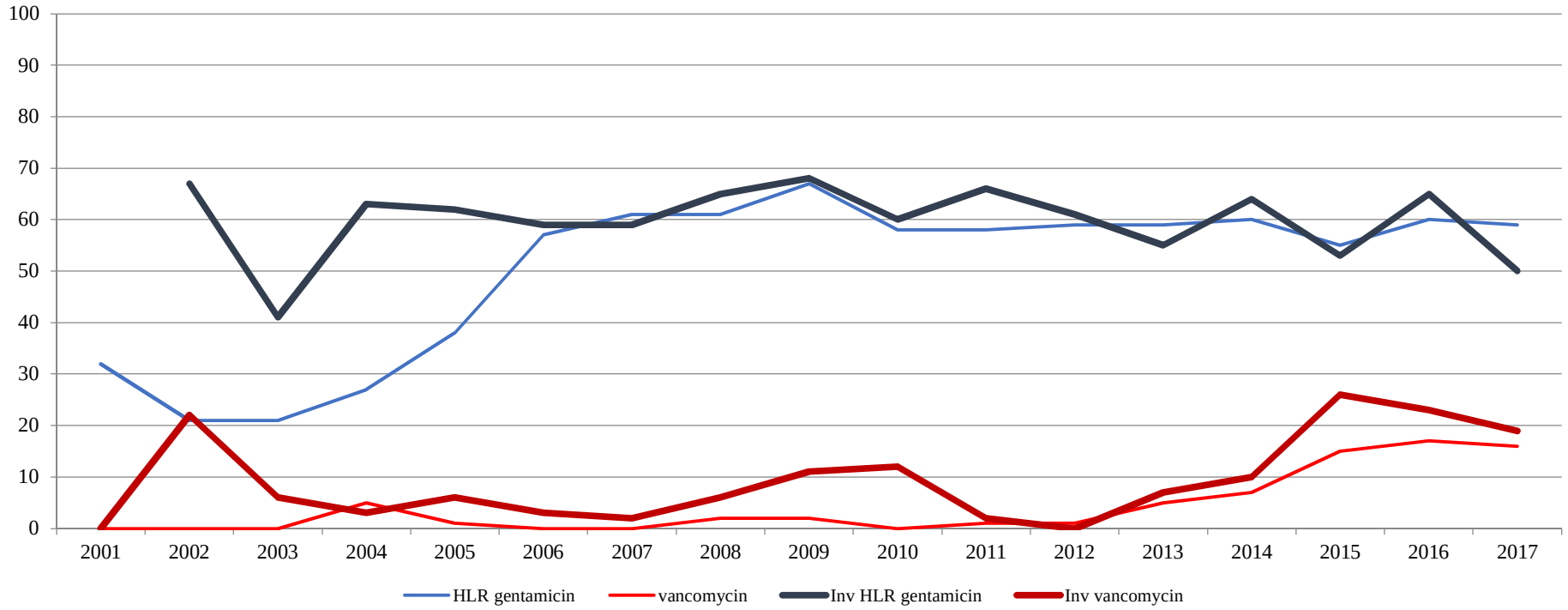
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	4 492	3 (0)	0 (0) - 50 (0)
Gentamicin	4 318	26 (0)	6 (0) - 46 (0)
Vancomycin	4 485	0 (0)	0 (0) -7 (0)
Nitrofurantoin	4 294	2 (0)	0 (0) - 15 (0)
Norfloxacin	4 296	22 (0)	1 (0) - 39 (0)

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



Enterococcus faecium

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2001. - 2017.



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

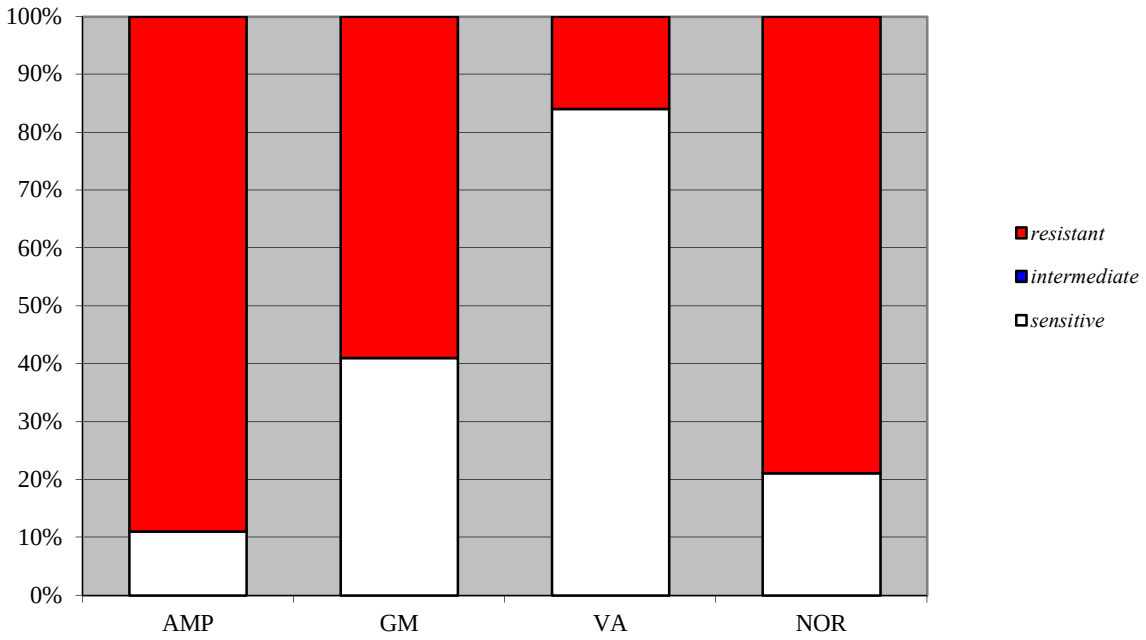
Akademija Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Enterococcus faecium

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the isolates from 37 centers in Croatia

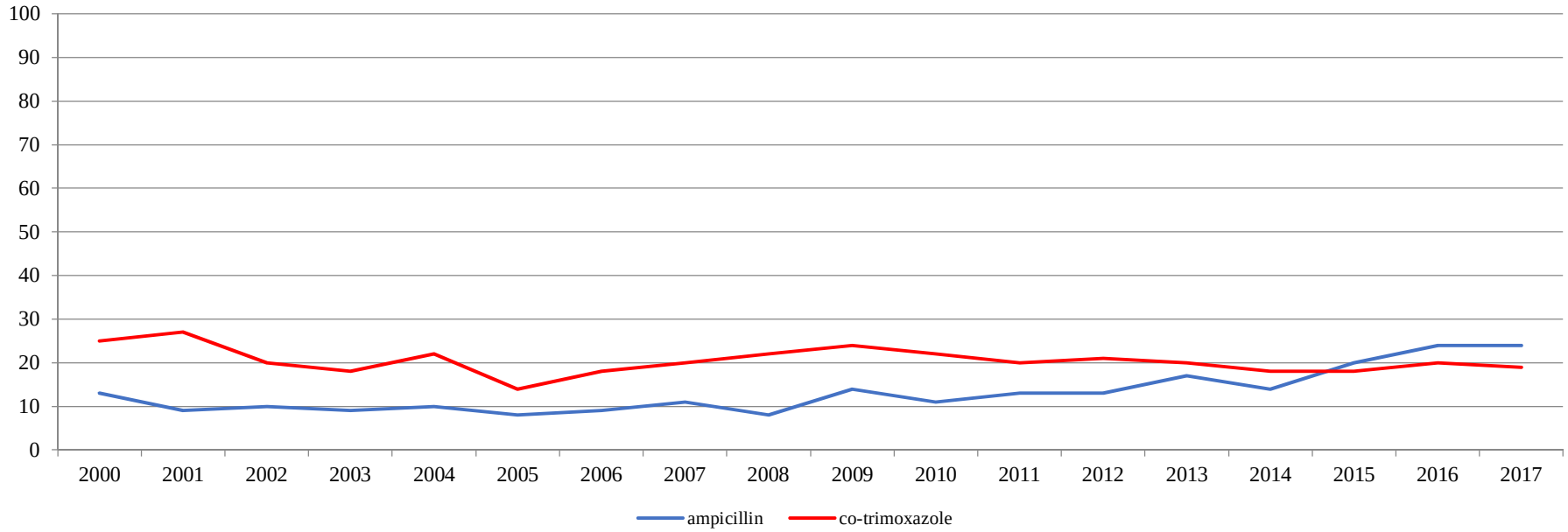
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	607	89 (0)	48 (0) - 100 (0)
Gentamicin	607	59 (0)	40 (0) - 89 (0)
Vancomycin	727	16 (0)	2 (0) - 71 (0)
Norfloxacin	599	75 (0)	13 (0) - 100 (0)

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



Haemophilus influenzae

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2017.



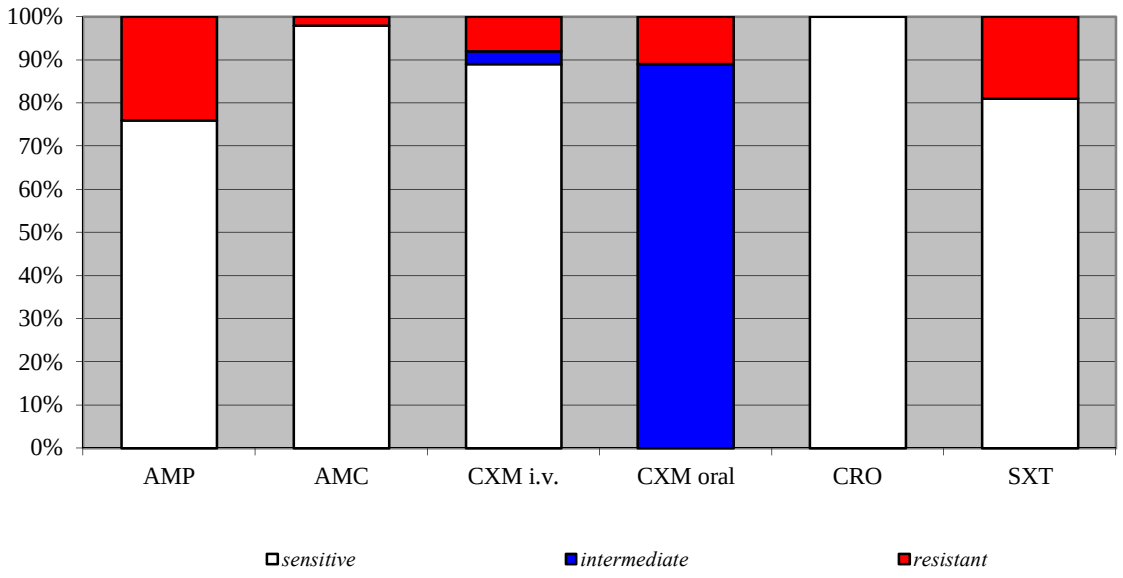
Akademija Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Haemophilus influenzae

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the isolates from 37 centers in Croatia

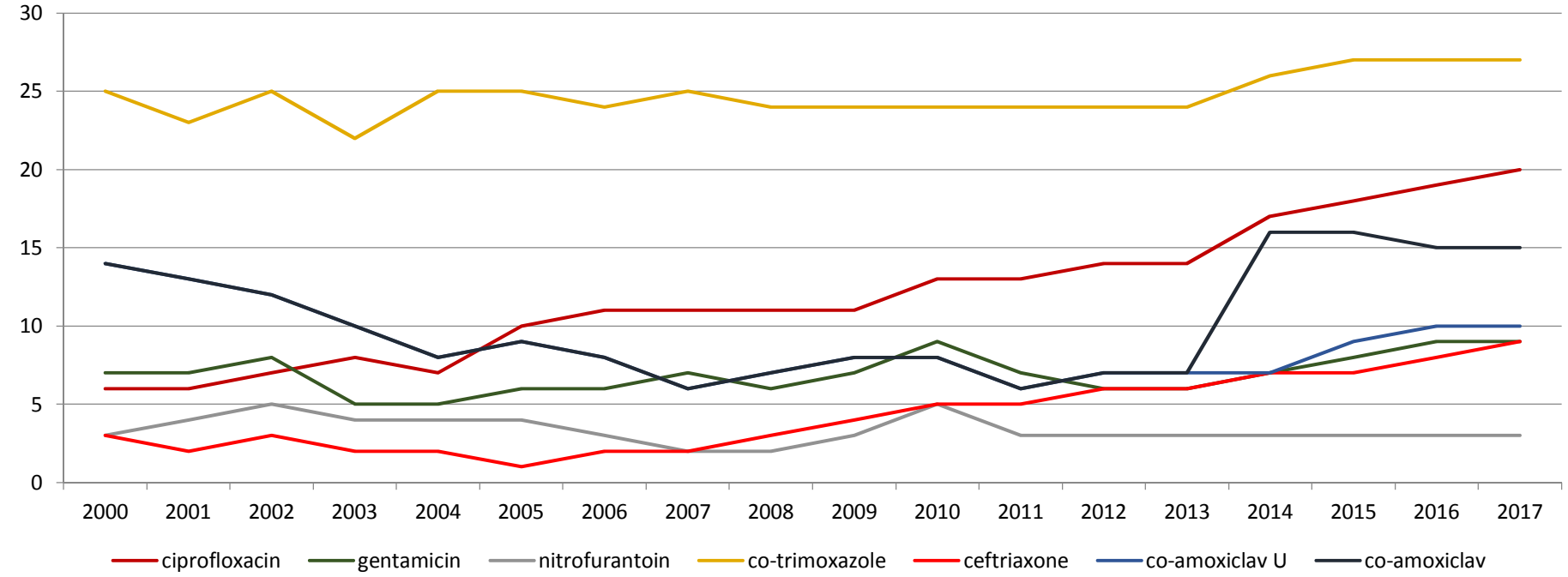
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	1 350	24 (0)	4 (0) - 84 (0)
Amoxicillin + clav. acid	1 354	1 (0)	0 (0) - 6 (0)
Cefuroxime i.v.	1 354	5 (2)	0 (0) - 26 (0)
Cefuroxime oral	1 354	7 (93)	0 (100) - 27 (73)
Ceftriaxone	1 255	0 (0)	0 (0) - 0 (0)
Co-trimoxazole	1 355	19 (0)	0 (0) - 40 (0)

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



Escherichia coli

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2017.



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

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

Escherichia coli

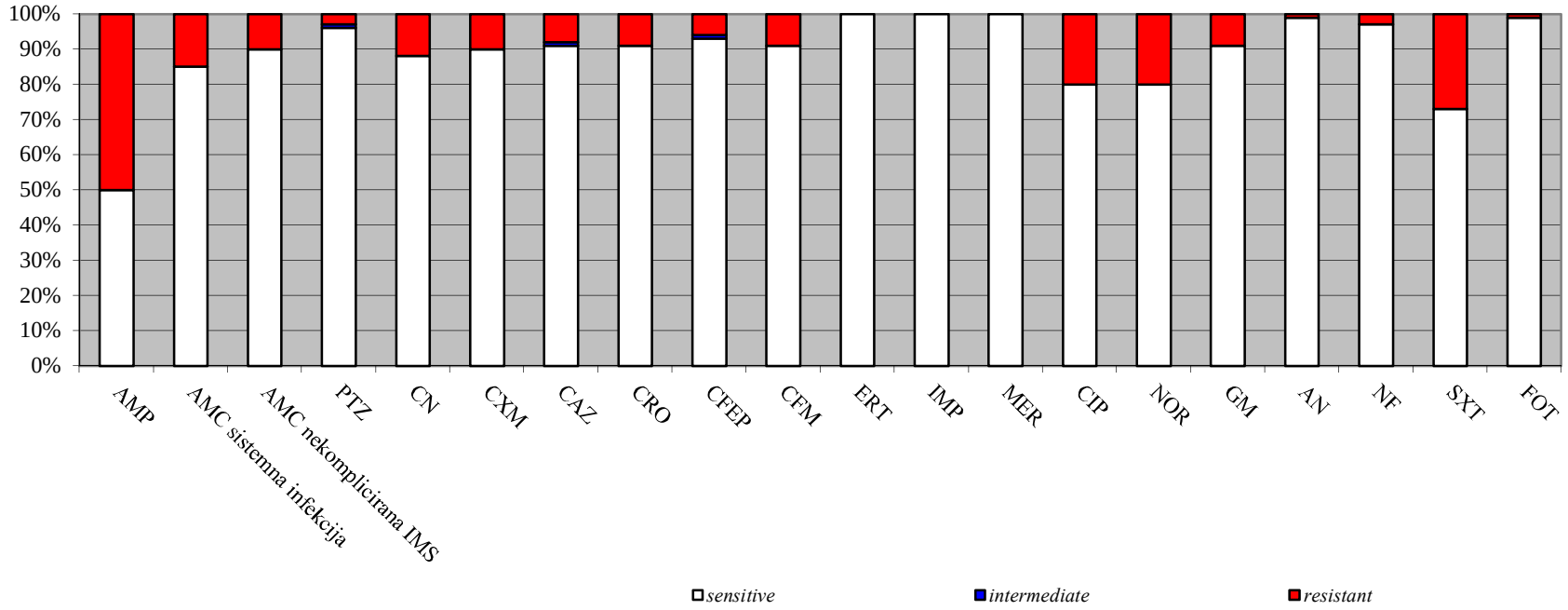
rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the isolates from 37 centers in Croatia

ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	18 065	50 (0)	22 (0) - 63 (0)
Amoxicillin + clav. acid sistemna infekcija	18 065	15 (0)	4 (0) - 43 (0)
Amoxicillin + clav. acid nekomplicirana IMS	18 054	10 (0)	2 (0) - 28 (0)
Piperacillin + tazobactam	17 981	3 (1)	0 (0) - 10 (0)
Cephalexin	18 037	12 (0)	6 (0) - 22 (0)
Cefuroxime	18 045	10 (0)	2 (0) - 22 (0)
Ceftazidime	18 051	8 (1)	2 (0) - 16 (0)
Ceftriaxone	18 049	9 (0)	2 (0) - 20 (0)
Cefepime	17 982	6 (1)	0 (0) - 18 (0)
Cefixime	17 847	9 (0)	4 (0) - 21 (0)
Ertapenem	17 518	0 (0)	0 (0) - 2 (1)
Imipenem	17 980	0 (0)	0 (0) - 0 (0)
Meropenem	17 980	0 (0)	0 (0) - 1 (0)
Ciprofloxacin	18 060	20 (0)	9 (0) - 35 (0)
Norfloxacin	18 030	20 (0)	11 (1) - 35 (0)
Gentamicin	18 043	9 (0)	3 (0) - 20 (0)
Amikacin	17 820	1 (0)	0 (0) - 5 (0)
Nitrofurantoin	18 018	3 (0)	0 (0) - 7 (0)
Co-trimoxazole	18 060	27 (0)	15 (0) - 36 (0)
Fosfomycin	16 891	1 (0)	0 (0) ï 5 (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

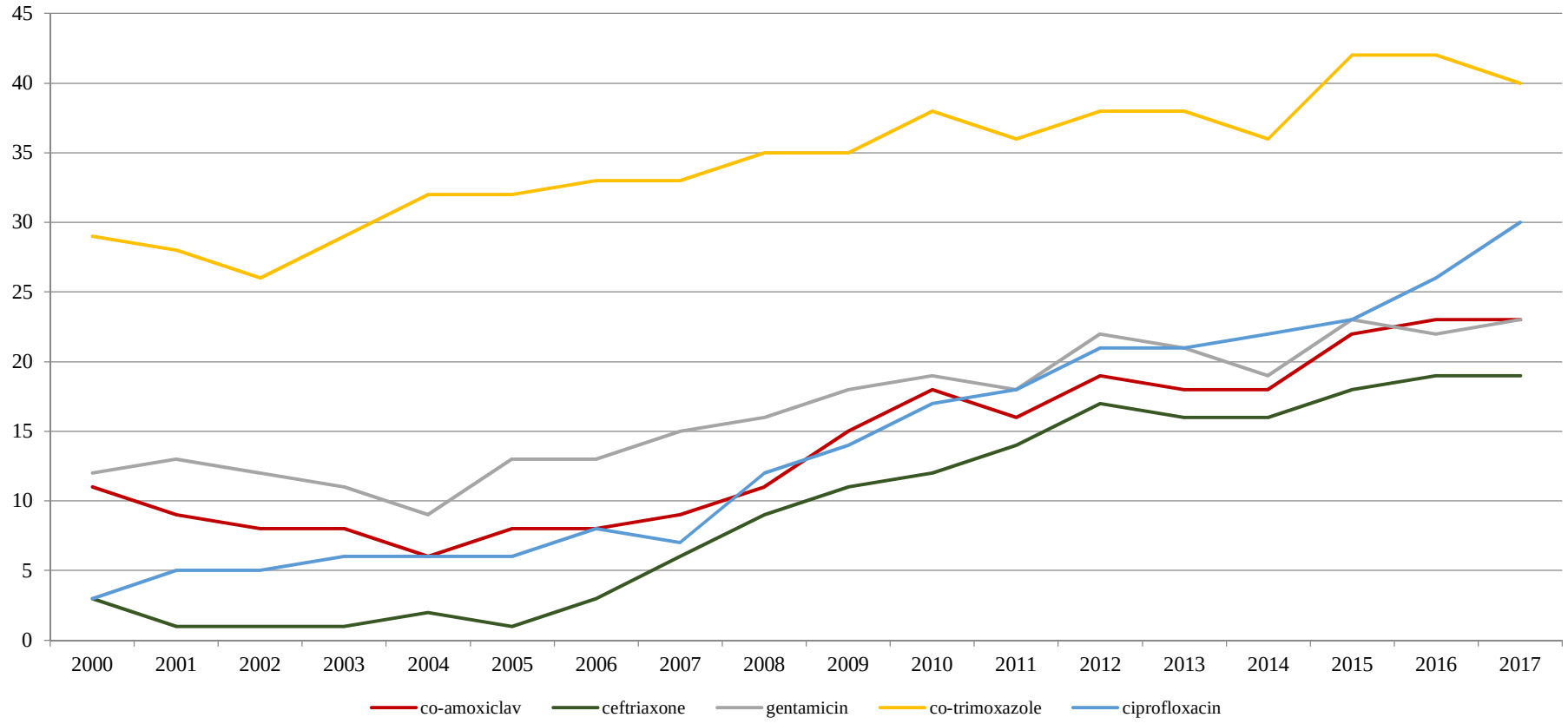
Escherichia coli

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. ï 31.12.2017.



Proteus mirabilis

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. ï 2017.



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

Proteus mirabilis

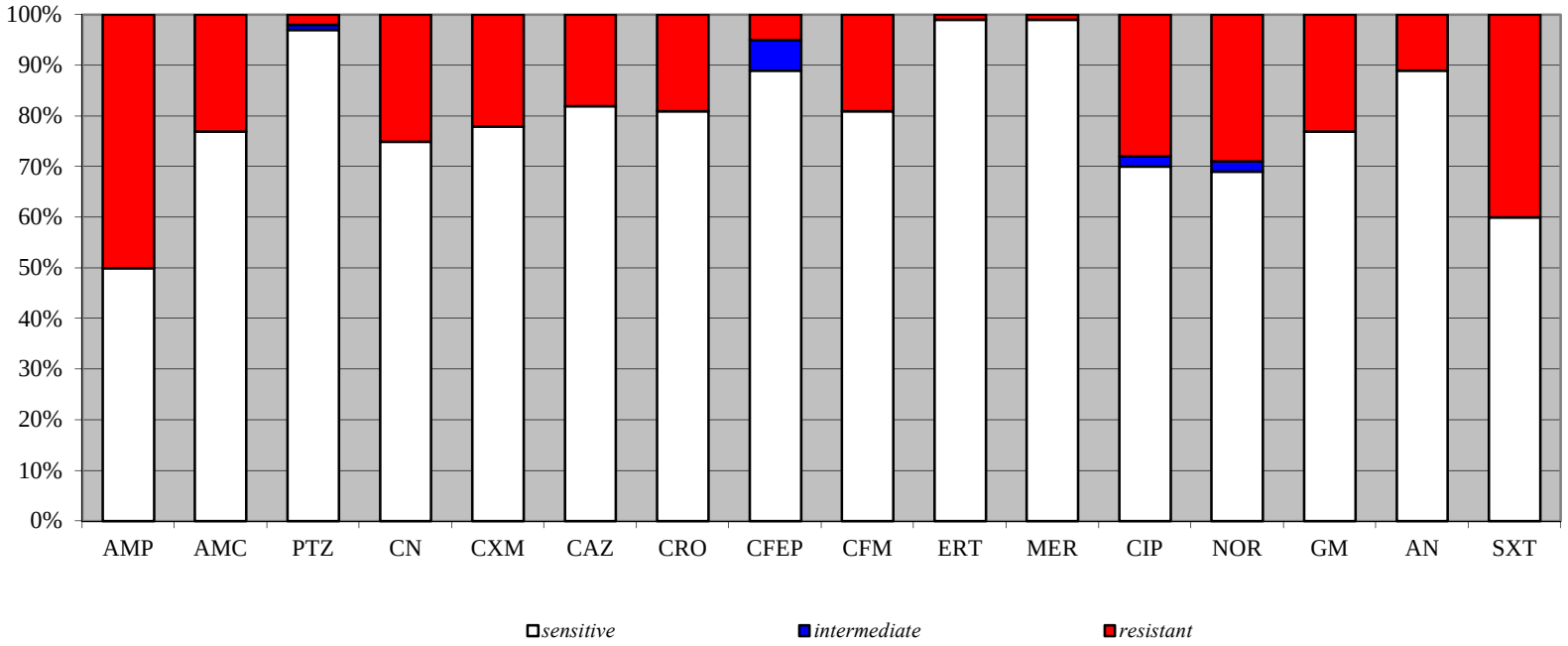
rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the *isolates from 37 centers in Croatia*

ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	3 720	50 (0)	21 (0) - 100 (0)
Amoxicillin + clav. acid	3 720	23 (0)	4 (0) - 59 (0)
Piperacillin + tazobactam	3 700	2 (1)	0 (0) - 7 (7)
Cephalexin	3 715	25 (0)	4 (0) - 43 (0)
Cefuroxime	3 720	22 (0)	3 (0) - 42 (0)
Ceftazidime	3 716	18 (0)	1 (0) - 36 (1)
Ceftriaxone	3 716	19 (0)	2 (0) ï 36 (1)
Cefepime	3 699	5 (6)	0 (0) - 15 (15)
Cefixime	3 606	19 (0)	1 (0) - 36 (0)
Ertapenem	3 699	1 (0)	0 (0) - 23 (0)
Meropenem	3 699	1 (0)	0 (0) - 23 (0)
Ciprofloxacin	3 719	28 (2)	2 (24) - 49 (5)
Norfloxacin	3 712	29 (2)	2 (24) - 60 (2)
Gentamicin	3 719	23 (0)	2 (0) - 44 (1)
Amikacin	3 671	11 (0)	0 (0) - 30 (1)
Co-trimoxazole	3 712	40 (0)	17 (1) - 60 (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

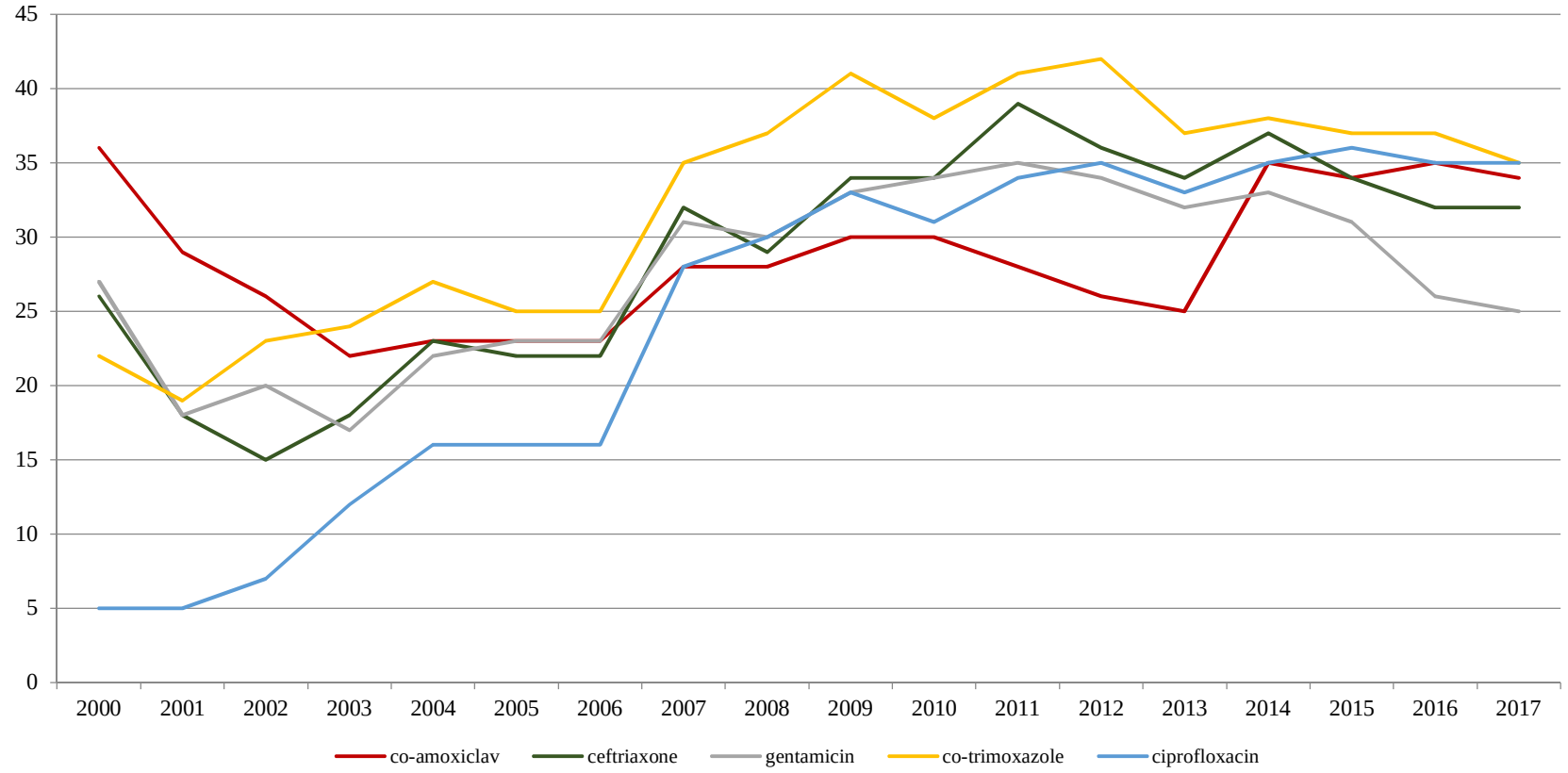
Proteus mirabilis

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia,* 1.10. ï 31.12.2017.



Klebsiella pneumoniae

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2017.



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

Klebsiella pneumoniae

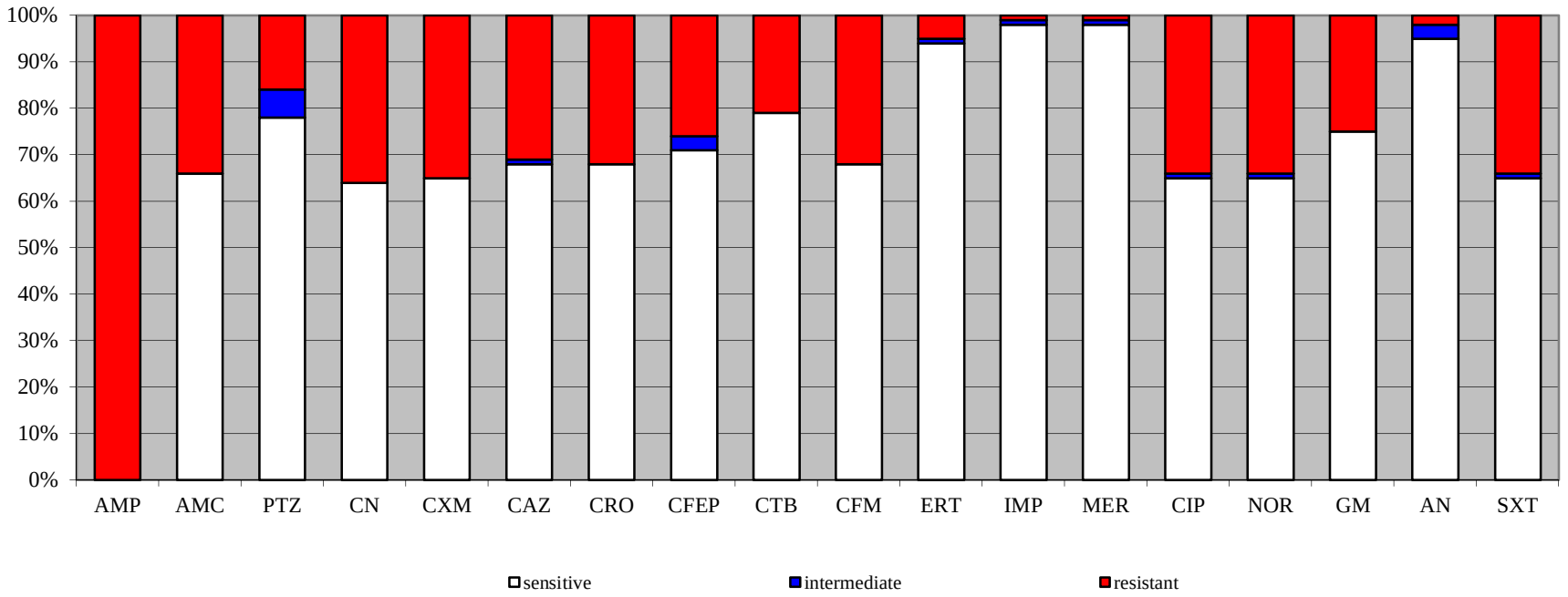
rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the isolates from 37 centers in Croatia

ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	4 541	100 (0)	100 (0) - 100 (0)
Amoxicillin + clav. acid	4 541	34 (0)	11 (0) - 76 (0)
Piperacillin + tazobactam	4 514	16 (6)	2 (0) - 37 (8)
Cephalexin	4 517	37 (0)	13 (0) - 75 (0)
Cefuroxime	4 541	35 (0)	11 (0) - 76 (0)
Ceftazidime	4 537	31 (1)	10 (0) - 57 (0)
Ceftriaxone	4 537	32 (0)	9 (0) - 74 (0)
Cefepime	4 512	26 (3)	4 (0) - 49 (4)
Cefixime	4 369	32 (0)	10 (0) - 68 (0)
Ertapenem	4 511	5 (1)	0 (0) - 28 (3)
Imipenem	4 511	1 (1)	0 (0) - 9 (1)
Meropenem	4 512	1 (1)	0 (0) - 7 (1)
Ciprofloxacin	4 539	34 (1)	9 (0) - 61 (2)
Norfloxacin	4 514	34 (1)	9 (0) - 61 (2)
Gentamicin	4 539	25 (0)	8 (0) - 63 (0)
Amikacin	4 471	2 (3)	0 (0) - 10 (10)
Co-trimoxazole	4 524	34 (1)	17 (0) - 62 (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

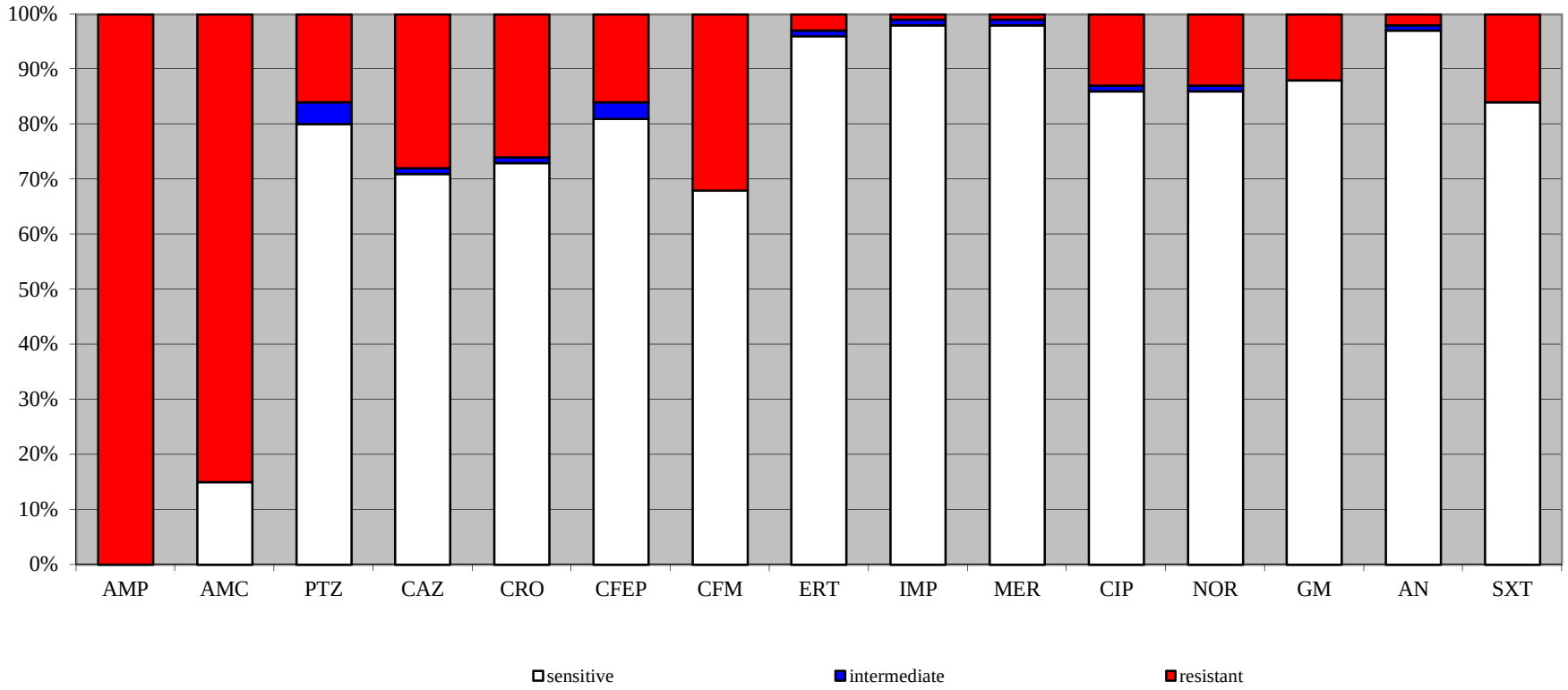
Klebsiella pneumoniae

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. ï 31.12.2017.



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

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. ï 31.12.2017.



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

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

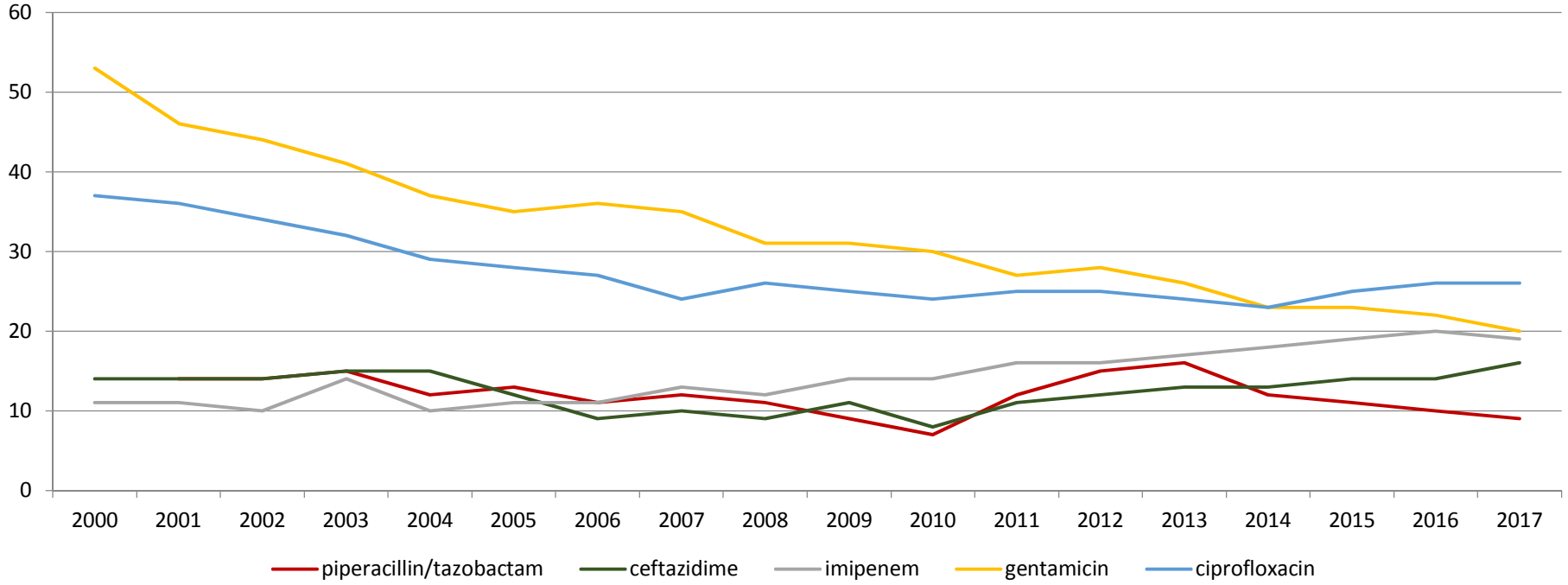
rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the isolates from 37 centers in Croatia

ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Ampicillin	3 117	100 (0)	79 (0) - 100 (0)
Amoxicillin + clav. acid	3 116	85 (0)	45 (0) - 100 (0)
Piperacillin + tazobactam	3 087	16 (3)	0 (0) - 72 (0)
Ceftazidime	3 116	28 (1)	0 (0) - 100 (0)
Ceftriaxone	3 117	26 (1)	0 (0) - 72 (0)
Cefepime	3 089	16 (3)	0 (0) - 72 (0)
Cefixime	2 947	32 (0)	2 (0) - 72 (0)
Ertapenem	3 087	3 (1)	0 (0) - 11 (1)
Imipenem	3 088	1 (1)	0 (0) - 4 (0)
Meropenem	3 088	1 (1)	0 (0) - 4 (0)
Ciprofloxacin	3 117	13 (1)	0 (0) - 29 (2)
Norfloxacin	3 088	13 (1)	0 (0) ï 29 (2)
Gentamicin	3 117	12 (0)	0 (0) - 34 (0)
Amikacin	3 062	2 (1)	0 (0) - 21 (2)
Co-trimoxazole	2 978	16 (0)	5 (1) - 32 (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. - 2017.



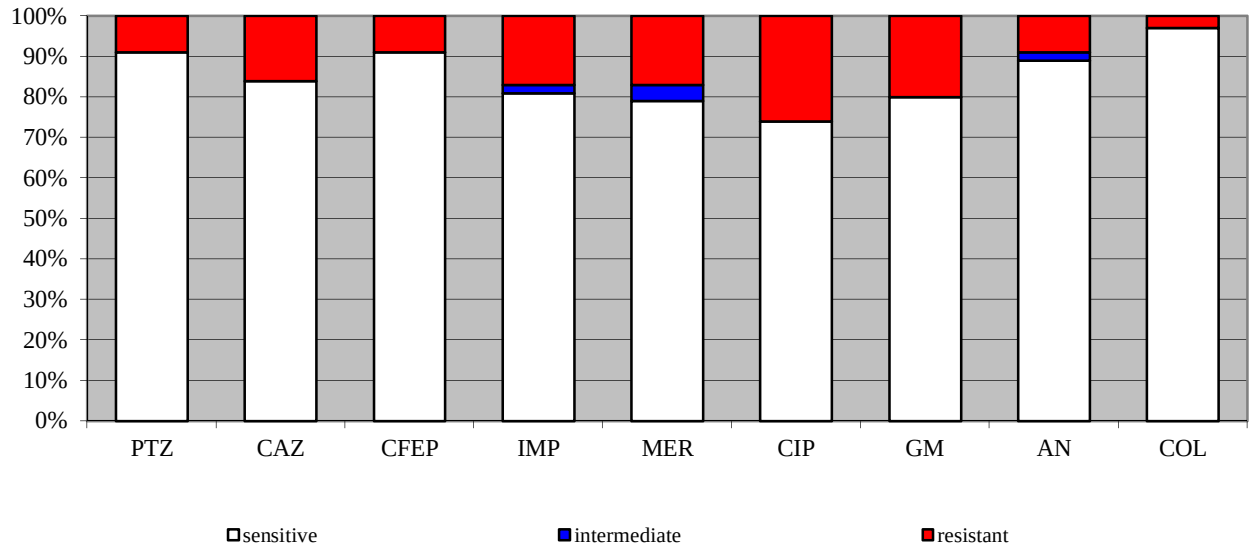
Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Pseudomonas aeruginosa

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the isolates from 37 centers in Croatia

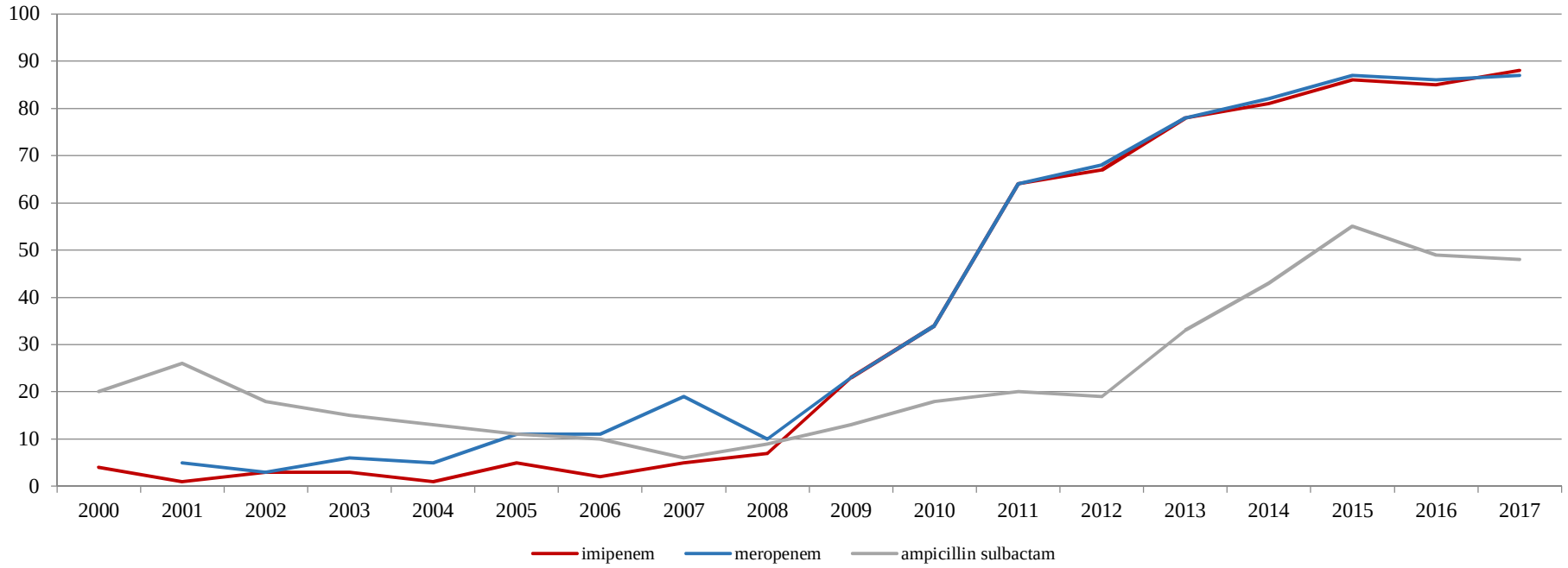
ANTIBIOTIK / *ANTIBIOTIC*	Broj izolata / *No. of isolates*	% rezistentnih (% intermedijarnih) izolata / *% of resistant (% of intermediate) isolates*	Raspon lokalnih rezultata* / *Range of local results**
Piperacilin + tazobaktam	3 726	9 (0)	1 (0) - 26 (0)
Ceftazidim	3 725	16 (0)	3 (0) - 45 (0)
Cefepim	3 727	9 (0)	1 (0) - 28 (0)
Imipenem	3 724	17 (2)	1 (0) - 38 (0)
Meropenem	3 723	17 (4)	1 (0) - 41 (6)
Ciprofloxacin	3 725	26 (0)	8 (0) - 50 (6)
Gentamicin	3 726	20 (0)	6 (0) - 48 (0)
Amikacin	3 682	9 (2)	0 (0) - 18 (3)
Colistin	677	3 (0)	0 (0) - 13 (0)

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



Acinetobacter baumannii

neosjetljivost (R+I) na antibiotike u RH / *non-susceptibility (R+I) to antibiotics in Croatia*, 2000. - 2017.



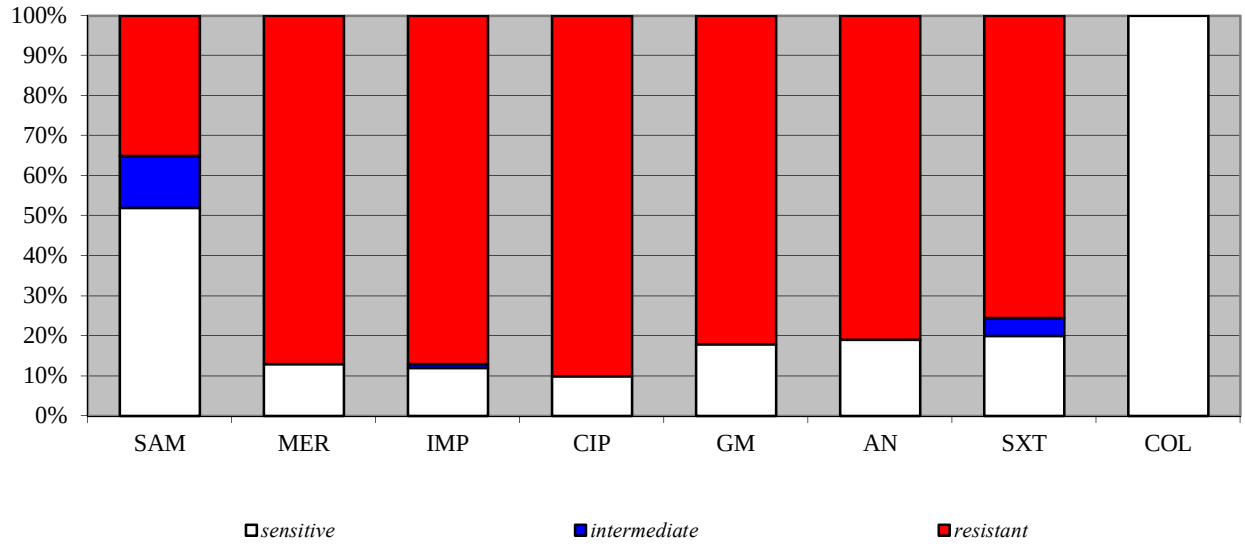
Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Acinetobacter baumannii

rezistencija na antibiotike u razdoblju od 1.10. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12. 2017,
summary results for the isolates from 37 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 + sulbactam	1 563	35 (13)	0 (0) - 93 (0)
Meropenem	1 566	87 (0)	63 (0) - 98 (0)
Imipenem	1 566	87 (1)	63 (0) - 98 (0)
Ciprofloxacin	1 566	90 (0)	63 (0) - 100 (0)
Gentamicin	1 567	82 (0)	45 (0) - 98 (0)
Amikacin	1 564	81 (0)	57 (0) - 95 (0)
Co-trimaxazole	1 470	68 (4)	43 (0) - 94 (0)
Colistin	1 249	0 (0)	0 (0) - 4 (0)

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



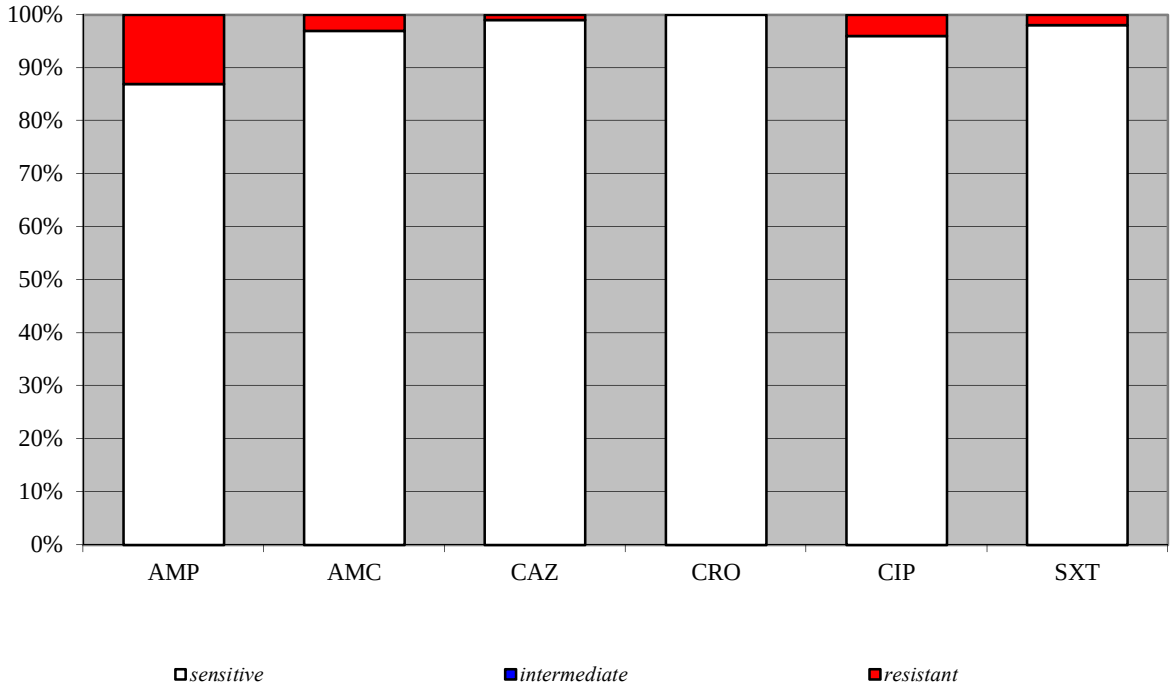
Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Salmonella spp.

rezistencija na antibiotike u razdoblju od 01.01. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 01.01. - 31.12. 2017,
summary results for the isolates from 37 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	1 876	13 (0)	3 (0) - 27 (0)
Amoxicillin + clav. acid	1 880	3 (0)	0 (0) - 11 (0)
Ceftazidim	1 880	1 (0)	0 (0) - 5 (0)
Ceftriaxone	1 880	0 (0)	0 (0) - 5 (0)
Ciprofloxacin	1 696	4 (0)	0 (0) - 10 (0)
Co-trimoxazole	1 880	2 (0)	0 (0) - 6 (0)

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



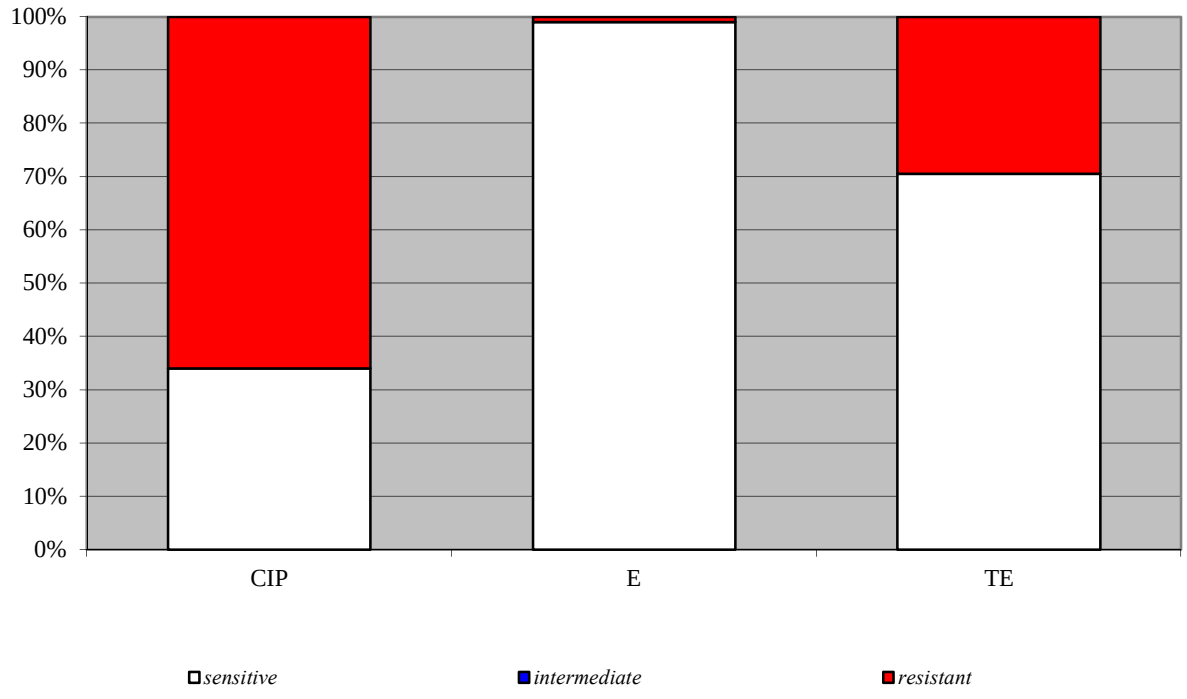
Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Campylobacter jejuni

rezistencija na antibiotike u razdoblju od 1.01.- 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.01. - 31.12. 2017,
summary results for the isolates from 37 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**
Ciprofloxacin	2 550	66 (0)	55 (0) - 76 (0)
Erythromicin	2 552	1 (0)	0 (0) - 4 (0)
Tetracycline	2 552	30 (0)	18 (0) - 42 (0)

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



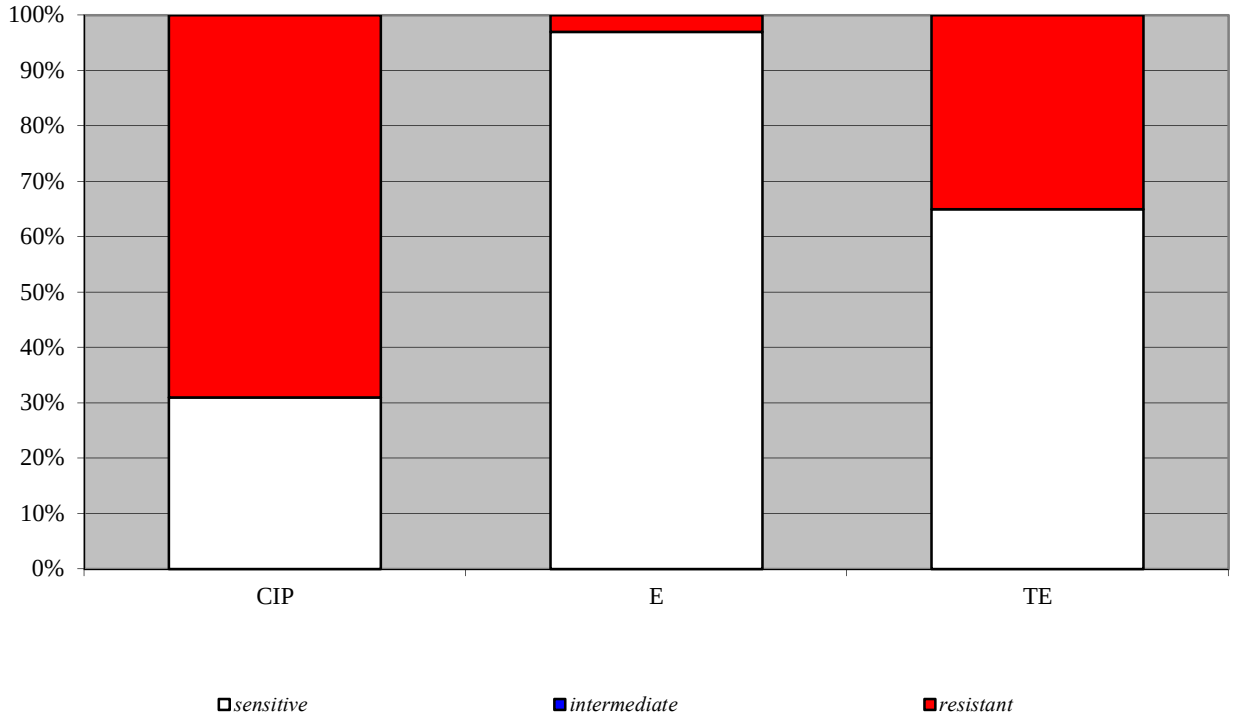
Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Campylobacter coli

rezistencija na antibiotike u razdoblju od 1.01. - 31.12. 2017.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.01. - 31.12. 2017,
summary results for the isolates from 37 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*
Ciprofloxacin	622	69 (0)	53 (0) - 74 (0)
Erythromicin	622	3 (0)	0 (0) - 10 (0)
Tetracycline	622	35 (0)	19 (0) - 45 (0)

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



Shigella spp.

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia,* 1.01 ï 31.12.2017.

***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*	2	0	**100**	2	0	**50**	2	0	**0**	2	0	**0**	2	0	**100**	2	0	**100**
Shigella flexneri*	5	0	**100**	5	0	**60**	3	0	**0**	5	0	**0**	5	0	**20**	5	0	**20**
UKUPNO* / *TOTAL**	7	0	**100**	7	0	**57**	7	0	**0**	7	0	**0**	7	0	**43**	7	0	**43**

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

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

Anaerobne bakterije / *Anaerobes*

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia,* 1.01 - 31.12.2017.

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*	499	1	**8**	459	0	**1**	244	1	**0**	385	0	**0**	494	0	**58**	508	0	**16**
Gram negativni anaerobi / *Gram-negative anaerobes*	401	0	**76**	368	1	**4**	299	3	**2**	351	0	**3**	401	0	**13**	362	0	**27**
UKUPNO / *TOTAL*	900	1	**38**	827	1	**2**	543	2	**1**	736	0	**2**	895	0	**38**	870	0	**21**

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

Candida spp.

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia,* 1.01. ï 31.12.2017.

	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*

POGLAVLJE / CHAPTER **2.**

OSJETLJIVOST *M. TUBERCULOSIS* U HRVATSKOJ U 2017. GODINI

SENSITIVITY OF M. TUBERCULOSIS IN CROATIA, 2017

Ljiljana Žmak
Mihaela Obrovac
Vera Katalinić-Janković

Hrvatski zavod za javno zdravstvo
Služba za mikrobiologiju
Odjel za tuberkulozu
Croatian Institute of Public Health
Microbiology Service
Department for Tuberculosis

HRVATSKI ZAVOD ZA JAVNO ZDRAVSTVO
Croatian Institute of Public Health
Rockefellerova 7, 10 000 Zagreb
Sluġba za mikrobiologiju
Odjel za tuberkulozu
Microbiology Service
Department for Tuberculosis

Dr. sc. Ljiljana Ġmak
Dr. sc. Mihaela Obrovac
e-mail: ljiljana.zmak@hzjz.hr
Tel.: 01/48 63 360

Mikobakterije izolirane u Hrvatskoj u 2017. godini

Podaci Registra za tuberkulozu Sluġbe za epidemiologiju Hrvatskog zavoda za javno zdravstvo ukazuju na ponovni trend sniġenja broja oboljelih od tuberkuloze. U 2017. godini prijavljeno je 369 novooboljelih, ġto daje stopu uļ estalosti od 8,8/100.000, dok je u 2016. godini bilo gotovo 100 oboljelih viġe, 464 (incidencija 11/ 100 000 stanovnika). Razlike u pobolu po ġupanijama su u rasponu od 4,9 ï 19,3 na 100.000 stanovnika. U 2017., kao niti u prethodnih deset godina, nije zabiljeġen niti jedan sluļ aj tuberkuloznog meningitisa u dobi izmeĽu 0 i 19 godina.

Za analizu podataka o bakteriološkoj dijagnostici tuberkuloze (TBC) u Hrvatskoj u 2017. godini koristio se ĂUpitnik o radu TBC laboratorija u 2017. godiniñ. Mreġa TBC laboratorija je ostala nepromijenjena (15 laboratorija). Ukupno je pregledano 36.948 kliniļ kih uzoraka na TBC ġto je pad od 4,3% u odnosu na broj uzoraka iz 2016. godine. Iako je preporuļ eni minimalni godiġnji broj uzoraka za obradu na mikobakterije 2000, ļ ak 5 laboratorija u 2017. obradilo je manje od 1000 uzoraka, a dodatnih 5 manje od 2000. Nadalje, svi laboratoriji iz naġe mreġe joġ uvijek ne koriste tekuĺ e podloge za sve uzorke nego samo za paucibacilarne ili izvanpluĺ ne uzorke. U 4,3% uzoraka kultivacijom su otkrivene mikobakterije, a raspon pozitivnih kultura meĽu laboratorijima se kretao od 0,4 do 12,5%. Ukupno je izolirano 1.596 sojeva mikobakterija (Tablica 1).

Tijekom 2017. godine genotipizirana su 336 izolata *M. tuberculosis* iz cijele Hrvatske. Genotipizacijom je jedan od sojeva identificiran kao *M. pinnipedii*, ļ lan *M. tuberculosis* kompleksa koji uzrokuje tuberkulozu u morskih lavova, tuljana te ġivotinja koje dolaze u kontakt s tim vrstama. Ovo je prva izolacija *M. pinnipedii* iz humanog uzorka. U skladu s oļ ekivanim, *M. tuberculosis* je najļ eġ́ e izoliran iz pluĺ nih uzoraka, a meĽu 41 (12,2%) izvanpluĺ nih bakterioloġki dokazanih sluļ ajeva TBC najļ eġ́ a je bila TBC pleure (N=15), limfoglandularna TBC (N=11) i TBC srediġnjeg ġivļ anog sustava (N=3).

MeĽutim, iako je *M. tuberculosis* i dalje dominantna mikobakterija s 1.246 (78,1%) izolata, udio netuberkuloznih mikobakterija (NTM) sve je veĺ i te ove godine iznosi 21,9% (Tablica 1).

Tijekom 2017. godine iz humanih kliniļ kih materijala nije izoliran *M. bovis*, a zabiljeġena su ļ etiri izolata *M. bovis* ï BCG soja. Nastavlja se trend visokog broja izolata NTM i broja moguĺ ih bolesnika s mikobakteriozom, osobito uzrokovanom spororastuĺ im uvjetno patogenim mikobakterijama (Tablica 2.). Osobe s izolatima NTM se biljeġe od 1982. godine, a kod viġekratnih izolacija se utvrĽuju mikrobioloġki kriteriji za mikobakterioze i popunjava obrazac za NTM. U 2017. godini je otkriveno 45 osoba sa zadovoljenim mikrobiološkim kriterijima za dijagnozu mikobakterioze (dva i viġe izolata). Kod 11 bolesnika izoliran je *M. xenopi*, slijede ga *M. avium* koji je izoliran kod pet bolesnika te izolati *M. intracellulare* i *M. mucogenicum* kod po ļ etiri bolesnika. Kod devet bolesnika naĽena je brzorastuĺ a mikobakterija *M. chelonae*, a *M. fortuitum* kod pet bolesnika. U 2017. godini od uvjetno patogenih spororastuĺ ih mikobakterija najviġe je izoliran *M. xenopi* (63 izolata), *M. intracellulare* (43 izolata) te *M. avium* (24 izolata). Od brzorastuĺ ih mikobakterije najveĺ i broj izolata odnosio se na *M. fortuitum* (N=41), a slijede ga *M. chelonae* sa 37 izolata te *M. mucogenicum* sa 14 izolata. *M. gordonae* kao saprofitna mikobakterija je identificiran u 24,3% izolata NTM. Najļ eġ́ e se radi o kontaminaciji uzoraka, sluļ ajnim nalazima i prolaznim kolonizacijama.

Nastavljen je izrazito povoljan trend broja rezistentnih sojeva *M. tuberculosis*, a time i bolesnika s rezistentnom tuberkulozom. Od 1.190 testiranih sojeva *M. tuberculosis* samo je 56 (4,7%) bilo rezistentno na prvu liniju antituberkulotika, a otkriveni su kod 13 bolesnika s rezistentnom tuberkulozom (Tablica 3). MeĽu bolesnicima s rezistentnim oblikom tuberkuloze, njih 11 (85%) je imalo monorezistentni oblik, dok je kod dva bolesnika otkrivena tuberkuloza rezistentna na dva antituberkulotika iz prve linije (Tablica 3). Monorezistencija na izonijazid je utvrĽena kod ļetiri bolesnika, a monorezistencija na streptomicin kod pet bolesnika. U 2017. godini nismo izolirali niti jedan multirezistentan soj.

Mycobacteria isolated in Croatia in 2017

According to the data obtained from the Epidemiology Service at the Croatian Institute of Public Health, there is again a decreasing trend in TB incidence. In 2017 there were 369 new TB patients giving an incidence of 8.8/100.000 inhabitants, while in the previous year there were almost 100 patients more, 464 (incidence 11/100.000). The difference in morbidity between different counties was 4.9-19.3/100.000 inhabitants. In 2017, 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 2017ò was used. A total of 36.948 clinical samples were analyzed for tuberculosis, which is 4.3% less than in 2016. 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 ten 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 4.3% of samples, cultivation detected mycobacteria and the range of positivity of cultivation in different laboratories was from 0.4 to 12.5%. A total of 1.596 mycobacterial isolates were cultivated (Table 1.)

During 2017, a total of 336 *M. tuberculosis* isolates were genotyped. One of genotyped strains was identified as *M. pinnipedii*, a *M. tuberculosis* complex member that causes TB in sea lions, seals and animals that are in close contact with these species. This is the first isolation of *M. pinnipedii* from a human sample. As expected, *M. tuberculosis* was most frequently isolated from pulmonary samples. Among bacteriologically confirmed extrapulmonary TB (N=41; 12.2%), the most frequent forms were pleural TB (N=15), lymphoglandular TB (N=11), and TB of the central nervous system (N=3).

Although *M. tuberculosis* remained the predominant mycobacterium with 1,246 (78.1%) isolates, the number of nontuberculous mycobacteria (NTM) is increasing, accounting for 21.9% of all isolates in 2017 (Table 1). There were no *M. bovis* strains isolated from human clinical samples, while there were four *M. bovis* - BCG strains isolated. 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 2017, a total of 45 cases that fulfilled the microbiological criteria for mycobacteriosis (two or more isolates) were documented. In 11 patients, *M. xenopi* was isolated, *M. avium* was isolated in five patients, while *M. intracellulare* and *M. mucigenicum* were isolated in four patients each. In nine patients mycobacteriosis was caused by the rapidly growing NTM *M. chelonae*, whereas *M. fortuitum* was isolated in five patients. *M. gordonae*, a saprophytic mycobacterium, was identified in 24.3% 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 2017 prevailed isolates of *M. xenopi* (N=63), *M. intracellulare* (N=43), and *M. avium* (N=24), while in the rapidly growing group the most commonly isolated species were *M. fortuitum* (N=41) and *M. chelonae* (N=37) (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 1,190 tested *M. tuberculosis* strains, only 56 (4.7%) were resistant to the first line antituberculotics, isolated in 13 patients with resistant TB (Table 3). Among patients with resistant TB, 11 patients (85%) had monoresistant strains, while two patients were infected with *M. tuberculosis* isolates resistant to two or more first-line antituberculotics. Monoresistance to isoniazid was established in four patients and monoresistance to streptomycin in five patients. In 2017, there were no multiresistant strains isolated.

Tablica /*Table* **1.**
Mikobakterije izolirane u Hrvatskoj, 2007. – 2017. /
Mycobacteria strains isolated in Croatia, 2007-2017

Godina	**Ukupno mikobakterija**	***M. tuberculosis***		***M. bovis***		**Netuberkulozne mikobakterije**	
		Broj	**%**	***M. bovis***	**BCG soj**	**Broj**	**%**
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
2017.	1596	1246	78,1	-	4	350	21,9

Tablica / *Table* **2.**
Netuberkulozne mikobakterije (NTM) izolirane u Hrvatskoj u 2017. /
Nontuberculous mycobacteria (NTM) isolated in Croatia in 2017

	Vrsta	Broj	%
Uvjetno patogene mikobakterije	*M. xenopi*	63	18
	M. avium	24	6,9
	M. intracellulare	43	12,3
	M. kansasii	1	0,3
	M. lentiflavum	3	0,9
	M. intermedium	4	1,1
	M. scrofulaceum	1	0,3
	M. fortuitum	41	11,7
	M. chelonae	37	10,6
	M. abscessus	9	2,5
	M. mucogenicum	14	4
	M. celatum	1	0,3
	M. szulgai	1	0,3
Saprofitne mikobakterije	*M. gordonae*	85	24,3
	M. neoaurum	1	0,3
	M. interjectum	1	0,3
	M. malmoense	5	1,3
	M. smegmatis	1	0,3
	Mycobacterium sp.	15	4,3
Ukupno		350	100

Tablica / *Table* 3**.**
Bolesnici s rezistentnom tuberkulozom u Hrvatskoj, 2017. /
Resistant tuberculosis in Croatia, 2017

	Broj / *Number*	**%**
Ukupno bolesnika / *Patients total*	**13**	**100**
Monorezistencija / *Monoresistance*		
S	5	38,5
H	4	30,7
Z	2	15,4
Polirezistencija / *Polyresistance*		
HS	2	15,4

Legenda - *Key*: **S** - streptomicin **H** ï izoniazid **Z** - pirazinamid

POGLAVLJE / CHAPTER **3.**

OSJETLJIVOST GONOKOKA U HRVATSKOJ U 2017. GODINI

SENSITIVITY OF GONOCOCCI IN CROATIA IN 2017

Blaženka Hunjak
Andrea Babić-Erceg
Tatjana Unukić

Hrvatski zavod za javno zdravstvo,
Rockefellerova 2, 10000 Zagreb, Hrvatska
Služba za mikrobiologiju,
Odjel za bakteriologiju
Odjel za molekularnu dijagnostiku
Croatian Institute of Public Health,
Rockefeller str. 2, 10000 Zagreb, Croatia
Division for Microbiology,
Department for Bacteriology
Department for Molecular Diagnostics

Hrvatski zavod za javno zdravstvo,
Rockefellerova 2, 10000 Zagreb, Hrvatska
Sluġba za mikrobiologiju
Odjel za bakteriologiju
Odjel za molekularnu dijagnostiku

Dr.sc.B. Hunjak, prim.dr.med.
Tatjana UnukiĆ, prvostupnik medicinsko laboratorijske dijagnostike
Dr.sc.A. BabiĆ-Erceg, prim.dr.med.

Antimikrobna rezistencija u gonokoka izoliranih Hrvatskoj u 2017. godini

Gonoreja je i dalje druga najĻeġĆa spolno prenosiva infekcija (SPI) bakterijskog podrijetla danaġnjice. Posebice je uĻestalost gonoreje visoka u zemljama zapadne Europe u osoba mlaĽe ġivotne dobi.

U 2014. godini, mlaĽe odrasle osobe obuhvaĆale su 14% odrasle populacije EU / EEA (Ó15 godina), a upravo je toj ġivotnoj dobi ustanovljeno najviġe infekcija klamidijom i gonokokom: 65% svih infekcija klamidijom i 39% sluĻajeva infekcije gonokokom otkriveno je upravo u osoba dobi izmeĽu 15 i 25 godina.

Viġe od jedne treĆine pogoĽenih osoba, bilo je izmeĽu 15 i 24 godine; infekcija je bila tri puta ĻeġĆa kod muġkaraca, a od ukupnog broja prijavljenih sluĻajeva, oko polovice (43%) odnosilo se na muġkarce koji su imali spolne odnose s muġkarcima (MSM).

PoveĆanje stope oboljelih od gonoreje, dijelom se objaġnjava poveĆanjem testiranja meĽu skupinama s veĆim rizikom za zarazu. Navedene podatke joġ uvijek treba tumaĻiti s oprezom zbog razliĻitosti u sustavima praĆenja u pojedinim zemljama i nepotpunim epidemioloġkim podacima.

Vaġnost praĆenja infekcija uzrokovanih bakterijom Neisseria gonorrhoeae (NG), vaġan je i javno zdravstveni problem zbog dokazano nepovoljnog utjecaja na populaciju trudnica i novoroĽenĻadi. Naime, nepravilno lijeĻenje infekcije sa NG moġe dovesti do upalne bolesti zdjelice (PID), izvanmaterniĻne trudnoĆe, neplodnosti, epididimitisa ili ġirenja gonokokne infekcije na druge organe .

Pojava antimikrobne otpornosti (AMR) u NG je ozbiljna prijetnja lijeĻenju i kontroli gonoreje. Mnogobrojni donedavno uĻinkoviti antimikrobni lijekovi (antibiotici), viġe se ne mogu koristiti zbog pojave otpornosti i brzog globalnog ġirenja AMR. Najviġe zabrinjava brzi razvoj i ġirenje otpornosti u NG na cefalosporine treĆe generacije koji dodatno ograniĻavaju moguĆnosti lijeĻenja. Trenutne europske struĻne smjernice preporuĻuju istovremenu primjenu dvaju antimikrobnih lijekova: ceftriakson i azitromicin, kako bi se odgodio razvoj i/ili ġirenje AMR.

Jedan od specifiĻnih ciljeva nadzora SPI u Europi je otkrivanje i praĆenje uĻestalosti gonokoka i osjetljivosti na antibiotike, povezano s epidemioloġkim obiljeġjima, kako bi se pridonijelo uĻinkovitim kliniĻkim smjernicama dijagnostike gonoreje i osigurala odgovarajuĆa terapija. Stoga se radi na promicanju koordinacije mreġe mikrobioloġkih laboratorija, ukljuĻujuĆi i kontrolu kvalitete i obuku. Kako bi se taj cilj postigao, u kolovozu 2009. godine pokrenut je Europski program nadziranja pojave gonokoknih infekcija i antimikrobne osjetljivosti gonokoka (Euro-GASP), koji trenutno vode meĽunarodni timovi ustanova iz Engleske i Ġvedske :

- Public Health England (United Kingdom); Antimicrobial resistance and healthcare associated infection, National Infection Service; Örebro University Hospital (Sweden).

Od poĻetka ukljuĻivanja RH u Euro-GASP (krajem 2014.) pokuġava se struĻnoj javnosti u RH propagirati vaġnost praĆenja uĻestalosti NG, a od 2015, ukljuĻeno je praĆenje AMR NG u godiġnje izvijeġĆe o rezistenciji u Publikaciju Odbora za praĆenje antimikrobne rezistencije u RH. Izolati NG iz svih laboratorija koji sudjeluju u praĆenju, ġalju se u Odjel za bakteriologiju Sluġbe za mikrobiologiju HZJZ-a u okviru koje djeluje Hrvatski Nacionalni Referentni Laboratoriji ECDC-a.

U HZJZ se provodi i potvrĎuje identifikacija NG metodama kultivacije, molekularnom metodom PCR na ureĎaju ABI Prism sequence detection system 7000 (Applied Biosystems, USA) metodom Real time ï PCR (prema J Clin Microbiol. Nov 2005; 43(11): 5653ï 5659. doi: 10.1128/JCM.43.11.5653-5659.2005), te se provodi testiranje osjetjivosti na antibiotike (metoda E-test).
Izolati koji zbog vrlo velike osjetljivosti NG zadrģe vijabilnost, prosljeĎuju se u suradnu ustanovu ECDC-a: Antimicrobial resistance and healthcare associated infection, National Infection Service Public Health England (United Kingdom). Redovito se provodi i godišnja Vanjska kontrola kvalitete na izolatima NG (NEQUAS, specijalni program).
U listopadu 2015. g. poslano je prvih deset uzoraka gonokoka na analizu u ECDC (Public Health England), 2016. god. 11., a 2017. 9 izolata.

U 2015.g. poļeli su stizati izolati NG ili samo podaci o osjetljivosti na NG (obzirom na zahtjevni transport i osjetljivost izolata) u HZJZ, iz mikrobioloģkih laboratorija u RH koji sudjeluju u praĆenju rezistencije, te je za 2015. god zaprimljeno podataka za 15 sojeva, u 2016. g. za 35, a u 2107. za 36 izolata (Tablice 1. i 2.).

U Tablici 1., navedene su i vrijednosti gradijenata koje pokazuje rezultate testiranja metodom E-testa. Vidljivo je da su rezultati testiranja sliļni u veĆine zaprimljenih izolata.

Usporedivši rezultate za 2016. i 2017. god., nema velikih razlika u osjetljivosti na antibitiotike u NG sojeva.
Od ukupno 36 testiranih sojeva u 2017., rezultati su kako slijedi:
- na penicillin je bilo 47,2% osjetljivih, 44,4% umjereno osjetljivih, i 8,3% rezistentnih izolata; u usporedbi s 2016., kada je podjednako rezistentnih izolata (8.6%),
- na ceftriakson je kod jednog izolata ustanovljena rezistencija, za razliku od podataka za 2016. kada niti u jednog izolata nije ustanovljena rezistencija,
- na cefiksim je u 6,9% izolata ustanovljena rezistencija. Podatke treba uzeti s rezervom, jer su neki laboratoriji testiranje provodili metodom disk difuzije, zbog tehniļkih razloga (Tablica 1.)
- na azitromicin je u samo 5,7% izolata ustanovljena rezistencija, za razliku od podataka za 2016., kada je bilo 15,2% rezistentnih NG
- na ciprofloksacin je bilo 42,4% rezistentnih izolata, ģto je neģto manje u odnosu na 2016. (51,6%)

Ponovo je osim navedenih antimikrobnih lijekova, takoĎer testirana osjetljivost na spektinomicin.
U 2017.g. na spektinomicin testirano je 9 sojeva, a rezistencija nije ustanovljena niti kod jednog izolata.

Iako je rezistencija na cefalosporine višIh generacija u Europi u porastu, naši rezultati i dalje pokazuju dobru osjetljivost izolata na ceftriakson, cefiksim i azitromicin (>90%), a slabiju osjetljivost na ciprofloksacin i penicillin.

Prema preporukama i smjernicama programa Euro-GASP (Gonococcal Antimicrobial Surveillance Reporting Protocol 2018 Euro-GASP Surveillance data for 2017 and 2018, TESSy - The European Surveillance System March 2018), svakako bi bilo potrebno testirati isolate NG na slijedeĆe antimikrobne lijekove navedenim metodama :
ÅCiprofloksacin (tehnika prijelomne toļke agar dilucijom ili ispitivanje ispitivanje MIC-a gradijentnom trakom)
Å Azitromicin (ispitivanje MIC-a gradijentnom trakom)
Å Cefixime (ispitivanje MIC-a gradijentnom trakom)
Å Ceftriakson (ispitivanje MIC-a gradijentnom trakom)
Ispitivanje produkcije ß-lactamase test (nitrocefin test) za detekciju visokog stupnja rezistencije na penicillin. Osim navednih antimikrobnih lijekova, takoĎer je testirana osjetljivost na spektinomicin.U 2015.g. na spektinomicin testirano je 9 sojeva, a rezistencija je ustanovljena kod 3/9 (33,3%).
Uzevši u obzir porast rezistencije na cefalosporinske antibiotike višIh generacija u EU, koje ļesto prati i unakrišna rezistencija na kinolone, potrebno je i u hrvatskim uvjetima podiĆi svijest o AMR na

gonokoke. Naġi rezultati pokazuju dobru osjetljivost na cefalosporine, azitromicin i tetracikline, dok je TakoĽer, preporuke koje su produkt iskustava dobivenih kroz program Euro-GASP su kako slijedi:

Ispitivanje osjetljivosti i identifikacija vrste NG treba ponoviti za :

- sve izolate rezistentne na ceftriakson (MICs> 0.125 mg / L), izolate koji pokazuju poviġenu rezistenciju na cefixime (MICs> 0.25 mg / L), sve izolate koji pokazuju visoku otpornost na azitromicin (MICs256 mg / L).

TakoĽer se preporuļuje da se ti izolati ġalju u Reference Laboratory Hub (London / Örebro) za daljnju provjeru i sekvencioniranje cijelog genoma (ukljuļujuĺi odreĽivanje NG-MAST ST i genogroupa, MLST ST i determinante genetske rezistencije), kako bi se toļno mogao pratiti razvoj AMR i predvidjeti uļinkovitost pojedinih antibiotika.

Iako u HZJZ postoji tradicija praĺenja epidemiologije SPI i praĺenja izolata koji su uzroļnici SPI joġ uvijek postoji nesrazmjer izmeĽu prijavljenih sluļajeva gonoreje i izolata NG potvrĽenih u mikrobiološkim laboratorijma u RH.

U svjetlu promjena u vrsti i dobi populacije RH, migrantskih kriza i razvoja turizma, bilo bi za oļekivati da ĺe se broj uļestalosti infekcija sa NG poveĺavati.

Stoga je i dalje , potrebno pratiti pojavnost NG i osjetljivost na antibiotike, kako bi se toļno mogao pratiti razvoj AMR i predvidjeti uļinkovitost pojedinih lijekova.

Tablica 1. Osjetljivost sojeva N. gonorrhoeae na antibiotike u RH , sa vrijednostima ispitivanja MIC-a metodom graduirane trake (E-test), ukupno: 36
Izuzetak: osjetljivost na cefiksim ispitivana i metodom disk – difuzije /
Table 1. Susceptibility testing of N. gonorrhoeae strains to antibiotics in Croatia, with MIC gradient band (E-test) test values, total: 36
Exception: sensitivity to cefixime: disk - diffusion methods

Ustanova	Penicilin			Ceftriakson			Cefixim			Ciprofloxacin			Azithromycin			Tetracycline			Spektinomycin		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
ZG KZIB																					
1		0,094		0,003			32mm			0,008			0,064			0,094					
2		0,094		0,003					30mm	0,008			0,094			0,064					
3	0,064			0,002			50mm			0,003			0,064			0,064					
4	0,047			<0,002			50mm			0,004			0,064			0,19					
5	0,064			<0,002			>50mm					8	0,125					8			
6	0,064			0,003			32mm			0,004			0,064			0,25					
7	0,047			0,002						0,002			0,047			0,38					
8	0,064			<0,002			>50mm					3	0,047			0,5					
9		0,125		0,004								6	0,125			0,5					
HZZJZ																					
1		0,094		0,003			0,032								4			16	2		
2		0,094		0,003			0,032								4			16	2		
3	0,047			<0,002			<0,016			0,002			0,094			0,016			1,5		
4			>1	0,003			0,032			0,032			0,25			0,5			2		
5	0,064			0,003			0,016			1			0,023			0,25			0,19		
6	0,002			0,016			0,016			0,003			0,19			0,38			4		
7			>1	0,002			0,016					4	0,094			0,38			0,09		
ZD ZZJZ																					
1		*		*								*	*			*					
2	0,0045			0,002						0,002			0,016			0,064					
3		*		*						*			*					*			
4		0,5		0,032								6	0,125					1			
KA ZZJZ																					
1	0,023			0,002																	
2	0,032			0,006			0,125					0,16	0,094			0,032					
OS ZZJZ																					
1		0,094				0,38			4			32	0,094					1,5	4		
2	0,048			0,004			38mm					0,38	0,064					2			
RI ZZJZ																					
1	0,023			<0,002			<0,016			<0,002			<0,016			0,38					
2		0,125		<0,002			<0,016			<0,0025			0,38			0,018					
ST NZZJZ																					
1	0,012			0,002			0,016					4	0,094			0,38			0,09		
2		1		0,047			0,125					6	0,19					3			
3	0,047			0,003			0,016			0,002			0,023			0,25					
ZG NZZJZ																					
1		0,64		<0,002			<0,016			<0,002			0,25			0,5					
2			>32	0,002			<0,016					3	0,19					8			
3		0,32		<0,003			<0,016			<0,002			0,032			0,125					
4	0,047			<0,002			<0,016			<0,002			0,016			0,047					
5		0,19		0,012			0,023					1	0,19			0,5					
6		0,094		0,003			<0,016					3	0,25			0,25					
7		0,094		<0,002			<0,016			<0,002			0,094			0,25					
	S(%)	I (%)	R (%)	S(%)	I (%)	R (%)	S(%)	I (%)	R (%)	S(%)	I (%)	R (%)	S(%)	I (%)	R (%)	S(%)	I (%)	R (%)	S(%)	I (%)	R (%)
	ukupno 36			ukupno 36			* ukupno 29			* ukupno 33			* ukupno 35			* ukupno 35			* ukupno 9		
	17(47,2)	16(44,4)	3(8,3)	35(97,2)	0	1(2,778)	27(93,1)	0	2(6,89)	19(57,57)	0	14(42,42)	33(94,28)	0	2(5,71)	26(74,28)	0	9(25,71)	9(100)	0	0

*nema podatka o brojčanoj vrijednosti testiranja, samo kategorija (S,I,R)

Tablica 2. Osjetljivost sojeva *N. gonorrhoeae* na antibiotike u Hrvatskoj 2017. /
Table 2. Antimicrobial susceptibility of N. gonorrhoeae strains to antibiotics in Croatia, 2017

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	9	3 (33,3)	0	9	0	0	7	0	1 (14,28)	9	0	3 (33,3)	9	0	0	9	0	1 (11,1)			
ZG HZJZ	7	2 (28,6)	2 (28,6)	7	0	0	7	0	0	5	0	1 (20)	7	0	2 (28,6)	7	0	2 (28,6)	7	0	0
ZG NZZJZ	7	5 (71,4)	1 (14,3)	7	0	0	7	0	0	7	0	3 (42,9)	7	0	0	7	0	1 (14,3)			
ZD ZZJZ	4	3 (75)	0	4	0	0				4	0	2 (50)	4	0	0	4	0	2 (50)			
KA ZZJZ	2	0	0	2	0	0	1	0	0	1	0	1 (100)	1	0	0	1	0	0			
OS ZZJZ	2	1 (100)	0	2	0	1 (100)	2	0	1 (100)	2	0	2 (100)	2	0	0	2	0	2 (100)	1		
RI ZZJZ	2	1 (100)	0	2	0	0	2	0	0	2	0	0	2	0	0	2	0	0			
ST NZZJZ	3	1 (33,3)	0	3	0	0	3	0	0	3	0	2 (66,7)	3	0	0	3	0	1 (33,3)	1		
Ukupno*	36	16 (44,4)	3 (8,3)	36	0	1 (2,8)	29	0	2 (6,9)	33	0	14 (42,4)	35	0	2 (5,7)	35	0	9 (25,7)	9	0	0

*Iako je u praćenje uključeno 36 izolata, nije bilo moguće provesti testiranje svih izolata na sve antibitiotike zbog tehničkih razloga / although 36 isolates were included in the monitoring, it was not possible to test all isolates on all antimicrobial agents, due to technical reasons

Antimicrobial resistance in gonococci isolated in Croatia in 2017

Today, gonorrhea is still the second most common sexually transmitted infection (SPI) of the bacterial origin. Particularly, the frequency of gonorrhea is high in Western European countries in younger people. In 2014, young adults comprised 14% of the EU/EEA adult population (Ó15 years), but constituted 65% and 39% of chlamydia and gonorrhoea diagnoses, respectively.General EU/EEA morbidity rate in 2014 increased by 79% in comparison with that from 2008.

More than one-third of persons affected 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).

A surge in the rate of persons affected by gonorrhea is partly explained by an increase in testing among high-risk groups.

Although, gonorrhea trends need to be interpreted with caution due to differences in individual countriesô surveillance systems and to incomplete data.

The importance of monitoring infections caused by Neisseria gonorrhoeae (NG) is also a public health problem because of the adverse effect on the population of pregnant women and newborn babies.

Unless adequately treated, NG infection can result in severe complications: pelvic inflammatory disease (PID), ectopic pregnancy, infertility, epididimytis or spread of gonococcal infection to other organs.

The emergence of antimicrobial resistance (AMR) in NG is a serious threat to the treatment and control of gonorrhoea. Numerous formerly effective therapeutic agents can no longer be used due to the emergence of resistance and subsequent rapid global spread. The development and spread of resistance to third generation cephalosporins in recent decades has further limited treatment options. The current European guideline recommends dual treatment with ceftriaxone and azithromycin to try to delay the development and/or spread of resistance against the last options for treatment.

One of the specific objectives for surveillance of sexually transmitted infections in Europe is ñto detect and monitor the resistance patterns in gonococci, preferably by epidemiological characteristics, in Europe to contribute to the treatment guidelines of gonorrhoea and to ensure appropriate treatment by promoting the coordination of laboratory network on gonococci resistance testing, including quality assurance and training.ò In order to fulfill this objective, the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) was launched in August 2009, and is currently outsourced to an international team lead by Public Health England and Örebro University Hospital (Sweden).

Croatia has joined Euro-GASP in late 2014. There were several efforts to inform professional community about the importance of monitoring the NG incidence and antimicrobial susceptibility.

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. In CIPH, molecular diagnostics is performed on an ABI Prism sequence detection system 7000 (Applied Biosystems, USA) using real-time PCR assay (J Clin Microbiol. Nov 2005; 43(11): 5653ï 5659. doi: 10.1128/JCM.43.11.5653-5659.2005).

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). The annual External Quality Control on NG isolates (NEQUAS, special survey) is also regularly carried out.

The first ten gonococcal isolates were sent to ECDC (Public Health England, United Kingdom) for analysis in October 2015, 11 in 2016. and 9 in 2017.

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; 35 in 2016, and data on 36 strains were received from different institutions in 2017 (Table 1 and 2).

In Table 1 are presented gradient values showing the test results by the E-test method. It is evident that the test results are similar to most received isolates.

By comparing the results for 2016 and 2017, there is no significant difference in sensitivity to antibiotic in NG strains.
Findings of antimicrobial resistance testing in a total of 36 isolates in 2017, were as follows:
- penicillin:
47.2% sensitive, 44,4% moderately sensitive, and 8,3% resistant isolates; compared to 2016, when there were 8.6% resistant isolates
- ceftriaxone:
resistance was established in one isolate, unlike data for 2016, when no resistance was detected
- cefixim:
6.9% resistant isolates . The data should be taken with the reserve, as some laboratories have tested the disc diffusion method for technical reasons (Table 1)
- azithromycin:
5,7% resistant isolatas found, unlike data for 2016, when 15.2% isolates were resistant
- ciprofloxacin:
42.4% of resistant isolates, which is slightly less than in 2016 (51.6%)

Susceptibility to spectinomycin was additionally tested in nine strains collected in 2017, with no resistance observed.
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, and azithromycin, 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.

According to the recommendations and guidelines of the Euro-GASP (Gonoccocal Antimicrobial Surveillance Reporting Protocol 2018, Euro-GASP Surveillance data for 2017 and 2018, TESSy - The European Surveillance System March 2018), it would certainly be necessary to test NG isolates on the following antimicrobial drugs using the following methods:
Ciprofloxacin (agar dilution breakpoint technique or MIC gradient strip testing)
Azithromycin (MIC gradient strip testing)
Cefixime (MIC gradient strip testing)
Ceftriaxone (MIC gradient strip testing)
ß-lactamase test (nitrocefin test) for detection of high-level penicillin resistance

Also, the recommendations that are the product of the experiences gained through the Euro-GASP program are as follows:
The susceptibility testing and N. gonorrhoeae species identification should be repeated for all isolates that are resistant to ceftriaxone (MICs>0.125 mg/L), on isolates that show elevated resistance to cefixime (MICs>0.25 mg/L), and all isolates showing high-level resistance to azithromycin (MICsÓ256 mg/L). Those isolates are also recommended to be sent to the Reference Laboratory Hub (London/Örebro) for further verification and whole genome sequencing (including determination of NG-MAST ST and genogroup, MLST ST and genetic resistance determinants).

Although there is a tradition of monitoring the epidemiology of SPI and of isolates causing SPI there is still a differences between the reported cases of gonorrhea and NG isolates confirmed in microbiological laboratories in the Republic of Croatia.
Regarding changes in the type and age of the population of Croatia, migration crises and tourism development, it would be expected that the number of infections with NG will increase.
Therefore, it is still necessary to monitor the incidence of NG infections, and sensitivity to antibiotics in order to accurately monitor AMR development and predict the efficacy of antibiotics.

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

Silvija Šoprek
Arjana Tambić Andrašević

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

Važnost praćenja rezistencije u invazivnih izolata

Sustavno praćenje rezistencije na antibiotike na europskoj razini započelo je 1999.g. u okviru European Antimicrobial Resistance Surveillance System (EARSS) projekta. Za prioritete u praćenju odabrano je u početku šest bakterijskih vrsta *S. aureus, E. faecalis, E. faecium, S. pneumoniae* i *E. coli*, od 2005.g. dodano je praćenje rezistencije u *K. pneumoniae* i *P. aeruginosa*, a od 2013.g. započeto je i praćenje rezistencije u *Acinetobacter* spp. S obzirom na različitu praksu uzimanja uzoraka i interpretaciju nalaza u različitim zemljama 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 2017.g. bilježimo veći broj prikupljenih izolata nego 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 2017.g. prikupljeno je 132 izolata *S. pneumoniae,* 1201 izolata *E. coli*, 319 izolata *K. pneumoniae*, 540 izolata *S. aureus,* 272 izolata enterokoka (180 *E. faecalis* i 92 *E. faecium* izolata), 249 izolata *P. aeruginosa*, te 215 izolata *Acinetobacter* spp. (Tablica 1).

Trend rasta rezistencije *P. aeruginosa* na karbapeneme zabrinjavajuće je bio u porastu do 2016. g. kada smo zabilježili najveću stopu rezistencije ikad (41%), ali 2017. prvi puta zamjećujemo značajniji pad stope rezistencije koja iznosi 30%. Rezistencija *Acinetobacter* spp. na karbapeneme je i dalje izuzetno visoka (96%).

Među invazivnim izolatima pneumokoka u 2017.g. neosjetljivost na penicilin (22%) je podjednaka prošlogodišnjoj stopi rezistencije dok je stopa rezistencije na makrolide dosegnula 37% što je do sada najviša zabilježena stopa.

Udio MRSA izolata među invazivnim sojevima (28%) je u porastu, ali još uvijek ispod razine stopa zabilježenih prije 2010.g. (>30%). Kod ukupnog broja stafilokoka izoliranih iz bilo kojeg uzorka stopa MRSA (15%) nije porasla u odnosu na prethodnu godinu (16%) (Poglavlje 1).

Rezistencija na glikopeptide kod *E. faecalis* je niska (<1%) i zabilježena samo u nekoliko sporadičnih izolata. Rezistencija na glikopeptide u *E. faecium* (19%) nije nastavila trend porasta zabilježen prethodnih godina. 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 (16%), što je pretežno uzrokovano proizvodnjom beta-laktamaza proširenog spektra (engl. "extended spectrum beta-lactamases", ESBL). Rezistencija na kinolone pokazuje i dalje trend porasta i u 2017.g. doseže 30%.

Udio *K. pneumoniae* izolata rezistentnih na 3. generaciju cefalosporina (41%) se nije bitno mijenjao, a stopa neosjetljivih izolata na karbapeneme (imipenem i/ili meropenem) je i dalje u porastu i iznosi 5%.

Stope rezistencije detaljno su prikazane u tablici 2.

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

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

Impact of antibiotic resistance surveillance in invasive isolates

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

Results of the antibiotic resistance surveillance in invasive isolates

In 2017 a larger number of isolates was collected than 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 Health Care Associated Infections. During 2017 we have collected 132 isolates of *S. pneumoniae,* 1201 isolates of *E. coli*, 319 isolates of *K. pneumoniae*, 540 isolates of *S.aureus,* 272 enterococcal isolates (180 *E. faecalis* and 92 *E. faecium* isolates), 249 isolates of *P.aeruginosa* and 215 isolates of *Acinetobacter* spp. (Table 1).

The increasing trend of carbapenem resistance in *P. aeruginosa* was highly disturbing till 2016, when we detected the highest resistance rates ever (41%), but in 2017, for the first time, we detected a significant decrease of resistance rates, falling down to 30%. Carbapenem resistance in *Acinetobacter* spp. remains extremely high (95%).

In 2017 the rate of invasive pneumococci non-susceptible to penicillin was 22%, similar as in the previous year while resistance to macrolides reached 37% which is the highest value recorded so far.

The MRSA rate increased (28%), but is still under the values recorded before 2010 (>30%). MRSA rate observed in mass surveillance remains the same as in the previous year (16%) (Chapter 1).

Glycopeptide resistance is low in *E. faecalis* (<1%) and detected in only a few random isolates. Glycopeptide resistance in *E. faecium* (19%) did not continue the increasing trend recorded in previous years. The rates of high level aminoglycoside resistance are still high in both species.

Resistance to 3rd generation cephalosporins in *E.coli* (16%) continues to increase, mostly due to the production of extended spectrum beta-lactamases (ESBL). Quinolone resistance in *E.coli* is also steadily increasing and has reached as high as 30%.

Resistance to 3rd generation cephalosporins in *K. pneumoniae* (41%) did not change significantly, and the rate of non-susceptiblity to carbapenems (imipenem and/or meropenem) is increasing, reaching resistance rate of 5% in 2017.

Resistance rates in detail are 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.-2017. /
Number of laboratories and number of isolates reported for the period 2001-2017

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						
2002	14	90	14	279	15	490	13	96						
2003	12	88	14	360	16	570	11	101						
2004	12	103	13	392	14	535	11	115						
2005	15	129	17	354	16	638	11	120	14	112	10	72		
2006	14	116	17	391	17	780	16	178	15	205	15	170		
2007	15	136	15	375	17	852	13	174	17	279	16	189		
2008	13	100	18	474	17	915	16	232	17	333	14	221		
2009	14	100	14	463	16	911	20	223	16	318	15	212		
2010	11	103	15	363	16	897	12	176	16	286	15	217		
2011	16	127	14	451	16	1007	15	244	14	314	15	265		
2012	11	98	17	412	17	921	14	219	15	344	14	204		
2013	16	119	21	533	20	1066	17	250	19	396	19	256	13	114
2014	17	131	19	514	20	1104	18	226	18	341	18	251	16	170
2015	15	126	16	516	18	1062	16	308	17	395	17	267	17	203
2016	17	156	18	476	18	1078	14	288	17	339	16	269	14	188
2017	13	132	18	540	19	1201	17	272	19	319	17	249	17	215

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 %	2017 %
S. pneumoniae	Penicillin R	1	1	4	6	7	1	1	4	1	1	1	1
	Penicillin I+R	18	18	17	19	21	18	23	27	26	20	22	21
	Macrolides I+R	16	8	14	8	29	24	28	34	28	19	33	37
S. aureus	Oxacillin/Met R	36	38	35	37	27	27	22	24	21	25	25	28
E. coli	Aminopenicillins R	51	51	53	55	55	55	52	54	54	56	57	59
	Aminoglycosides R	6	6	6	8	6	7	7	7	10	12	14	16
	Fluoroquinolones R	15	13	15	16	17	20	17	21	20	25	28	30
	3. gen Cef R	1	3	4	5	8	7	8	9	11	13	12	16
	ESBL						9	7	9	11	13	14	16
E. faecalis	Aminopenicillins I+R	3	2	5		5	1	5	9	6	4	7	5
	HL Aminoglycosides R	37	37	46	36	37	33	39	35	33	35	33	32
	Glycopeptides R	<1	<1	<1	<1	<1	1	<1	<1	0	0	0	<1
E. faecium	Aminopenicillins I+R	69	78	79		82	98	98	90	94	97	98	96
	HL Aminoglycosides R	59	59	65	68	60	66	61	55	64	53	65	50
	Glycopeptides R	3	2	6	11	12	2	0	7	10	26	23	19
K. pneumoniae	Aminoglycosides R	33	38	51	47	49	43	45	51	48	40	31	28
	Fluoroquinolones R	23	34	44	51	48	43	43	45	46	50	44	50
	3. gen Cef R	34	40	54	53	56	50	44	50	48	46	42	41
	ESBL						51	52	50	48	47	46	41
	Carbapenems I+R						<1	<1	1	2	3	2	5
P. aeruginosa	Piperacillin R	38	30	34		23							
	Piperacllin/Tazobactam R					16	23	18	23	32	25	20	16
	Ceftazidime R	11	14	13	11	12	17	14	20	28	20	23	21
	Carbapenems R	25	26	30	31	26	30	21	25	35	37	41	30
	Aminoglycosides R	47	40	39	37	26	34	26	24	37	34	32	27
	Fluoroquinolones R	35	30	33	29	27	34	24	23	28	37	38	39
A. baumannii	Carbapenems R								91	88	89	95	96

Tablica 3. / *Table 3.*
Prikaz gram-pozitivnih invazivnih izolata u 2017.g. prema demografskim podacima pacijenata / *Selected details on gram-positive invasive isolates from the reporting period 2017*

	S.pneumoniae		***S.aureus***		***Enterococcus* spp.**	
	n=132		**n=540**		**n=272**	
	% tot	**% PNPS**	**% tot**	**% MRSA**	**% tot**	**% VRE**
UZORAK ***SAMPLE***						
Krv / Blood	94	18	100	28	99	7
Likvor / CSF	6	25	0	0	1	0
SPOL ***GENDER***						
M	46	20	58	27	64	80
Ç / F	50	2	39	28	35	4
Nepoznato / Unknown	4	20	3	45	1	0
DOB ***AGE***						
0-4	29	21	2	14	5	0
5-19	2	0	2	0	1	0
20-64	27	14	35	16	33	9
>65	41	20	60	37	59	5
Nepoznato / Unknown	1	0	1	29	2	50
ODJEL ***DEPARTMENT***						
Intenzivna / ICU	15	20	14	36	13	0
Interna / Medical	85	6	67	25	66	10
Kirurgija / Surgery	0	0	7	39	13	0
Ostalo/ Other	2	100	12	31	8	0

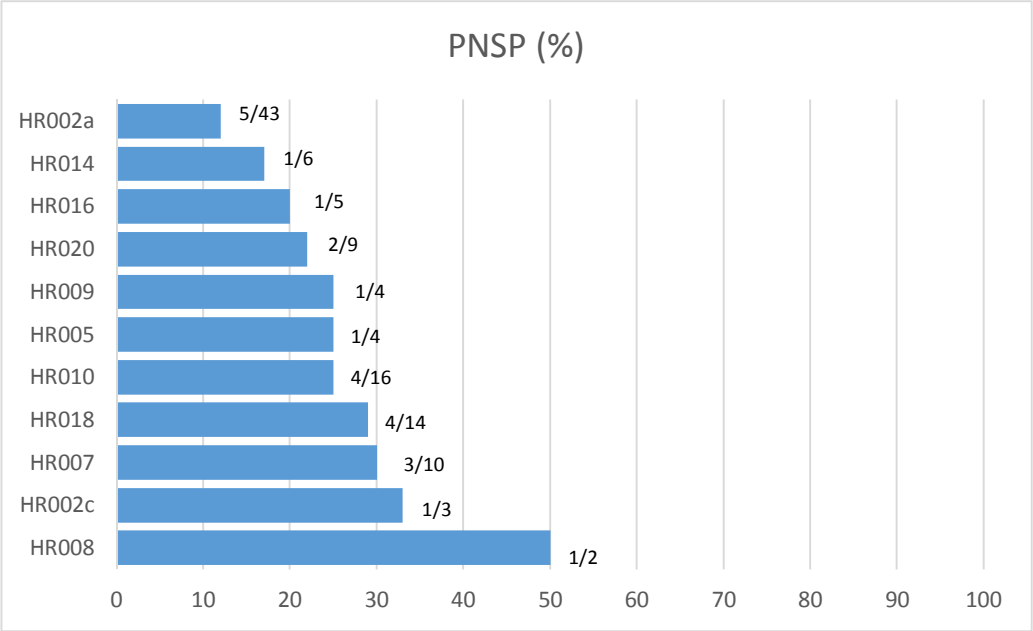
PNSP=Penicillin Non-Susceptible *S. Pneumoniae* MRSA=Methicillin Resistant *S.aureus* VRE=Vancomycin Resistant Enterococcus

Tablica 4. / *Table 4.*
Prikaz gram-negativnih invazivnih izolata u 2017.g. prema demografskim podacima pacijenata / *Selected details on gram-negative invasive isolates from the reporting period 2017*

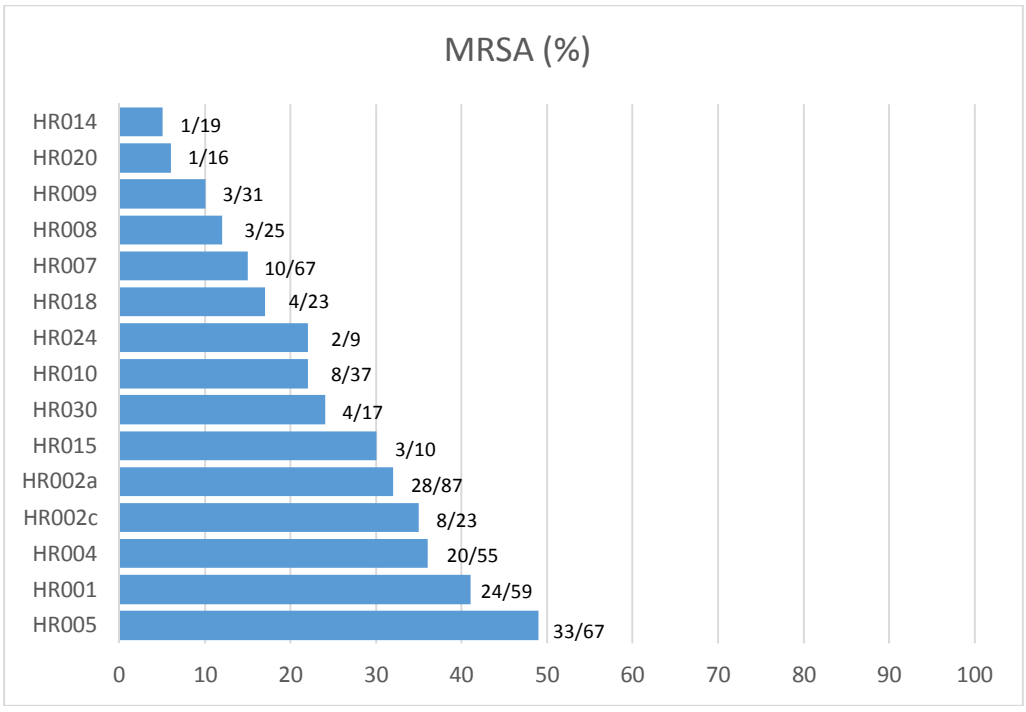
	E.coli			*Acinetobacter* spp.		*K.pneumoniae*		*P.aeuroginosa*	
	n=1201			n=215		n=319		n=249	
	% tot	% FREC	% CREC	% tot	% CRA	% tot	% CRKP	% tot	% CRPA
UZORAK ***SAMPLE***									
Krv / Blood	99	30	14	96	96	99	5	99	29
Likvor / CSF	1	33	33	4	100	1	0	1	50
SPOL ***GENDER***									
M	42	38	90	56	98	54	5	64	32
Ç / F	56	23	71	41	94	42	3	35	25
Nepoznato / Unknown	2	50	2	3	100	4	17	1	0
DOB ***AGE***									
0-4	3	18	21	3	100	7	0	6	43
5-19	<1	20	20	2	80	<1	0	2	20
20-64	27	26	11	40	97	31	6	43	30
>65	68	32	14	53	95	59	5	48	27
Nepoznato / Unknown	1	50	19	2	100	2	0	1	50
ODJEL ***DEPARTMENT***									
Intenzivna / ICU	6	30	12	36	100	18	12	16	33
Interna / Medical	77	28	14	40	96	50	4	49	25
Kirurgija / Surgery	9	48	19	10	95	8	4	17	35
Ostalo/ Other	7	32	9	14	53	24	0	18	32

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.

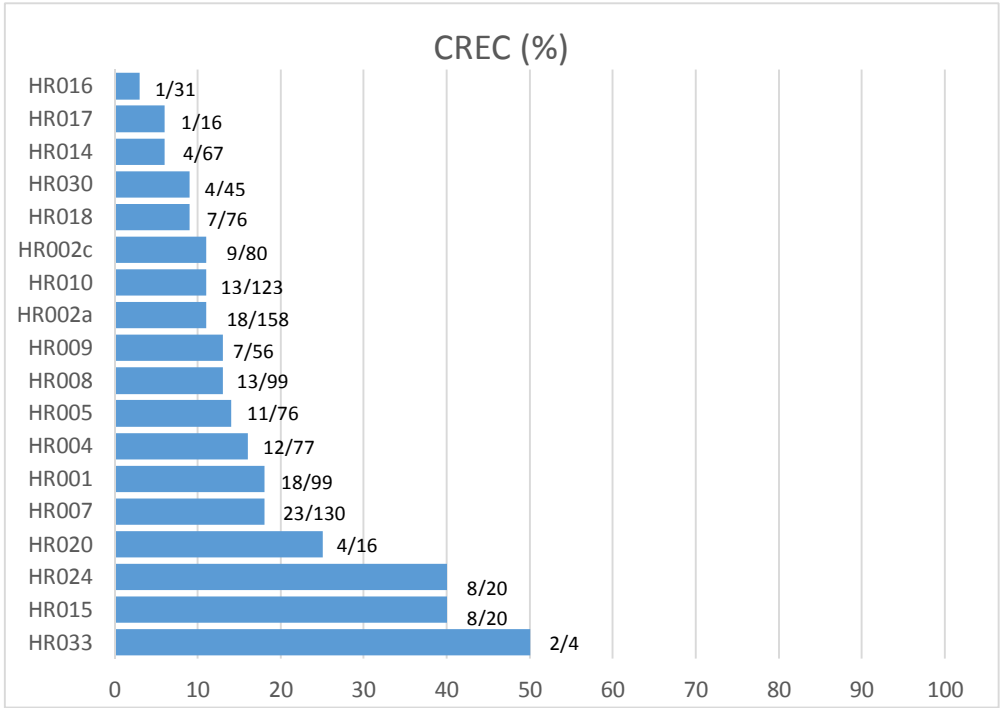
Slika 1. / *Figure 1.*
Udio (%) izolata *S. pneumoniae* smanjene osjetljivosti na penicilin (PNSP) po centrima, 2017. /
Proportion (%) of penicillin non-susceptible S. pneumoniae (PNSP) by center, 2017



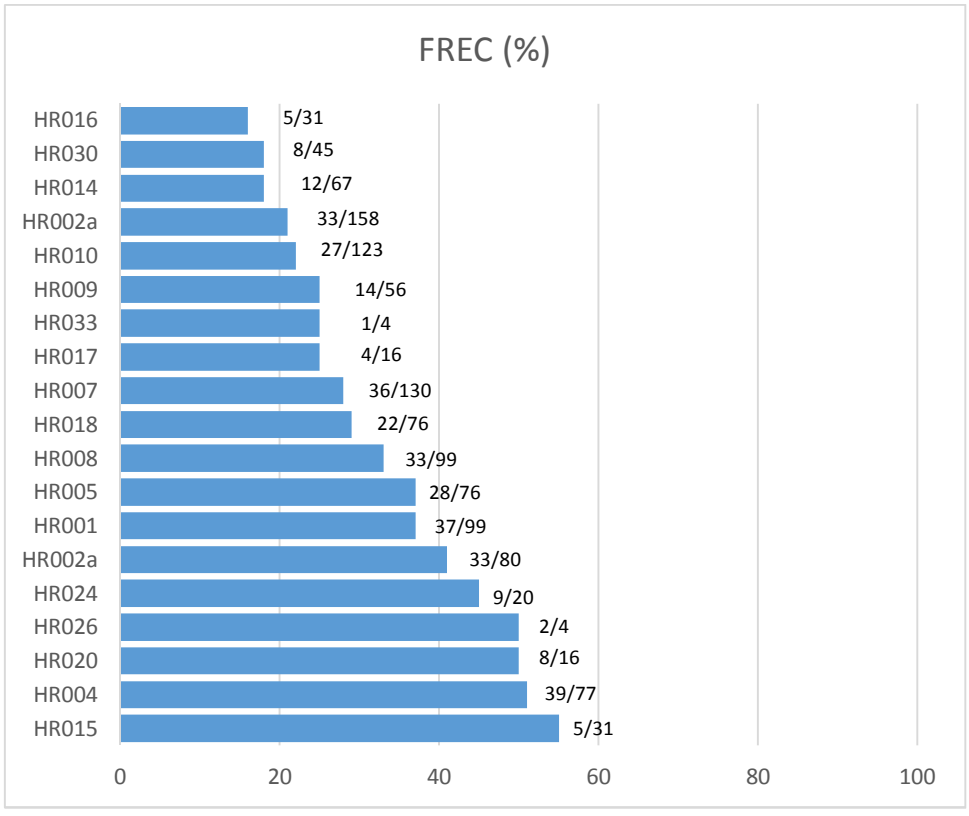
Slika 2. / *Figure 2.*
Udio (%) MRSA izolata po centrima, 2017. /
Proportion (%) of MRSA isolates by center, 2017



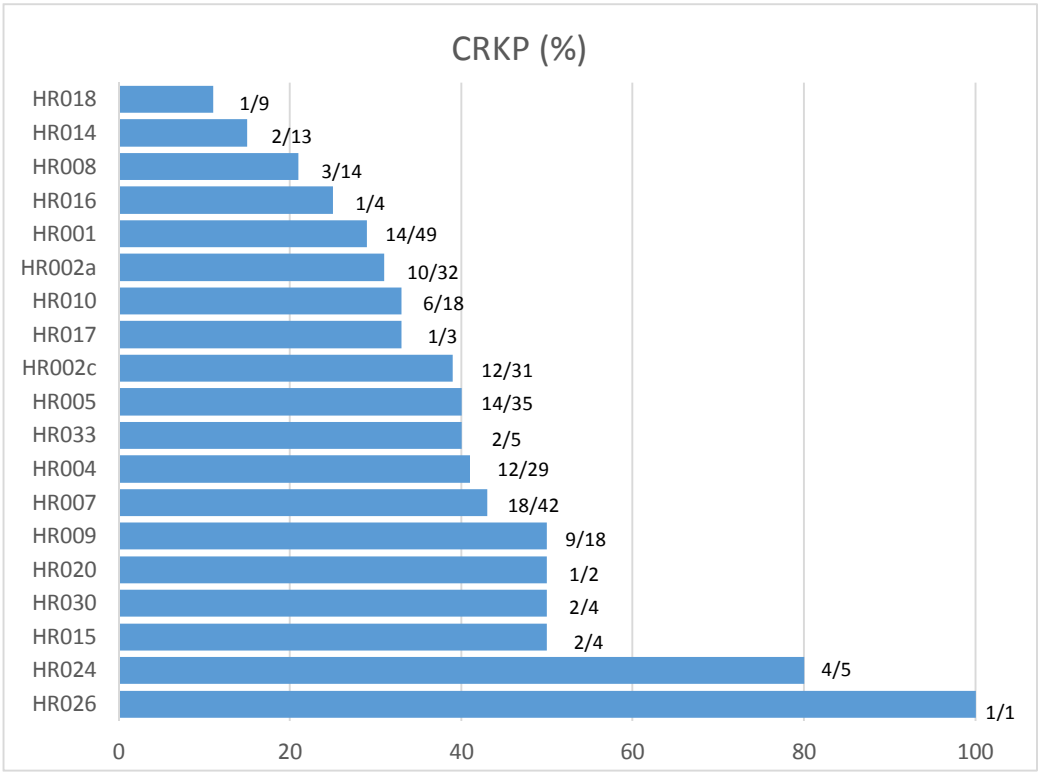
Slika 3. / *Figure 3.*
Udio (%) ceftazidim rezistentnih izolata *E. coli* (CREC) po centrima, 2017. /
Proportion (%) of ceftazidime resistant E. coli isolates (CREC) by center, 2017



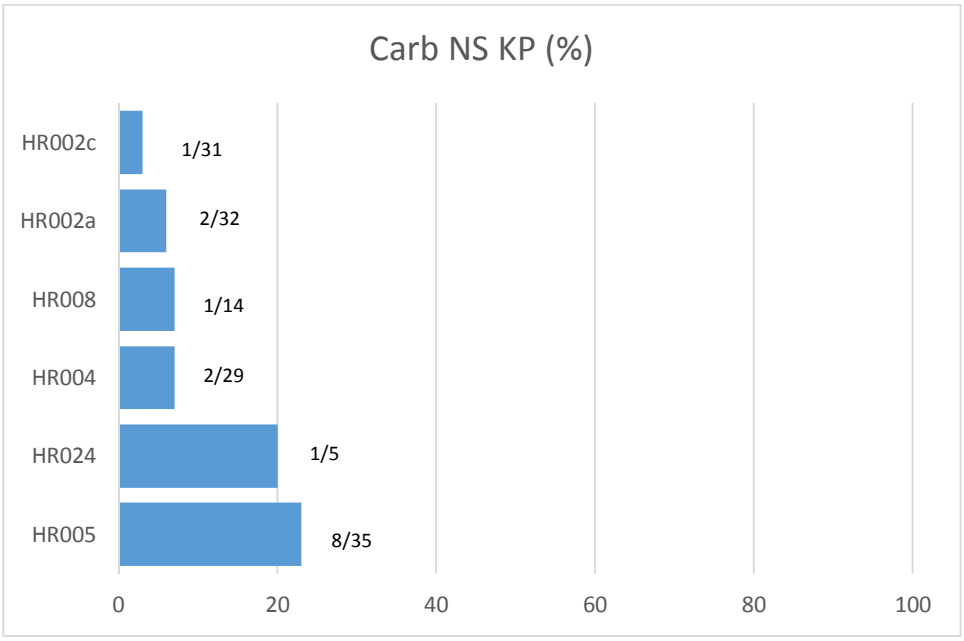
Slika 4. / *Figure 4.*
Udio (%) fluorokinolon rezistentnih izolata *E. coli* (FREC) po centrima, 2017. /
Proportion (%) of fluoroquinolone resistant E.coli isolates (FREC) by center, 2017



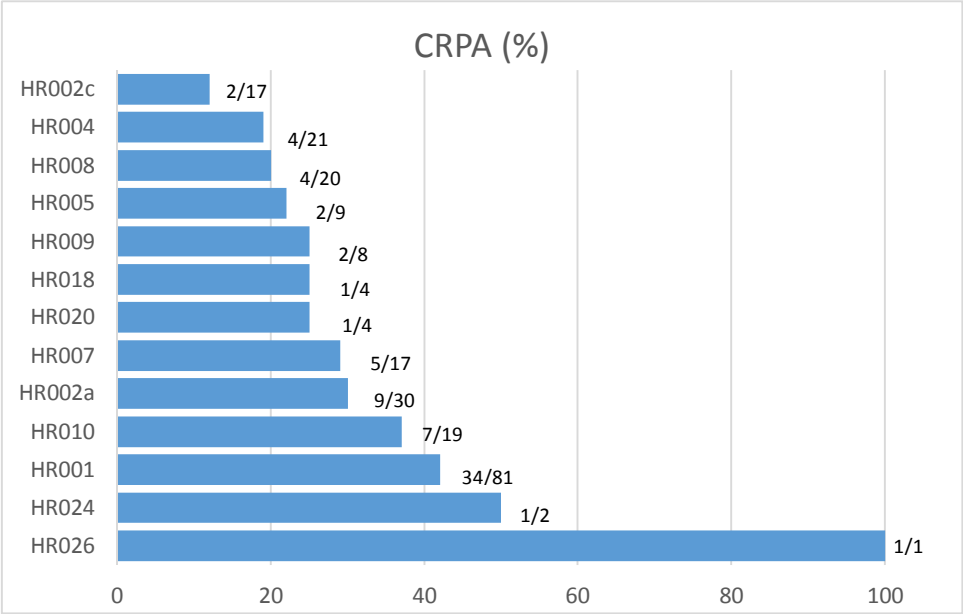
Slika 5. / *Figure 5.*
Udio (%) ceftazidim rezistentnih izolata *K. pneumoniae* (CRKP) po centrima, 2017. /
Proportion (%) of ceftazidime resistant K. pneumoniae (CRKP) by center, 2017



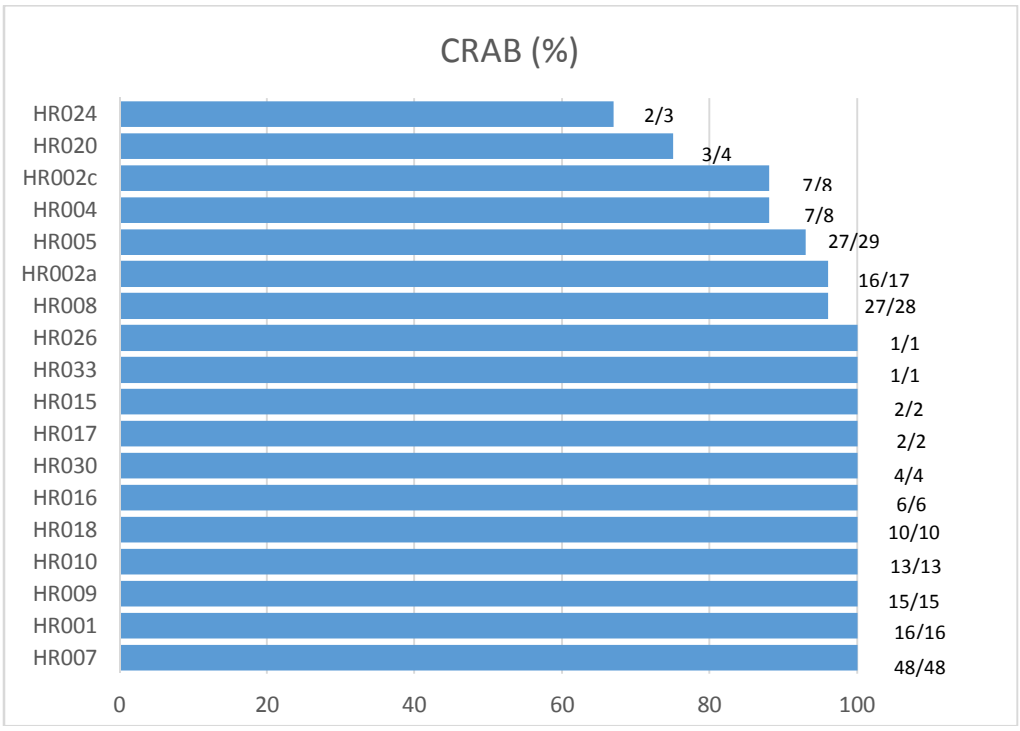
Slika 6. / *Figure 6.*
Udio (%) karbapenem neosjetljivih izolata *K. pneumoniae* (Carb NS KP) po centrima, 2017. /
Proportion (%) of carbapenem non-susceptible K. pneumoniae (Carb NS KP) by center, 2017



Slika 7. / *Figure 7.*
Udio (%) karbapenem rezistentnih izolata *P. aeruginosa* (CRPA) po centrima, 2017. /
Proportion (%) of carbapenem resistant P. aeruginosa (CRPA) by center, 2017



Slika 8. / *Figure 8.*
Udio (%) karbapenem rezistentnih izolata *Acinetobacter* spp. (CRAB) po centrima, 2017. /
Proportion (%) of carbapenem resistant Acinetobacter spp. by center, 2017



POGLAVLJE / CHAPTER 5.

POTROŠNJA ANTIBIOTIKA U HRVATSKOJ
ANTIBIOTIC CONSUMPTION IN CROATIA

Marina Payerl Pal
Damjan Debelec
Zavod za javno zdravstvo Međimurske županije, Čakovec
Public Health Institute Međimurje County, Čakovec

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

Izvanbolnička potrošnja antibiotika

Početak praćenja potrošnje antibiotika u Hrvatskoj seže u 2001. godinu, kada se u okviru European Surveillance of Antibiotic Consumption (ESAC) započelo s praćenjem potrošnje propisanom metodologijom. To znači da se podaci o potrošnji antibiotika (J01) prikupljaju u skladu s anatomsko-terapijsko-kemijskom klasifikacijom (ATK) na petoj razini, a objavljuju na trećoj i četvrtoj razini. Potrošnja antibiotika se prikazuje odvojeno za bolnički i ambulantnu (izvanbolnički) potrošnju.

Do 2013. godine prikupljeni podaci su unašani u ABC kalkulator, koji se redovito, svake godine usklađivao s hrvatskim tržištem. Za 2014. godinu prirađena je Excel tablica-predložak u koju lokalni centri unose svoje podatke o potrošnji antibiotika, u skladu s predloškom ESAC-Net programa europske mreže The European Surveillance System (TESSY). Potrošnja antibiotika se izražava u definiranim dnevnim dozama na 1000 stanovnika po danu (DDD/TID).

Od početka praćenja izvor podataka o izvanbolničkoj potrošnji su bili podaci veledrogerija, a od 2012. godine započeto je praćenje ambulantne potrošnje antibiotika u Hrvatskoj iz dva izvora, veledrogerija i Hrvatskog zavoda za zdravstveno osiguranje (HZZO). Od 2012.g. podatke dobivene od HZZO-a, koji se temelje na propisanim i izdanim receptima, koristimo kao službene podatke o potrošnji antibiotika (Tablica 1, Slika 1).

Kao i u prethodne četiri godine, u 2017. godini kao denominator je korišten broj stanovnika prema popisu stanovništva iz 2011. godine (4 284 889), dok je do 2012. denominator iznosio 4 555 219 stanovnika prema popisu stanovništva iz 2001. godine.

Kao i prethodnih godina, uočava se razlika u potrošnji antibiotika ovisno o izvoru podataka, tako je u 2017. godini veća potrošnja, kada se računa prema podacima iz veledrogerija (21.91 DDD/TID) u odnosu na podatke dobivene iz HZZO-a (20.48 DDD/TID) (tablica 3; slika 2). Najveća razlika se uočava kod klase penicilina J01C (0.83 DDD/TID), što je gotovo dvostruko veća razlika u odnosu na godinu prije, te klase makrolid-linkozamid J01F (0.21 DDD/TID) (tablica 4; slika 3), što je slično prethodnoj godini, kada je razlika iznosila 0.18 DDD/TID. Iako su svi antibiotici u Hrvatskoj dostupni na recept HZZO-a, neki pacijenti koriste privatne recepte što može biti uzrokom različitih podataka o potrošnji ovisno o izvoru podataka. Mogući razlog razlike u podacima može biti i opskrba ambulanti primarne zdravstvene zaštite antibioticima za rijetke prigode direktne primjene uglavnom parenteralnih antibiotika u ambulanti.

Širokospektralni penicilinski antibiotici (J01CA) nastavljaju s trendom pada potrošnje petu godinu za redom, ali ne i kombinacija širokospektralnih antibiotika s inhibitorima beta laktamaza (J01CR) koji bilježe, do sada, najveću potrošnju (8.01 DDD/TID) (Tablica 1, Slika 1). Kod klase cefalosporina (J01D) prati se trend pada potrošnje kod prve (J01DB) i druge generacije (J01DC), ali trend porasta treće generacije (J01DD) (Tablica 1, Slika 1). Kontinuirano se prati trend pada u potrošnji klase tetraciklina (J01A) (1.00 DDD/TID) i klase sulfonamida s trimetoprimom (J01E). Kod obje klase se bilježi najniža potrošnja od početka praćenja potrošnje antibiotika.

Kod nitrofurantoina (J01XE) se prati trend porasta potrošnje u zadnjih pet godina (0.68; 0.72; 0.79; 0.83; 0.87) do 2017. godine, kada se uočava značajniji pad potrošnje sa 0.87 na 0.68 DDD/TID. Vjerojatni razlog pada potrošnje nitrofurantoina je veći porast potrošnje fosfomicina u 2017. godini za istu indikaciju, tj. liječenje nekompliciranog cistitisa, što je navedeno u dopuni ISKRA smjernica kao preporučena opcija za liječenje nekompliciranih urinarnih infekcija. Fosfomicin se nedavno pojavio na našem tržištu, tako da se njegova potrošnja prati tek od 2016. godine, kada je potrošnja bila iznimno mala i nije se mogla prikazati.

Ambulantna potrošnja u Hrvatskoj u 2017. godini iznosi 91% ukupne potrošnje, što odgovara rezultatima prethodnih godina. Ambulantna potrošnja (20.48 DDD/TID) je niža u odnosu na godinu prije (20.73 DDD/TID). Taj podatak se mora sagledati imajući u vidu činjenicu da se za izračun potrošnje od 2012. godine, koristi isti denominator, prema popisu stanovništva iz 2011. godine (4 284

889 stanovnika), dok se prema podacima EURO STAT-a broj stanovnika iz godine u godinu smanjuje, tako da denominator koji koristimo moġe biti podcijenjen.
U tablici 5 i na slici 4 poredani su antibiotici prema potroġnji, tzv. ñtop listaò najpropisivanijih antibiotika. Daleko najļeģe propisani antibiotik je kombinacija penicilina ġirokog spektra i inhibitora beta-laktamaza (amoksicilin+klavulanska kiselina), slijedi penicilin ġirokog spektra (amoksicilin), cefalosporin druge generacije (cefuroksim aksetil), zatim makrolid (azitromicin) te tetraciklin (doksiciklin).

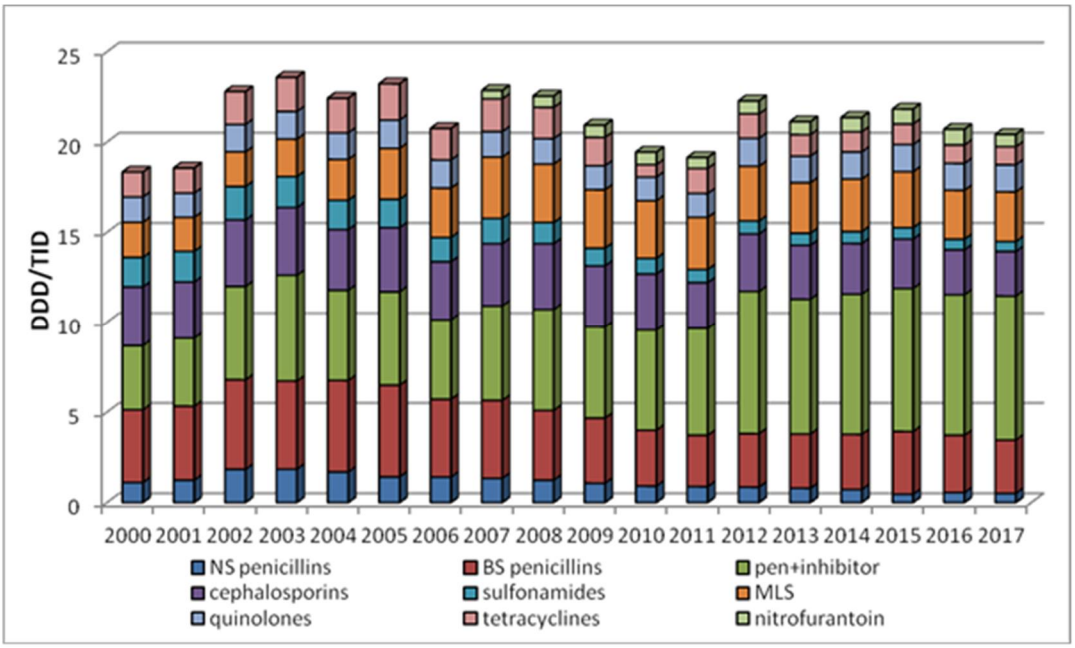
Po prvi puta, potroġnja antibiotika je analizirana i po kvartalima (tablica 6; slika 5), iz ļega je vidljiva znatno veća potroġnja u zimskim kvartalima (5,90; 4,64; 4,42; 5,52), kada su ļeģe respiratorne infekcije, poglavito virusne etiologije.

U tablici 7 i na slici 6 navedene su dijagnoze, prvih pet (ñtop listaò) za koje se ambulantno propisuju antibiotici. Prvo mjesto dijele akutna upala mokraćnog mjehura i akutna upala tonzila, zatim slijede infekcije respiratornog sustava te bolest pulpe i periapikalnih tkiva.

I dalje smo suoļeni sa ļinjenicom da je ambulantna potroġnja antibiotika prevelika, da je mnogo antibiotika nepotrebno propisano te posebno nepovoljnim nalazom da se smanjuje potroġnja antibiotika uskog spektra, a raste potroġnja antibiotika ġirokog spektra. Analizirajući potroġnju antibiotika prema dijagnozama i kvartalima uoļava se najveća potroġnja za respiratorne infekcije i shodno tome najļeģe u zimskim mjesecima. Respiratorne infekcije jesu najļeģe infekcije kod ljudi, ali one su primarno virusne etiologije i nisu ļesta indikacija za propisivanje antibiotika.

Razvijanje i provoĽenje programa rukovoĽenja antimikrobnom terapijom jedini je moguć i put kojim bi se moglo smanjiti neprimjereno propisivanje antibiotika te osigurati njihova optimalna primjena, koja znaļi najbolji ishod lijeļenja, optimalan odnos cijene i uļinka terapije te smanjivanje neġeljenih posljedica antimikrobne terapije, od kojih je smanjivanje uļinaka na razvoj i ġirenje rezistencije na antibiotike jedna od najvaġnijih.

Slika 1. */ Figure 1.*
Ambulantna potrošnja antibiotika (DDD/TID) u Hrvatskoj, 2000 - 2017.
Ambulant antibiotic consumption (DDD/TID) in Croatia, 2000 – 2017



Outpatient Antibiotic Consumption

Standardised surveillance of antibiotic consumption in Croatia started in 2001 within the European Surveillance of Antibiotic Consumption (ESAC). 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 annually harmonised with the Croatian market. Since 2014 data on antibiotic consumption are entered into Excel template table, which is harmonised with the ESAC-Net template of The European Surveillance System (TESSy). Data on consumption are expressed in defined daily doses per 1.000 inhabitants daily (DDD/TID).

Since the beginning of surveillance wholesales data were the source of data for outpatient consumption. Since 2012 data are collected from two sources (wholesales data and Croatian Health Insurance Fund, CHIF reimbursement data). CHIF reimbursement data are considered as an official national data since 2012 (Table 1, Figure 1).

As well as in the previous four years, in 2017 the Census of 2011 was used as a denominator (4 284 889), while up until 2012 a denominator was the Census of 2001 (4 555 219).

As in the previous years, there is a difference in antibiotic consumption depending on the source of data. In 2017 consumption was higher when expressed as wholesales data (21.91 DDD/TID) than as CHIF reimbursement data (20.48 DDD/TID) (Table 3 and Figure 2). The biggest difference is observed in the penicillins class J01C, and in the macrolide-lincosamide class J01F (Table 4 and Figure 3). In the penicillins class the difference is 0.83 DDD/TID which is twice as much as in the previous year. The difference in the macrolide-lincosamide class is 0.21 DDD/TID which is similar to the difference recorded in the previous year (0.18 DDD/TID). All antibiotics in Croatia are reimbursed but some patients choose to purchase antibiotics with private prescriptions which may create difference in obtained consumption data. Another reason may be a direct administration of mostly parenteral antibiotics in primary care offices which however is not a very common practice.

In the last five years, there has been a continuous decrease in the broad spectrum penicillins (J01CA) consumption. However, consumption of the class J01CR (combinations with inhibitors) is the highest so far (8.01 DDD/TID) (Table 1, Figure 1). Consumption of the first and the second generation of cephalosporins (J01DB and J01DC) is decreasing, but consumption of the third generation cephalosporins (J01DD) is increasing (Table 1 and Figure 1). Consumption of tetracyclines (J01AA) and sulphonamides + trimethoprim (J01E) has a decreasing trend and is the lowest ever.

Nitrofurantoin (J01XE) had an increasing trend in consumption in the last five years (0.68; 0.72; 0.79; 0.83; 0.87), up to 2017 when a significant decrease in consumption was recorded (from 0.87 DDD/TID to 0.68 DDD/TID). This may be due to an increasing trend in fosfomycin consumption. In 2017, according to the ISKRA guidelines, fosfomycin was introduced for the treatment of acute uncomplicated lower urinary tract infections. Surveillance of fosfomycin consumption started last year, but consuption was too low to be presented.

In 2017, the outpatient antibiotic consumption makes up 91% of total antibiotic consumption and that is similar as recorded in the previous years. Ambulatory consumption in 2017 (20.48 DDD/TID) is lower than in the previous year (20.73 DDD/TID). However this decrease should be interpreted with caution since the Census of 2011 (4 284 889 inhabitants) is being used as a denominator ever since 2012, but according to the EURO STAT data the number of inhabitants in Croatia is constantly decreasing. It appears that our denominator does not follow the current dynamics of changes in the number of inhabitants in Croatia.

Table 5 and Figure 4 show the consumption of the most frequently used antibiotics (ñthe top listò). The most used are combinations of broad spectrum penicillins with inhibitors, then broad spectrum

penicillins (amoxicillin), second generation cephalosporins (cefuroxime axetil), macrolides (azythromycin) and tetracylines (doxycycline).

For the first time outpatient antibiotic consumption is analysed by quarters (Table 6, Figure 5). Antibiotic consumption is highest in winter (5.90; 4.64; 4.42; 5.52) reflecting the higher incidence of viral respiratory tract infections.

Table 7 and Figure 6 show the most frequent indications ñtop five diagnosisò for antibiotic prescribing in a community. In the first place there are cystitis and acute tonsillitis, then respiratory tract infections and pulp and periapical tissue diseases.

The fact is that outpatient antibiotic consumption is still very high and that there is a lot of unnecessary antibiotic prescribing but the most unfavourable indicator is that the consumption of the broad spectrum antibiotics is increasing and the consumption of narrow spectrum antibiotics is decreasing. The highest use of antibiotics is recorded for respiratory tract infections and therefore expectedly during winter time. Respiratory tract infections are the most common infections in humans, but they are mostly of viral origin and therefore not frequently an indication for antibiotic therapy.

Much desired decrease and rationalization in antibiotic consumption can only be achieved through the well organized antibiotic stewardship. Rational use of antibiotics provides the best treatment outcome, optimal cost-benefit and therapeutic effect and reduces the side effects of antibiotic treatment of which development of antibiotc resistance is the most dangereous one.

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

ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2007	2008	2009	2010	2011	2012 *	2013	2014	2015	2016	2017
JO1AA	Tetraciklini Tetracylines	1,87	1,83	1,66	1,15	1,39	1,19	1,19	1,12	1,14	1,02	1,00
JO1CA	Penicilini širokog spektra Broad spectrum penicillins	4,45	4,05	3,77	3,07	2,82	2,74	2,98	3,05	3,47	3,17	2,95
JO1CE	Penicilini uskog spektra Narrow spectrum penicillins	1,36	1,29	1,12	0,91	0,88	0,82	0,79	0,72	0,46	0,55	0,51
JO1CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0,06	0,05	0,00	0,00	0,00	0,00	0,00	0,00	0,01	0,00	0,01
JO1CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	5,42	5,93	5,35	5,55	5,93	7,63	7,50	7,80	7,96	7,82	8,01
JO1DB	Cefalosporini I gen. I gen. cephalosporins	1,91	1,65	1,28	1,05	0,84	0,79	0,77	0,72	0,66	0,60	0,47
J01DC	Cefalosporini II gen. II gen. cephalosporins	1,11	1,72	1,77	1,59	1,26	1,95	1,77	1,85	1,85	1,69	1,67
J01DD	Cefalosporini III gen. III gen. Cephalosporins	0,69	0,74	0,86	0,82	0,77	0,79	0,45	0,24	0,23	0,20	0,33
JO1EE	Sulfonamides + trimethoprim	1,44	1,24	1,03	0,87	0,73	0,67	0,67	0,65	0,63	0,59	0,55
JO1F	Macrolides, lincosamides	3,49	3,43	3,43	3,04	2,89	2,97	2,80	2,91	3,10	2,71	2,75
JO1G	Aminoglikozidi Aminoglycosides	0,01	0,01	0,01	0,01	0,01	0,00	0,00	0,04	0,01	0,00	0,01
JO1MA	Fluorokinoloni Fluoroquinolones	1,45	1,49	1,41	1,31	1,32	1,49	1,47	1,50	1,50	1,49	1,50
JO1XE	Nitrofurantoin	0,49	0,66	0,72	0,69	0,60	0,68	0,72	0,79	0,83	0,87	0,68
J01XX	Fosfomycin	-	-	-	-	-	-	-	-	-	0,004	0,05
UKUPNO TOTAL		**23,74**	**24,09**	**22,42**	**20,05**	**19,44**	**21,72**	**21,10**	**21,40**	**21,84**	**20,73**	**20,48**

* Do 2012.g. izvor podataka su bile veledrogerije, poslije 2012.g. izvor podataka je Hrvatski zavod za zdravstveno osiguranje / Until 2012 wholesalers were the sourse of data and starting with 2012 Croatian Health Insurance Fund data are used

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

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

ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2007	2008	2009	2010 *	2011	2012 **	2013	2014	2015	2016	2017
JO1AA	Tetraciklini Tetracylines	0,06	0,06	0,06	0,04	0,06	0,06	0,05	0,04	0,04	0,04	0,04
JO1CA	Penicilini širokog spektra Broad spectrum penicillins	0,10	0,08	0,05	0,06	0,05	0,06	0,09	0,04	0,05	0,06	0,04
JO1CE	Penicilini uskog spektra Narrow spectrum penicillins	0,04	0,02	0,01	0,01	0,03	0,03	0,03	0,02	0,02	0,02	0,02
JO1CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0,04	0,02	0,00	0,04	0,03	0,04	0,03	0,03	0,03	0,03	0,03
JO1CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	0,23	0,26	0,24	0,42	0,45	0,52	0,45	0,48	0,49	0,48	0,49
JO1DB	Cefalosporini I gen. cephalosporins	0,11	0,06	0,04	0,10	0,20	0,10	0,08	0,09	0,10	0,10	0,10
J01DC	Cefalosporini II gen. cephalosporins	0,23	0,20	0,16	0,20	0,21	0,23	0,21	0,20	0,20	0,19	0,20
J01DD + J01DE	Cefalosporini III + IV gen. cephalosporins	0,14	0,23	0,17	0,16	0,16	0,17	0,19	0,19	0,20	0,17	0,19
JO1DH	Carbapenems	0,04	0,04	0,04	0,06	0,06	0,07	0,06	0,07	0,08	0,08	0,11
JO1EE	Sulfonamides + trimethoprim	0,07	0,07	0,06	0,05	0,04	0,06	0,04	0,05	0,04	0,04	0,04
JO1F	Macrolides, lincosamides	0,11	0,12	0,13	0,13	0,14	0,16	0,15	0,14	0,15	0,15	0,16
JO1G	Aminoglikozidi Aminoglycosides	0,10	0,11	0,10	0,14	0,12	0,11	0,10	0,10	0,10	0,09	0,09
JO1MA	Fluorokinoloni Fluoroquinolones	0,20	0,21	0,20	0,26	0,22	0,22	0,22	0,23	0,24	0,25	0,27
JO1XA	Glycopeptides	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,04	0,03	0,04
JO1XD	Metronidazole	0,07	0,07	0,05	0,07	0,06	0,07	0,08	0,09	0,10	0,10	0,11
JO1XE	Nitrofurantoin	0,01	0,01	0,01	0,01	0,01	0,02	0,01	0,02	0,01	0,01	0,01
JO1XX	Fosfomycin	-	-	-	-	-	-	-	-	-	0,002	0,01
UKUPNO TOTAL		**1,55**	**1,50**	**1,38**	**1,82**	**1,88**	**1,97**	**1,79**	**1,87**	**1,91**	**1,88**	**1,98**

∗ Do 2010.g. korišteni su podaci dobiveni putem veledrogerija, a poslije od 2010.g. podaci iz bolničkih ljekarni / Until 2010 wholesales data were used and starting in 2010 hospital pharmacy data were used
** Do 2012.g. korišten je popis stanovništva iz 2001, poslije s 2012.g. korišten je popis iz 2011/ The Croatian Bureau of Statistics, Census 2001was used until 2012 and starting with 2012 Census 2011 was used

Potrošnja antibiotika u hrvatskim bolnicama

Potrošnja antibiotika u Hrvatskoj prati se odvojeno, bolničkа i ambulantna potrošnja. Od 2010. godine podaci se prikupljaju iz dva izvora, iz bolničkih ljekarni i putem veledrogerija, dok su do tada bili dostupni samo podaci prikupljeni putem veledrogerija. U tablici 2 prikazani su podaci dobiveni putem veledrogerija do 2010.g., a poslije od 2010.g. podaci dobiveni iz bolničkih ljekarni.

Za izračun bolničke potrošnje antibiotika, uz podatke o njihovoj potrošnji, bolnice dostavljaju i administrativne podatke, o broju bolničkih dana, broju primitaka pacijenata te broju bolničkih kreveta. Podaci se prikupljaju za čitavu 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 razini pojedinačne bolnice, tako i na nacionalnoj razini. Od 2011. godine u praćenje bolničke potrošnje uključena je i potrošnja antibiotika u dnevnim bolnicama a denominatoru su uz bolničke dane pridruženi terapijski dani dnevne bolnice.

Bolnička potrošnja antibiotika u 2017. godini prikazana je u tablici 2, za što je korišten denominator prema popisu stanovništva iz 2011. godine. Usporedba bolničke potrošnje antibiotika prema podacima dobivenim od veledrogerija i podacima iz bolničkih ljekarni prikazana je u tablici 8 i slici 7. Kao i prethodnih godina, ne postoji potpuna podudarnost, tako da za prošlu godinu razlika, ovisno o izvoru podataka, iznosi 0.15 DDD/TID u korist podataka dobivenih iz bolničkih ljekarni.

Podatke o bolničkoj potrošnji antibiotika su poslale sve bolnice (67) 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 informatičkih sustava bolničkih ljekarni, što su u 2017. godini učinile tri bolnice. Radi se o jednostavnom i sigurnom načinu dostave podataka s minimalnom mogućnošću pogreške tijekom daljnje obrade.

Bolnička potrošnja antibiotika u 2017. godini iznosi 1.98 DDD/TID (tablica 2), što je više u odnosu na prethodne dvije godine. Od 2013. godine prati se trend porasta bolničke potrošnje antibiotika koji dolazi do izražaja i kad se kao denominator koriste bolnički koopskrbni dani (DDD/100BOD) (40.10; 41.00; 41.67; 42.59; 45.30). U 2017. godini zabilježen je najveći porast bolničke potrošnje (za 2.71 DDD/100 BOD).

Porast potrošnje se bilježi za klasu tetraciklina (J01A), klasu cefalosporina (J01D), klasu makrolid-linkozamid (J01F), klasu kinolona (J01M) i klasu ostali (J01X). Najveći skok u potrošnji bilježe cefalosporini (za 1.39 DDD/100 BOD veća potrošnja) koji su preuzeli primat u potrošnji pred penicilinima. Prvi puta tijekom praćenja bolničke potrošnje cefalosporini su na prvom mjestu. Beta-laktamski antibiotici (penicilini i cefalosporini) čine 60% udjela u bolničkoj potrošnji antibiotika. Tri klase bilježe pad potrošnje: klasa penicilina (J01C), klasa aminoglikozida (J01G) te klasa sulfonamid i trimetoprim (J01E) (tablica 10, slika 9).

Skupina kinolona (J01M) je treća najzastupljenija klasa antibiotika, koja u bolničkoj potrošnji pokazuje daljnji trend porasta. Isto je vidljivo i kod potrošnje skupine ostali antibiotici (J01 X), u kojoj su zastupljeni glikopeptidi, imidazoli i polimiksin (tablica 10, slika 9).

Poredak najzastupljenijih antibiotika u bolničkoj potrošnji vidljiv je u tablici 11 i na slici 10. Kao i u ambulantnoj potrošnji, daleko na prvom mjestu je amoksicilin s klavulanskom kiselinom, a slijede ga gotovo podjednaki cefuroksim aksetil i ciprofloksacin, zatim ceftriakson i metronidazol.

Podatke o potrošnji antibiotika dostavilo je 13 **kliničkih ustanova** (tablica 12). Raspon potrošnje se kretao od 26.5 do 139.5 DDD/100 BOD, ovisno o profilu kliničke ustanove. Kod pet kliničkih ustanova

K 03, K 04, K 06, K 07, K 08, uoļava se porast potrošnje. Sedam klinika bilježi pad potrošnje (K 01; K 02; K 05; K 09; K 11; K 14; K 15.), dok jedna klinika (K 13) nema razlike u potrošnji u zadnje dvije godine. Na slici 11 prikazani su trendovi u potrošnji antibiotika za svaku kliniļku ustanovu.

Najhomogeniju skupinu bolnica ļine **opće bolnice**, njih 21, koje se meĽusobno mogu usporeĽivati po potrošnji antibiotika. Potrošnja antibiotika u opĺim bolnicama se kreĺe u širokom rasponu od 48.6 do 85.2 DDD/100 BOD, što odražava velike razlike u propisivanju antibiotika u ovoj skupini bolnica (tablica 13). Samo jedna bolnica se nalazi u najnižem rasponu potrošnje izmeĽu 41-50 DDD/100 BOD (O 14), dok su prošle godine u tom rasponu bile tri opĺe bolnice. Opĺim bolnicama O 02, O 04, O 12, O 18, O 19; O 22; O 24 potrošnja se kreĺe u rasponu od 51 ï 60 DDD/BOD. Isti broj opĺih bolnica potrošio je antibiotika izmeĽu 61 i 70 DDD/BOD (O 01; O 03; O 05; O 11; O 15; O 17; O 23). Dvije bolnice bilježe potrošnju izmeĽu 71 i 80 DDD/100BOD (O 13; O 21), a ļetiri opĺe bolnice iznad 80, (O 07; O 08; O 09; O 20), dok je prošle godine samo jedna bolnica prelazila 80 DDD/100 BOD. Ļetrnaest opĺih bolnica poveĺalo je potrošnju antibiotika u 2017. godini, dok je kod šest uoļen pad potrošnje, a jedna bolnica (O 09) ima podjednaku potrošnju u zadnje dvije godine.

Potrošnja antibiotika u **psihijatrijskim bolnicama** kreĺe se od 2.1 do 14.1 DDD/100 BOD (tablica 14). U 2017. godini u tri psihijatrijske bolnice (P 05; P 06; P 09) uoļava se porast potrošnje, dok je u ļetiri bolnice potrošnja u padu (P 01; P 02; P03; P 08). NajveĺE oscilacije u potrošnji antibiotika bilježi psihijatrijska ustanova P 07 (slika 13), koja uz izniman skok u 2016. godini, u 2017. godini bilježi veliki pad i najnižu potrošnju od kada se prati potrošnja.

Specijalne bolnice su podijeljene u dvije velike grupe s obzirom na njihov profil rada i kao takve bilježe veliki raspon u potrošnji antibiotika. U prvoj skupini nalazi se 10 bolnica, koje su namijenjene liječenju (akutnom/kroniļnom), dok je u drugoj skupini 14 ustanova namijenjeno rehabilitaciji. U prvoj skupini ustanova raspon potrošnje se kreĺe od 14.5 do 66.6 DDD/100 BOD. U drugoj skupini kretanje potrošnje antibiotika je od 0.3 do 11.7 DDD/100 BOD (tablica 15, slika 14).

Bolniļka potrošnja antibiotika raste. U 2017. godini zabilježen je najveći porast do sada. NajveĺE razlike u potrošnji antibiotika uoļavaju se u skupini opĺih bolnica, kod kojih je vidljivo da postoje ogromna odstupanja u potrošnji antibiotika. Raspon potrošnje se kreĺe od 48.6 do 85.2 DDD/100 BOD. Uoļljiv je trend porasta potrošnje kod više od polovine (14) opĺih bolnica. To su zabrinjavajući pokazatelji.

Što prije je potrebno krenuti s implementacijom rukovoĽenog naļina propisivanja antibiotika u svim bolnicama, kako bi njihova primjena bila usklaĽena sa struļnim preporukama, stvarnim indikacijama/potrebama i korigtena na pravilan naļin. Jedino tako se mogu nesmetano koristiti suvremena dostignuća u medicini, a da njihovu primjenu ne ugroze višestrukootporne bakterije za koje nemamo odgovarajući antibiotik.

Antibiotic consumption in Croatian hospitals

Antibiotic consumption in Croatian hospitals is monitored separately from outpatient consumption. Since 2010 antibiotic consumption has been monitored using two sources of data, hospital pharmacies and wholesales data, and up until then only wholesales data was available for surveillance.

To calculate hospital antibiotic consumption, it is necessary to obtain essential administrative data (number of bed days, number of admissions, number of hospital beds). Data is collected separately for the whole hospital and intensive care units (mixed, surgical, intern, paediatrics and other). Data on consumption can be expressed in defined daily doses (DDD) per 100 bed days, which is a more reliable indicator, and enables more detailed and precise surveillance of antibiotic consumption, not only for individual hospital but also on the national level. Since 2011 antibiotics used in daily hospitals are included in hospital antibiotic consumption and the number of daily hospital therapy days was added to the number of hospital bed days in a denominator.

The overview of the hospital consumption in 2017 is shown in Table 2. Data from Census 2011 has been used as a denominator. Table 8 and the Figure 7 show parallel monitoring of antibiotic consumption from wholesales data and data from hospital pharmacies. As in previous years, the data obtained for 2017 does not entirely match, depending on which source it comes from (0.15 DDD/TID). Data from hospital pharmacies show higher antibiotic consumption.

All hospitals (67) 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 the results for previous years. All hospitals had the opportunity to send the data directly from pharmacy information systems, and three hospitals used this opportunity. That is a simple and secure way to send data and possible errors during processing are minimal.

The hospital antibiotic consumption in 2017 amounted to 1.98 DDD/TID (Table 2), which is more than in two previous years. Since 2013, there has been an increasing trend in hospital antibiotic consumption visible also when expressed as daily doses per 100 bed days (40.10; 41.00; 41.67; 42.59; 45.30) (Table 9; Figure 8). In 2017 an increase in consumption of antibiotics is the highest ever (2.71 DDD/100BD).

There was an increase in the consumption of tetracyclins (J01A), cephalosporins (J01D), macrolide/lincosamides (J01F), quinolones (J01M) and antibiotics classified as other (J01X). The highest leap in hospital consumption is registered in the class of cephalosporins (consumption is higher for 1.39 DDD/BD) and for the first time cephalosporins are the most frequently used antibiotics. The consumption of beta-lactam antibiotics (penicillins and cephalosporins) makes over 60% of total hospital consumption. There was a decrease in the consumption of three classes of antibiotics: penicillins (J01C), aminoglycosides (J01G) and sulphonamide trimethoprim (J01E) (Table 10, Figure 9).

The class of quinolones (J01M) is the third most common class of antibiotics with a constant increase in consumption over the last few years. Moreover, there was an increase in the consumption of antibiotics classified as other (J01X) (glycopeptides, imidazole and polymyxin) (Table 10, Figure 9).

The consumption of the most frequently used antibiotics is shown in Table 11 and Figure 10. In the first place are amoxicillin and clavulanic acid, then cefuroxime axetil and ciprofloxacin, with ceftriaxon and metronidazole following. This distribution is similar to the one observed in the community consumption surveillence.

Thirteen tertiary care hospitals sent their data on antibiotic consumption (Table 12), and their consumption ranges from 26.5 to 139.5 DDD/100 BD. The differences in consumption reflect different hospital institution profiles. In five clinics (K 03; K 04; K 06; K 07; K 08) there is an increase in antibiotic consumption. In seven clinics there is a decrease in consumption (K 01; K 02; K 05; K 09; K

011; K14; K15). In one clinic there has been no difference in consumption in the last two years (K 13). Figure 11 shows the consumption for each clinic.

The group consisting of 21 general hospitals is the most homogeneous group, so the data on antibiotic consumption can be easily compared. Antibiotic consumption in general hospitals ranges between 48.6 and 85.2 DDD/100 BD, which reflects quite different approaches in antibiotic prescribing (Table 13). There is only one hospital with a consumption range between 41-50 DDD/100 BD (O 14). Last year there were three hospitals in this group. Hospitals O 02; O 04; O 12; O 18; O 19; O22; O24 have a consumption range from 51 to 60 DDD/100 BD. The consumption in seven general hospitals varies between 61 and 70 DDD/100 BD (O 01; O 03; O 05; O 11; O 15; O 17; O 23). Two hospitals have a consumption range between 71-80 DDD/100 BD (O 13; O 21), and as much as four hospitals have consumption range over 80 (O 07; O 08; O 09; O 20) while only one hospital belonged to this group last year. In fourteen general hospitals there is an increase in antibiotic consumption in 2017, and in six hospitals there is a decrease in consumption. Only one hospital (O 09) has had no oscillations in consumption over the last two years.

Antibiotic consumption in psychiatric hospitals ranges between 2.1 and 14.1 DDD/100 BD (Table 14). In 2017, three psychiatric hospitals registered an increase in consumption (P 05; P 06; P 09), while four hospitals registered a decreasing trend in antibiotic consumption (P 01; P 02; P 03; P 08). Hospital P 07 has the highest oscillations in consumption (Figure 13). In 2016 this hospital antibiotic consumption had an increasing trend, but in 2017 consumption is the lowest ever.

Specialized hospitals are divided into two large groups with regard to their patient profile, and they are characterised by a wide range in antibiotic consumption. In the first group there are 10 hospitals where patients (acute/chronic) are treated, while in the other there are 14 rehabilitation facilities. The first group has the consumption range between 14.5 and 66.6 DDD/100 BD. In the other group, the range is between 0.3 and 11.7 DDD/100 BD (Table 15, Figure 14).

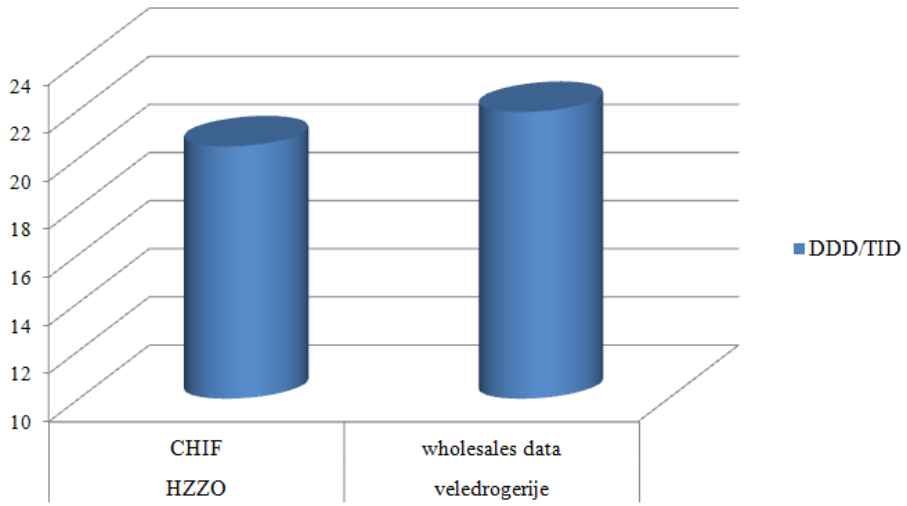
To sum up, there is an increasing trend in hospital antibiotic consumption. In 2017, consumption was the highest ever. In the group of general hospitals, there is the biggest difference in consumption, and it ranges between 48.6 and 85.2 DDD/100 BD, which reflects rather different approaches in antibiotic prescribing. In as much as fourteen hospitals there is an increase in antibiotic consumption and that indicates improper use of antibiotics.

Responsible prescribing of antibiotics and antibiotic stewardship need to be implemented in all hospitals as soon as possible, so that antibiotics are used in accordance with the professional guidelines, actual indications and in a proper way. The only way to implement the latest achievements in medicine is to develop strategies for controlling multidrug-resistant bacteria, for which we do not have an appropriate antibiotic.

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

	HZZO CHIF	veledrogerije wholesales data
DDD	32034042,88	34274404,47
DDD/TID	20,48	21,91

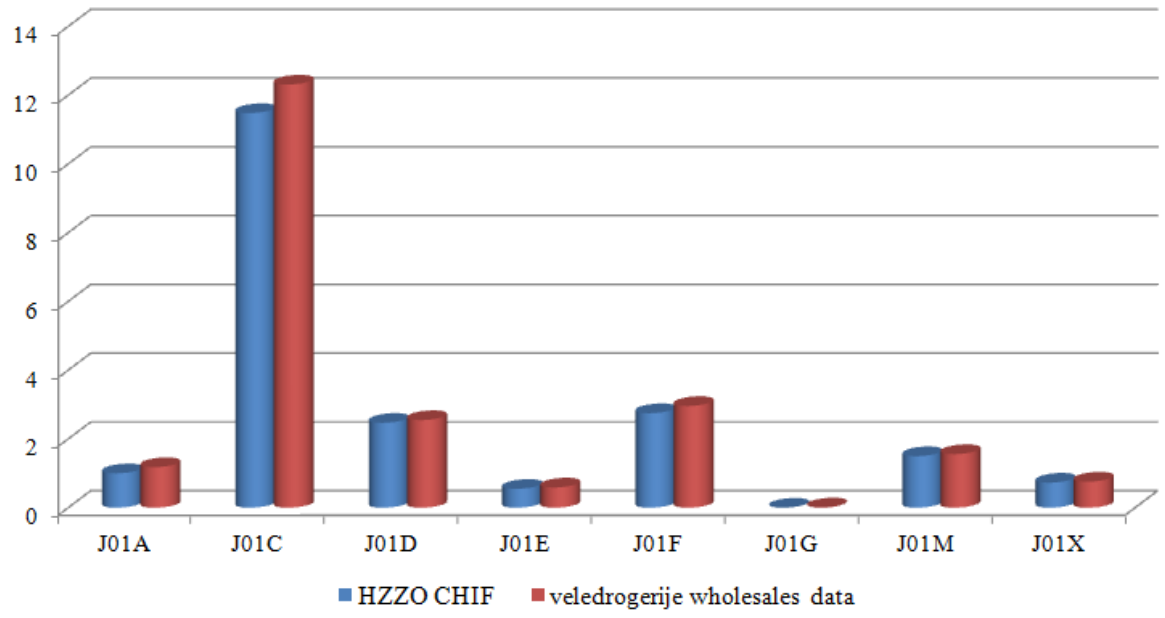
Slika 2. */ Figure 2.*
Ambulantna potrošnja antibiotika (DDD/TID) usporedba podataka HZZO i veledrogerija /
Ambulatory antibiotic consumption (DDD/TID) comparison between CHIF data and wholesales data



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

DDD/TID	HZZO CHIF	veledrogerije wholesales data
J01A	1,00	1,18
J01C	11,48	12,31
J01D	2,47	2,55
J01E	0,55	0,59
J01F	2,75	2,96
J01G	0,00	0,01
J01M	1,50	1,56
J01X	0,73	0,76

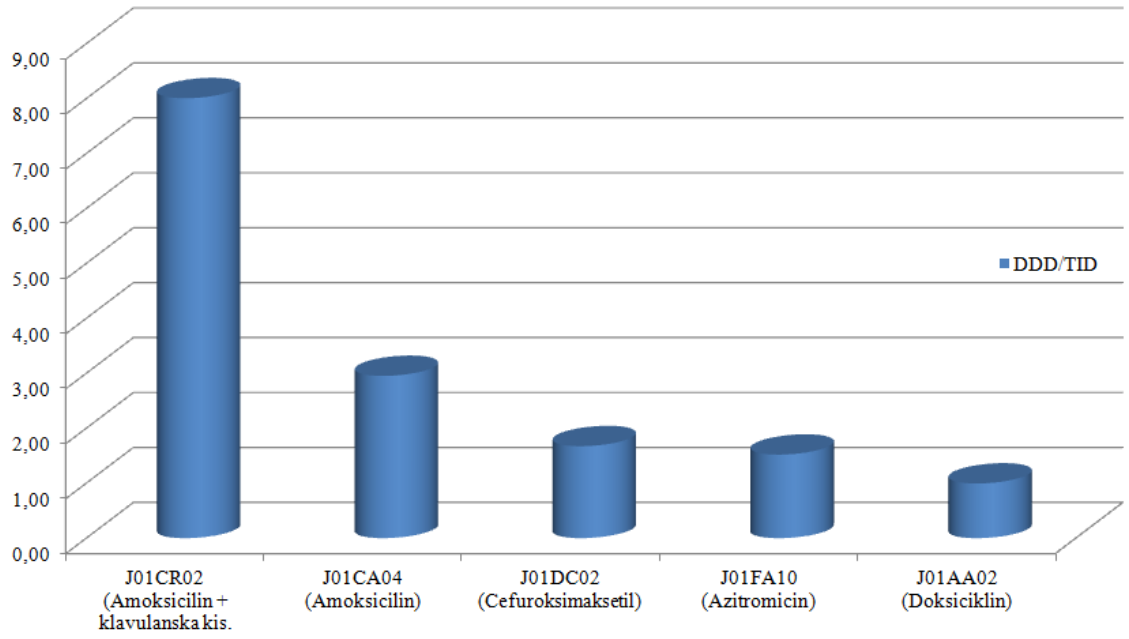
Slika 3. / *Figure 3.*
Ambulantna potrošnja antibiotika (DDD/TID) po klasama, usporedba podataka HZZO i veledrogerija /
Ambulatory antibiotic consumption (DDD/TID) *by class, comparison between CHIF data and wholesales data*



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

klasa	DDD/TID
J01CR02 (Amoksicilin + klavulanska kiselina)	8,01
J01CA04 (Amoksicilin)	2,95
J01DC02 (Cefuroksimaksetil)	1,67
J01FA10 (Azitromicin)	1,52
J01AA02 (Doksiciklin)	1,00

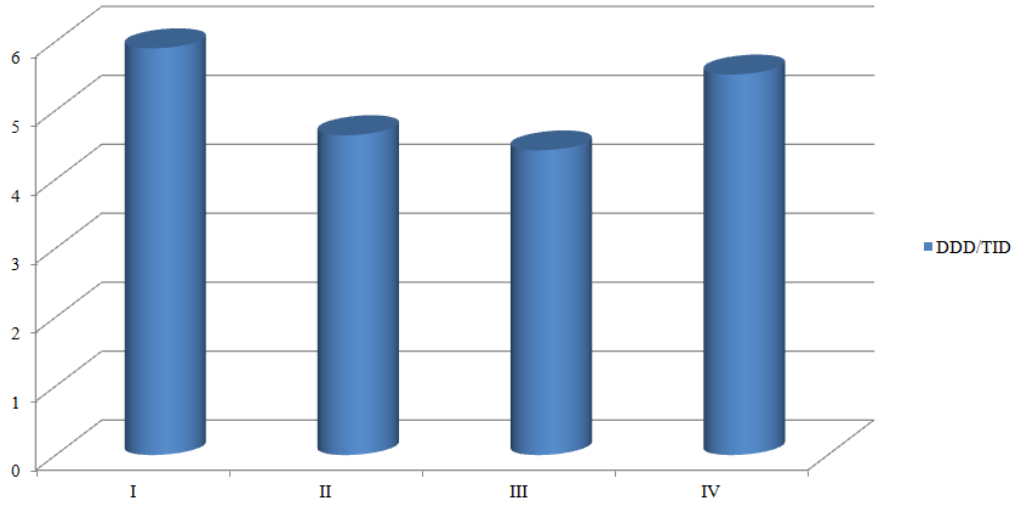
Slika 4. */ Figure 4.*
Ambulantna potrošnja antibiotika („top 5“ antibiotika – DDD/TID), izvor podataka - HZZO/ *Ambulatory antibiotic consumption („top 5“ antibiotics- DDD/TID); origin of data-CHIF*



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

kvartal	DDD/TID
I	5,90
II	4,64
III	4,42
IV	5,52

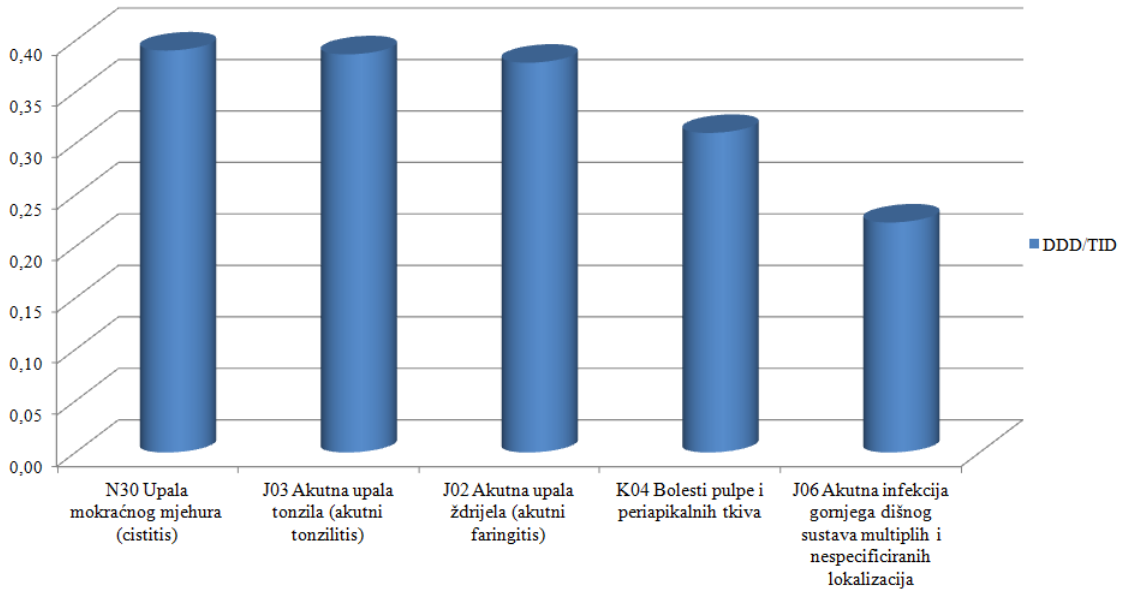
Slika 5. */ Figure 5.*
Ambulantna potrošnja antibiotika po kvartalima – DDD/TID, izvor podataka - HZZO
Ambulatory antibiotic consumption – by quarters DDD/TID; origin of data-CHIF



Tablica 7. */ Table 7.*
Ambulantna potrošnja antibiotika „top 5“ dijagnoza – DDD/TID, izvor podataka - HZZO
Ambulatory antibiotic consumption „top 5“ diagnosis – DDD/TID, origin of data-CHIF

MKB dijagnoza	DDD/TID
N30 Upala mokraćnog mjehura (cistitis)	0,39
J03 Akutna upala tonzila (acute tonzilitis)	0,39
J02 Akutna upala ždrijela (acute faringitis)	0,38
K04 Bolesti pulpe i periapikalnih tkiva (pulp and periapical tissue infections)	0,31
J06 Akutna infekcija gornjega dišnog sustava multiplih i nespecificiranih lokalizacija (upper respiratory tract infections)	0,22

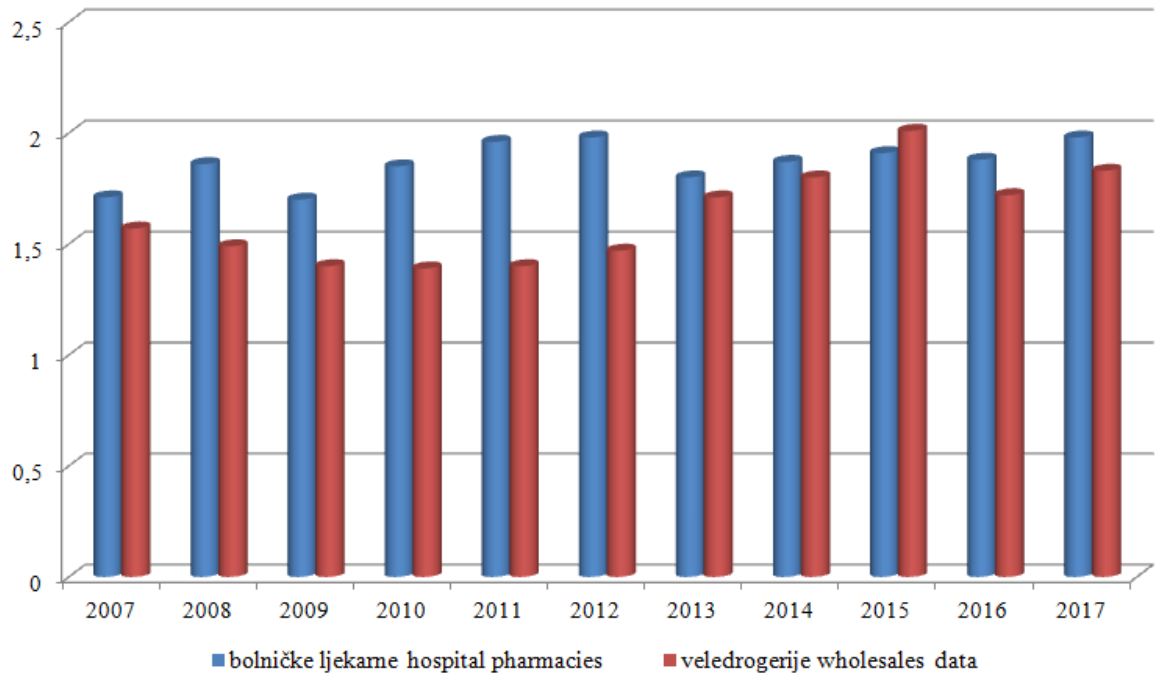
Slika 6. */ Figure 6.*
Ambulantna potrošnja antibiotika „top 5“ dijagnoza – DDD/TID, izvor podataka - HZZO
Ambulatory antibiotic consumption „top 5“ diagnosis – DDD/TID, origin of data-CHIF



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

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
2017	1,98	1,83

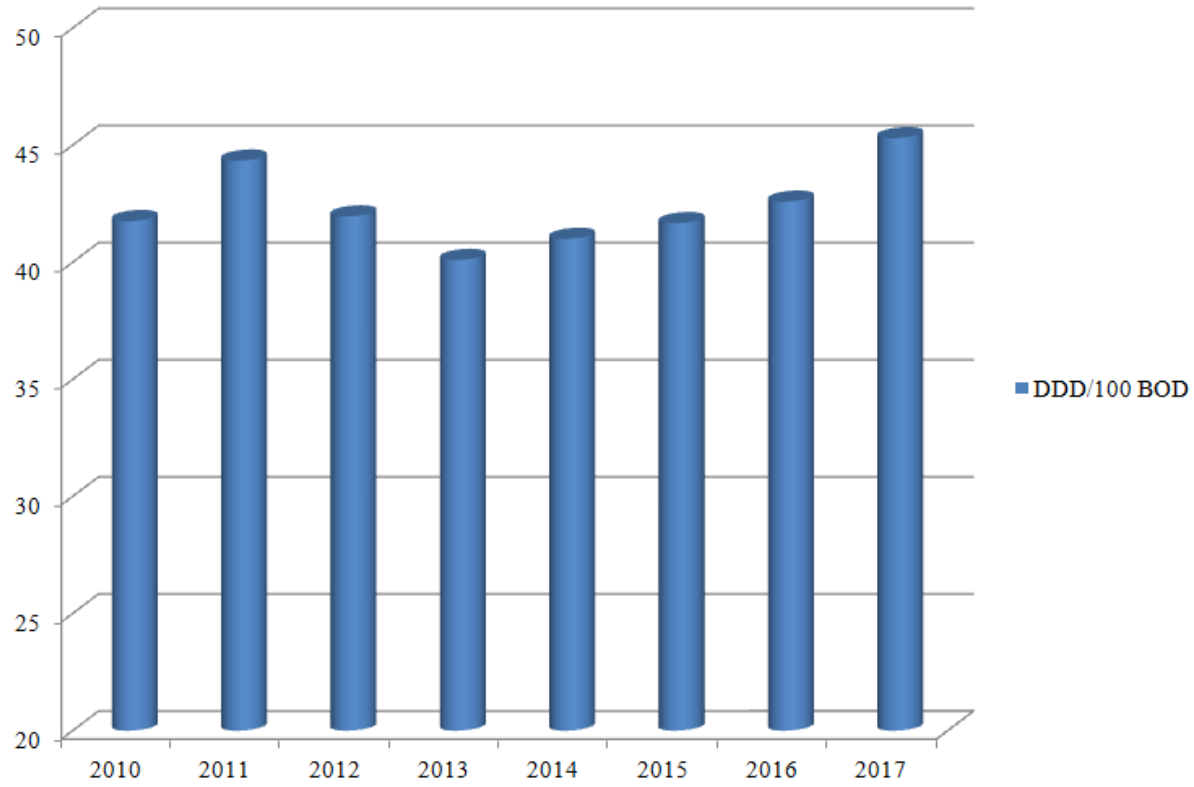
Slika 7. / *Figure 7.*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija
Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales data



Tablica 9. */ Table 9.*
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
2017	45,30

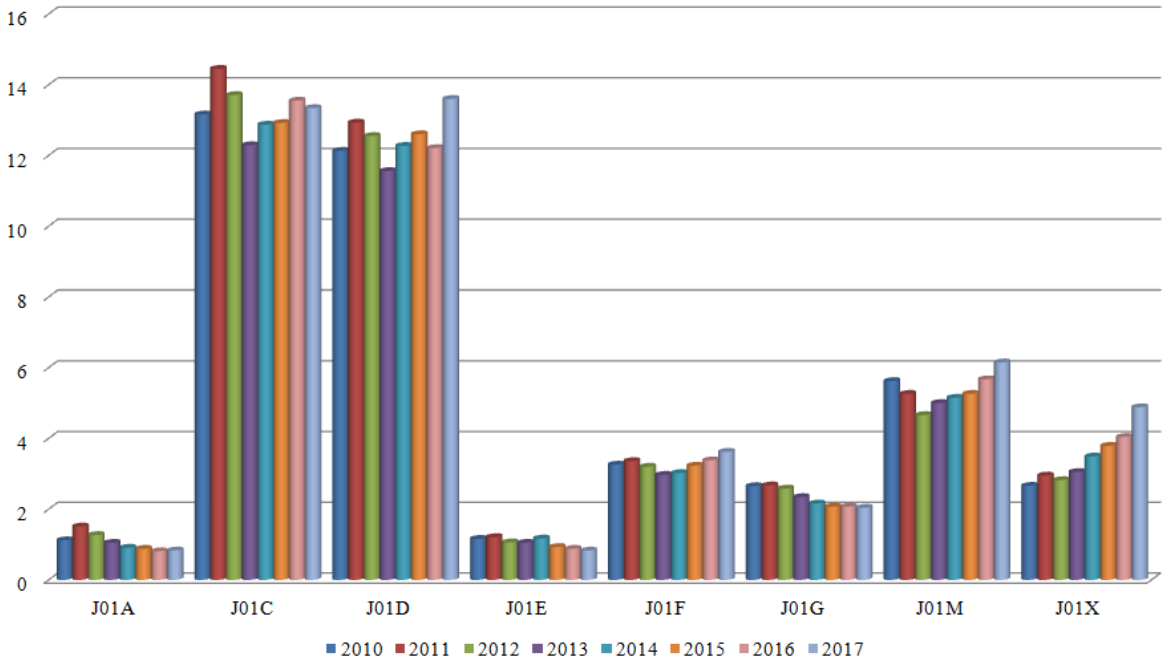
Slika 8. */ Figure 8.*
Bolnička potrošnja antibiotika (DDD/100BOD)
Hospital antibiotic consumption (DDD/100 BD)



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

Klasa / *class*	Godina / *year*							
	2010	2011	2012	2013	2014	2015	2016	2017
J01A	1,12	1,51	1,27	1,05	0,91	0,88	0,81	0,83
J01C	13,16	14,45	13,71	12,29	12,87	12,92	13,55	13,34
J01D	12,13	12,93	12,55	11,56	12,27	12,6	12,21	13,60
J01E	1,16	1,21	1,06	1,05	1,17	0,93	0,88	0,83
J01F	3,26	3,36	3,2	2,97	3,02	3,23	3,38	3,62
J01G	2,65	2,67	2,58	2,34	2,16	2,07	2,07	2,04
J01M	5,62	5,26	4,66	5,00	5,15	5,26	5,67	6,15
J01X	2,66	2,95	2,82	3,05	3,49	3,79	4,04	4,88

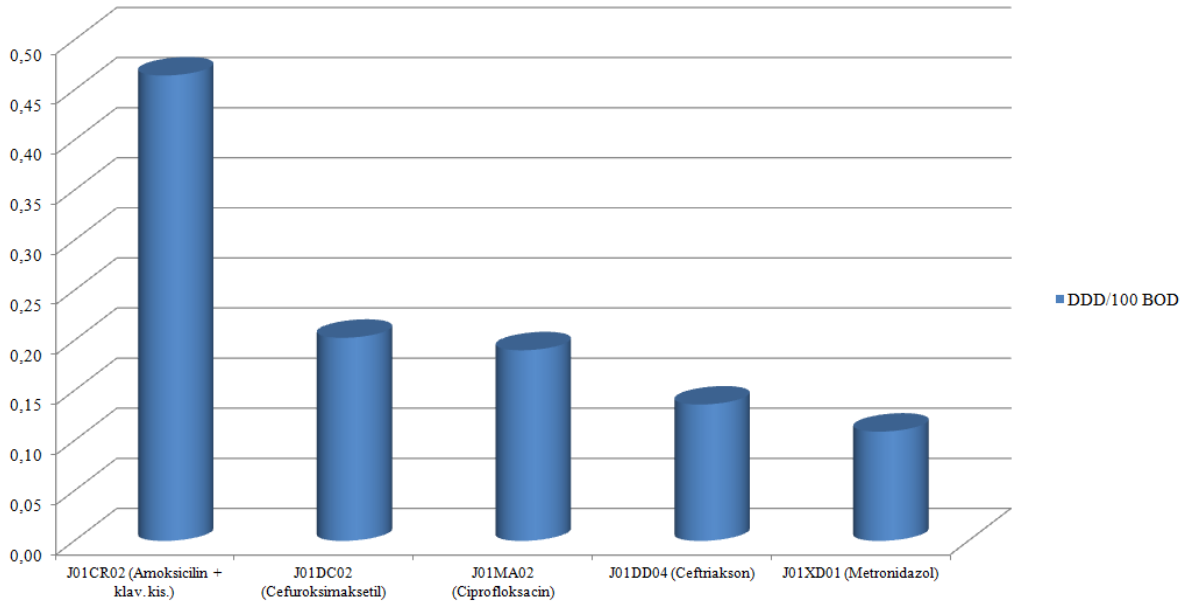
Slika 9. */ Figure 9.*
Bolnička potrošnja antibiotika (DDD/100 BOD) po klasama, izvor podataka - bolničke ljekarne /
Hospital antibiotic consumption (DDD/100 BD) by class, origin of data - hospital pharmacies



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

klasa	DDD/BOD
J01CR02 (Amoksicilin + klavulanska kiselina)	0,46
J01DC02 (Cefuroksimaksetil)	0,20
J01MA02 (Ciprofloksacin)	0,19
J01DD04 (Ceftriakson)	0,14
J01XD01 (Metronidazol)	0,11

Slika 10. */ Figure 10.*
Bolnička potrošnja antibiotika „top 5“ antibiotika – DDD/BOD, izvor podataka - bolničke ljekarne / *Hospital antibiotic consumption „top 5“ antibiotics – DDD/BD; origin of data - hospital pharmacies*

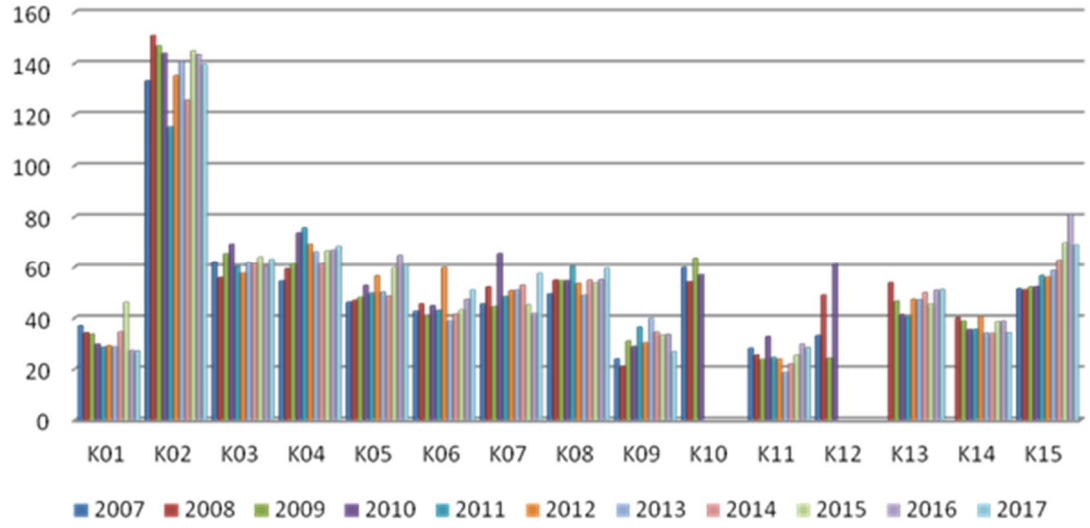


Tablica 12. */ Table 12.*
KLINIČKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2017.
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2017

	DDD/100 BOD, DDD/100BD								
USTANOVA INSTITUTION	UKUPNO TOTAL	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
K 01	26,8	0,0	5,3	11,1	0,0	4,1	3,9	0,4	1,9
K 02	139,5	3,1	47,7	49,5	2,2	10,5	2,8	7,2	16,6
K 03	62,9	0,1	20,3	16,1	1,0	3,4	2,5	10,8	8,7
K 04	68,1	0,9	20,6	19,7	1,3	4,5	1,5	11,4	8,0
K 05	60,6	1,0	18,1	16,2	0,7	4,3	3,6	9,6	7,2
K 06	50,7	0,6	7,9	22,7	0,9	3,2	2,8	5,4	7,2
K 07	57,2	0,7	11,2	19,5	0,9	4,6	2,5	8,8	9,0
K 08	59,3	1,6	13,9	20,2	0,9	3,0	1,5	9,3	8,8
K 09	26,5	0,0	7,0	10,2	0,4	0,3	0,7	7,2	0,8
K 10*									
K 11	28,2	1,1	6,9	13,1	0,2	1,1	1,0	0,8	4,1
K 12*									
K 13	50,9	0,1	16,8	15,8	1,7	5,0	2,7	2,5	6,5
K 14	34,0	0,2	10,1	14,5	0,5	2,6	1,8	1,1	3,1
K 15	68,7	0,4	21,7	17,8	0,0	5,8	1,5	13,6	7,9

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

Slika 11. */ Figure 11.*
KLINIČKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2007.-2017.
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2007-2017

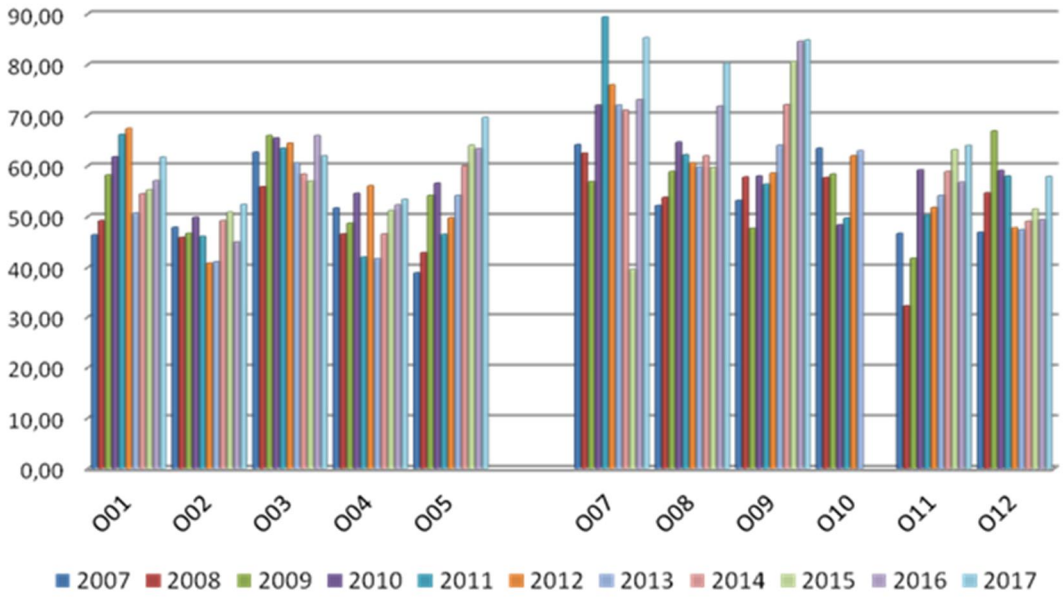


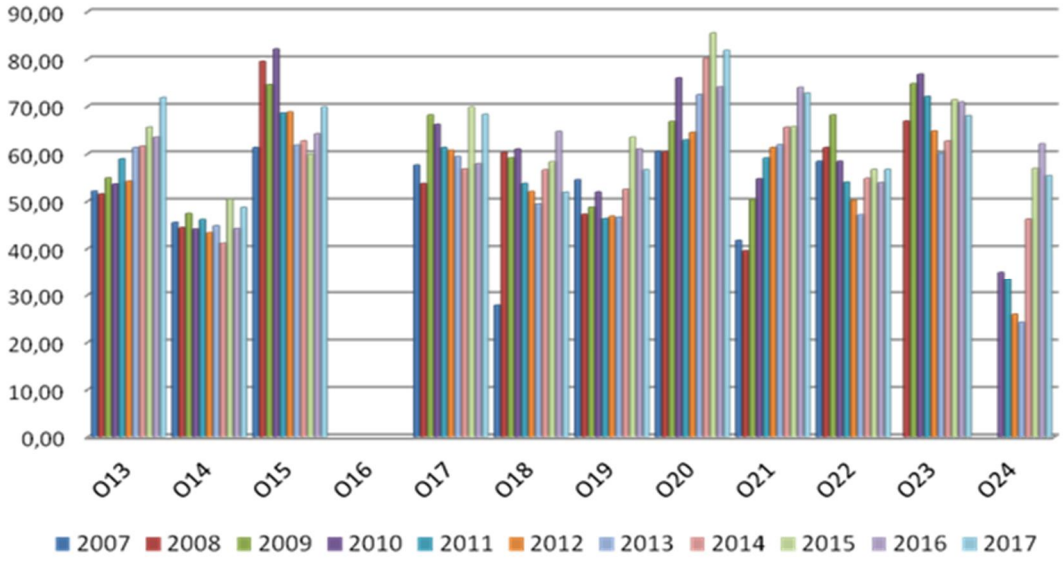
Tablica 13. */ Table 13.*
OPĆE BOLNICE - POTROŠNJA ANTIBIOTIKA 2017.
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2017

USTANOVA INSTITUTION	UKUPNO TOTAL	DDD/100 BOD, DDD/100 BD							
		JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
O 01	61,7	3,1	19,9	17,4	0,3	6,0	4,3	4,6	6,0
O 02	52,3	0,2	24,9	13,9	0,4	3,0	2,0	3,8	4,1
O 03	61,9	3,9	13,2	22,4	0,3	9,0	2,5	5,5	5,1
O 04	53,3	2,3	10,5	12,6	0,0	7,2	5,8	10,1	4,7
O 05	69,5	4,6	22,9	15,7	0,3	7,4	5,7	7,2	5,7
O 06*									
O 07	85,2	1,0	26,6	24,6	0,9	11,0	6,7	11,4	2,9
O 08	80,2	2,0	34,5	16,0	1,1	5,0	2,4	10,0	9,2
O 09	84,7	2,0	26,8	28,5	0,5	5,1	6,6	9,0	6,3
O 10									
O 11	63,9	0,9	19,7	20,6	0,4	3,0	3,1	9,7	6,5
O 12	57,8	1,6	18,4	16,6	0,5	6,0	1,4	8,7	4,6
O 13	71,8	0,5	21,5	28,4	0,3	7,5	1,8	5,6	6,1
O 14	48,6	1,0	21,0	11,6	0,5	2,8	2,0	5,5	4,3
O 15	69,8	2,3	24,4	22,0	0,3	3,6	5,9	3,6	7,9
O 16**									
O 17	68,2	0,6	19,6	22,4	0,7	7,2	3,4	6,2	8,1
O 18	51,8	1,4	22,2	11,6	0,2	2,5	1,8	7,7	4,4
O 19	56,5	0,2	2,01	13,3	0,1	5,5	3,7	9,6	4,0
O 20	81,7	1,8	18,5	29,4	0,3	5,3	3,3	16,7	6,4
O 21	72,7	0,7	24,6	15,8	0,2	9,1	4,3	10,7	7,4
O 22	56,6	0,2	17,4	11,8	0,4	4,1	2,6	16,8	3,2
O 23	67,9	1,6	23,7	16,9	0,3	9,4	5,7	4,5	5,9
O 24	55,3	0,8	24,9	9,9	1,1	2,8	1,7	10,9	3,3

*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 12. / *Figure 12.*
OPĆE BOLNICE - POTROŠNJA ANTIBIOTIKA 2007.-2017.
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION 2007-2017

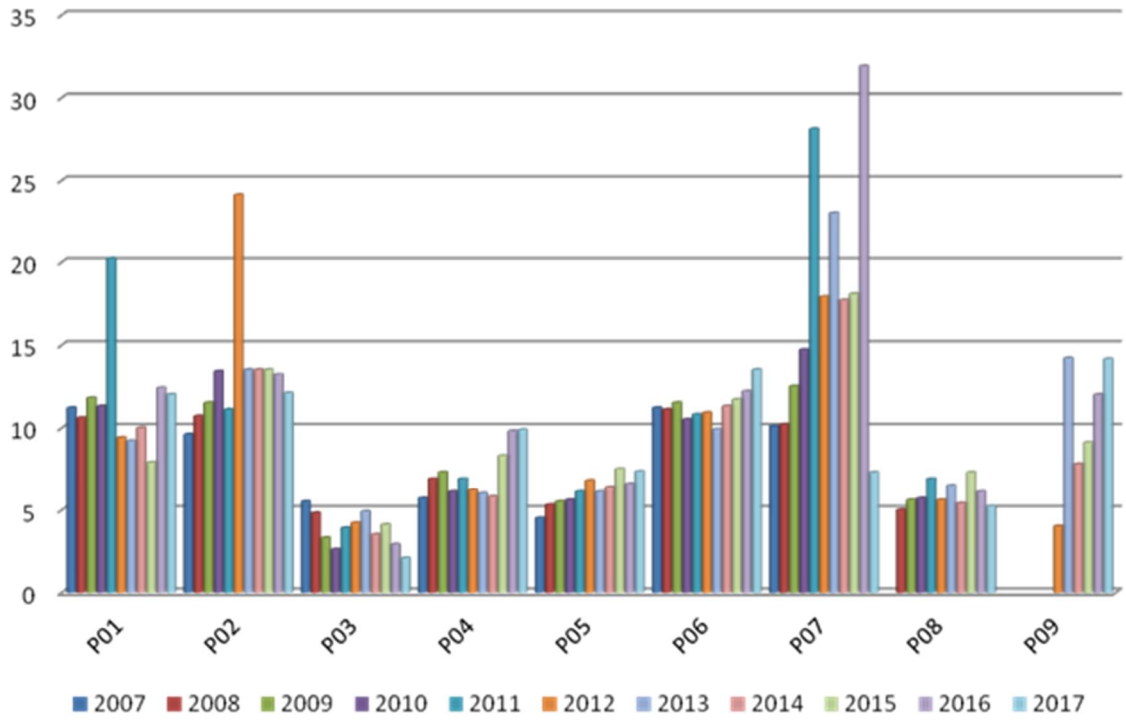




Tablica 14. */ Table 14.*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2017.
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION IN 2017

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100BD								
	UKUPNO / TOTAL	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
P 01	12,0	0,2	6,7	2,1	0,5	1,1	0,2	0,9	0,4
P 02	12,1	0,1	6,0	2,1	0,2	1,1	0,1	2,1	0,4
P 03	2,1	0,0	1,8	0,3	0,0	0,0	0,0	0,0	0,0
P 04	9,9	0,9	3,4	1,2	0,1	1,8	0,0	2,1	0,4
P 05	7,4	0,1	5,0	0,6	0,0	0,6	0,1	0,8	0,1
P 06	13,5	0,2	6,5	1,8	0,1	1,3	0,1	2,9	0,7
P 07	7,3	0,0	4,0	1,3	0,1	0,3	0,4	0,4	0,8
P 08	5,2	0,3	2,8	0,9	0,1	0,2	0,1	0,5	0,4
P 09	14,1	0,2	5,3	3,2	0,1	1,2	1,4	1,8	0,9

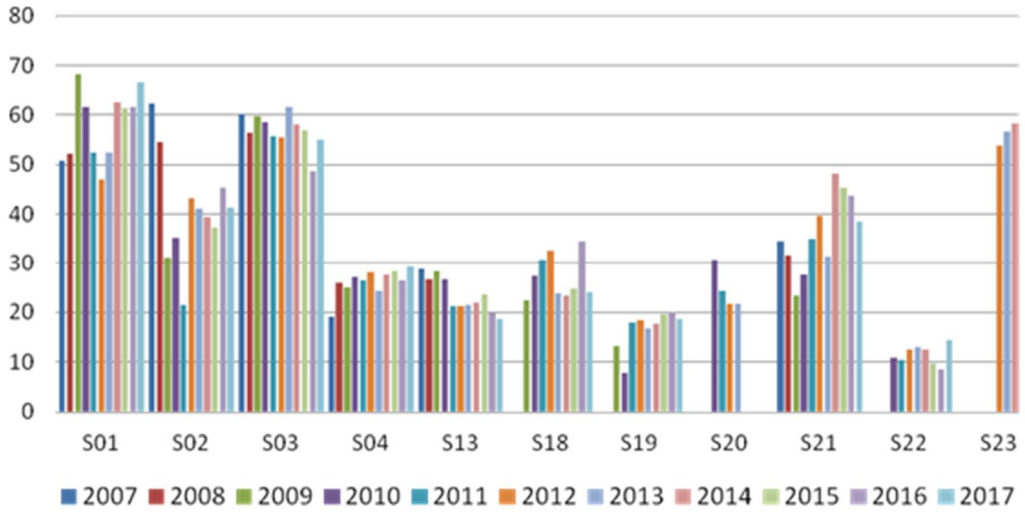
Slika 13. / *Figure 13.*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2007.-2017.
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION 2007-2017

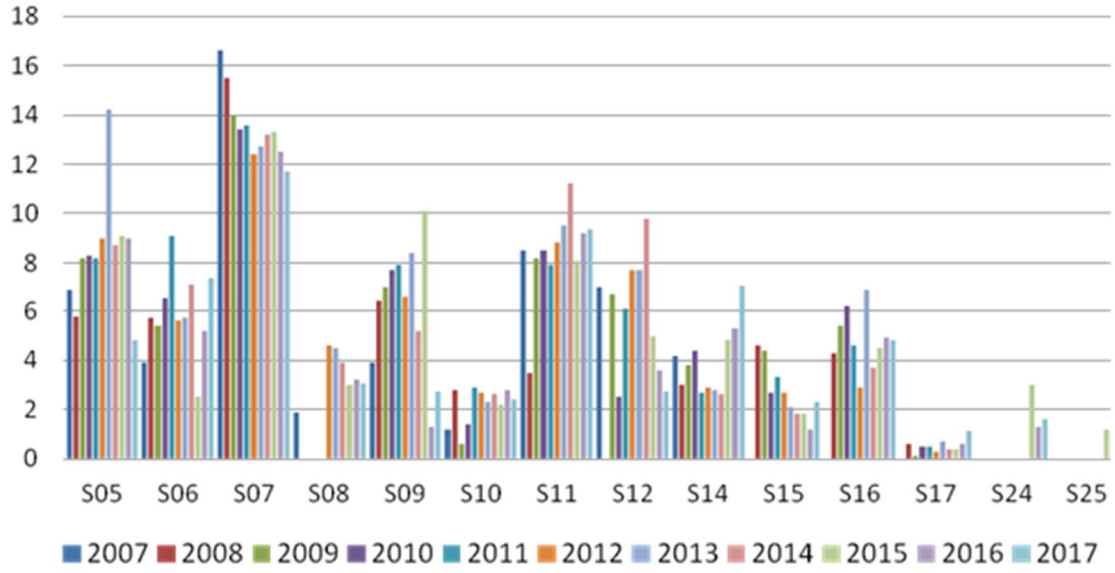


Tablica 15. */ Table 15.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2017.
SPECIALISED HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2017

	DDD/100 BOD, DDD/100 BD								
USTANOVA INSTITUTION	UKUPNO TOTAL	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
S 01	66,6	1,1	13,6	12,7	2,3	11,7	8,9	11,8	4,5
S 02	41,3	0,1	17,5	10,1	0,1	12,5	0,4	0,4	0,2
S 03	55,0	0,3	18,3	10,7	0,8	8,2	3,7	10,7	2,3
S 04	29,2	0,1	13,7	3,5	1,6	1,9	2,5	3,9	2,0
S 13	18,6	3,4	4,0	5,0	1,5	0,2	0,7	2,7	1,1
S 18	24,2	1,0	10,0	7,9	0,1	1,1	0,2	3,3	0,5
S 19	18,7	0,4	3,4	7,1	1,4	2,0	0,3	3,5	0,5
S 20									
S 21	38,4	0,0	14,3	10,9	0,4	1,8	0,0	7,6	3,4
S 22	14,5	0,2	3,1	7,5	0,0	1,1	2,5	0,0	0,0
S 23	34,7	0,0	0,0	31,4	0,0	1,1	0,0	1,5	0,8
S 05	4,8	0,0	0,1	1,6	0,2	0,9	0,6	1,1	0,5
S 06	7,4	0,0	3,1	0,9	0,2	0,3	0,1	2,6	0,2
S 07	11,7	0,0	3,6	2,7	0,2	1,0	0,3	3,0	0,9
S 08	3,1	0,0	1,8	0,3	0,2	0,4	0,0	0,4	0,0
S 09	2,7	0,1	1,1	0,2	0,0	0,9	0,4	0,0	0,0
S10	2,4	0,2	0,9	0,4	0,3	0,2	0,0	0,4	0,1
S11	9,3	0,2	5,3	0,6	0,1	0,8	0,1	1,6	0,7
S12	2,8	0,5	1,8	0,0	0,0	0,4	0,0	0,0	0,0
S14	7,1	0,3	2,1	2,7	0,2	1,2	0,0	0,5	0,0
S15	2,3	0,0	1,1	0,9	0,0	0,3	0,0	0,0	0,0
S16	4,8	0,0	2,2	0,3	0,1	0,3	0,0	0,8	1,1
S17	1,1	0,1	0,7	0,1	0,0	0,1	0,0	0,1	0,1
S24	1,6	0,0	0,7	0,1	0,0	0,0	0,0	0,6	0,2
S25	0,3	0,0	0,3	0,0	0,0	0,0	0,0	0,0	0,0

Slika 14. / *Figure 14.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2007.-2017.
SPECIALISED HOSPITALS – ANTIBIOTIC CONSUMPTION 2007-2017





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*