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 I SOCIJALNE SKRBI RH
UNIVERSITY HOSPITAL FOR INFECTIOUS DISEASES "DR. F. MIHALJEVIĆ"
REFERENCE CENTER FOR ANTIBIOTIC RESISTANCE SURVEILLANCE, CROATIAN MINISTRY OF HEALTH AND SOCIAL WELFARE

Osjetljivost i rezistencija bakterija na antibiotike u Republici Hrvatskoj u 2010.g.

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Suradne ustanove Akademije medicinskih znanosti Hrvatske na programu praćenja rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences collaborating institutions on the antibiotic resistance surveillance program

Krka farma d.o.o.
PharmaSwiss d.o.o.
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SADRŽAJ

PREDGOVOR:

Rezistencija bakterija na antibiotike predstavlja prirodnu prilagodbu bakterija na uvjete života u kojima je okoliš pun antibiotika. Preživljavanje i širenje uspješnih mutanti je prirodan tijek koji je teško kontrolirati ako se čimbenik koji dovodi do selekcije mutanti ne ukloni ili smanji. Prostora za racionalizaciju uporabe antibiotika u Hrvatskoj ima puno. Hrvatska se ubraja u europske zemlje s velikom potrošnjom antibiotika. Najveća količina antibiotika se troši ambulantno, no problem rezistencije je najočitiji u bolničkim sredinama gdje se već susrećemo i s panrezistentnim bakterijama. Sve veći broj imunokompromitiranih pacijenata i sve invazivniji dijagnostički i terapeutski zahvati doveli su do promjene u infektivnoj patologiji i do sve teže interpretacije bakterioloških nalaza. Granicu između komenzala i patogena je teško postaviti bez dobrog poznavanja patogenog potencijala izolata i kliničke slike domaćina. U Hrvatskoj nije još dobro razvijen program racionalnog rukovođenja propisivanjem antibiotika (engl. "antibiotic stewardship") koji se u zapadnoeuropskim bolnicama odvija kroz djelovanje timova infektologa, mikrobiologa i farmakologa (farmaceuta) te je vjerojatno to jedan od bitnih razloga visoke potrošnje antibiotika u hrvatskim bolnicama. U zemljama u kojima su se ovakvi timovi razvili i u kojima timovi rješavaju pitanje individualne antimikrobne terapije za većinu pacijenata rezistencija na antibiotike je niža negoli u zemljama gdje su ove struke izdvojene iz rutinskog rada rizičnih odjela. Očito je da je prvi preduvjet za racionalnu uporabu antibiotika vladati podacima o rezistenciji pojedinih bakterijskih vrsta u vlastitoj sredini. Odbor za praćenje rezistencije bakterija na antibiotike u RH, koji je 1996.g. osnovan pri Kolegiju za javno zdravstvo Akademije medicinskih znanosti Hrvatske (AMZH), u suradnji s Referentnim centrom za praćenje rezistencije bakterija na antibiotike Ministarstva zdravstva (MZSS), koji je osnovan 2003.g. pri Klinici za infektivne bolesti "Dr. F. Mihaljević", već dugi niz godina pruža podatke o rezistenciji u različitim krajevima Hrvatske. Tijekom godina mreža mikrobioloških laboratorija koji sudjeluju u praćenju je narasla tako da podaci obuhvaćaju >90% populacije Hrvatske. Svim aktivnostima na području kontrole širenja rezistencije od 2006.g. koordinira Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike (ISKRA), interdisciplinarno tijelo (engl. "intersectorial coordination mechanism", ICM) pri MZSS. U tijeku dugog niza godina rada Odbor se uključio u najvažnije internacionalne programe praćenja rezistencije (European Antimicrobial Resistance Surveillance System, EARSS) i potrošnje (European Surveillance of Antimicrobial Consumption, ESAC) antibiotika. U okviru Odbora AMZH osnovana je i hrvatska podružnica internacionalne organizacije The Alliance for the Prudent Use of Antibiotics (APUA). Prelaskom EARSS i ESAC projekata u EARS-Net i ESAC-Net, 2010.g. i 2011.g. u The European Surveillance System (Tessy) mrežu Europskog centra za kontrolu bolesti (engl. "European Center for Disease Control", ECDC) Hrvatska je nastavila suradnju s ECDC Tessy programom, koji trenutno zbog političkog statusa Hrvatske ne uključuje publiciranje hrvatskih podataka u sklopu Tessy rezultata. Odbor AMZH i Referentni centar MZSS nastavljaju, međutim, prikupljati podatke o rezistenciji i potrošnji, na način kako je to rađeno u okviru EARSS i ESAC programa i hrvatski podaci će biti i nadalje objavljivani u sklopu ove redovne godišnje publikacije. U sklopu obilježavanja Europskog dana svjesnosti o antibioticima (engl. "European Antibiotic Awareness Day", EAAD) 18. studenog 2010.g. održan je u Zagrebu EAAD Simpozij. Europska javna kampanja je u 2010.g. bila usmjerena prvenstveno na racionalizaciju potrošnje antibiotika u bolnicama pa su i teme Simpozija bile tome usmjerene, a prigodom EAAD podijeljen je i prikladni promidžbeni materijal. Jedan od važnih događaja u 2010.g. bilo je donošenje europskih standarada za testiranje osjetljivosti na antibiotike. Tim povodom krajem studenog održan je u Klinici za infektivne bolesti VI. tečaj o rezistenciji bakterija na antibiotike koji je tijekom 10 dana obuhvatio 75 polaznika. Ovaj tečaj je predstavljao pripremu za prelazak hrvatskih laboratorija na European Committee for Antimicrobial Sensitivity Testing (EUCAST) metodologiju.

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

PREFACE:

By developing resistance to antibiotics bacteria adapt to living conditions in an environment full of antibiotics. Survival and spread of resistant mutants is a natural process that is difficult to control as long as the selective pressure is not removed or diminished. There is plenty of space for improvement in antibiotic prescribing in Croatia. Croatia is among the European countries with high antibiotic consumption. The majority of antibiotics are spent ambulatory but the resistance problem is most obvious in hospitals where panresistant bacteria are already encountered. Increasing number of immunocompromised patients and invasive diagnostic and therapeutic procedures has changed the pathophysiology of infectious diseases and consequently correct interpretation of bacteriological findings is becoming ever more difficult. A distinction between commensals and pathogens is possible only if pathogenic potential of the microorganism and clinical status of the patient are well understood. In Croatia "antibiotic stewardship" program is not yet well developed and the lack of antibiotic management teams may well be the reason for high antibiotic prescribing in Croatian hospitals. In Western European hospitals where individual patient antibiotic treatment is guided by a team of infectious diseases, clinical microbiology and pharmacology doctors (pharmacists) resistance rates are lower than in countries where these professionals are not included in a routine work at high risk wards. It is obvious that knowing local resistance rates is essential for rational antibiotic use. The Croatian Committee for Antibiotic Resistance Surveillance that was founded in 1996 at the Public Health Collegium of the Croatian Academy of Medical Sciences (CAMS) in collaboration with the Croatian Ministry of Health and Social Welfare (MHSW) Reference Centre for Antibiotic Resistance Surveillance that was founded in 2003 at the University Hospital for Infectious Diseases "Dr. F. Mihaljević" provides antibiotic resistance data for Croatian regions for many years. Over the years the network of microbiological laboratories that take part in surveillance grew bigger and at present catchment population is >90%. All the activities related to antibiotic resistance control are coordinated by the Interdisciplinary section for antibiotic resistance control (Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike, ISKRA), an MHSW intersectorial coordination mechanism (ICM). The Committee took part in the most important international programs for antibiotic resistance (European Antimicrobial Resistance Surveillance System, EARSS) and antibiotic consumption (European Surveillance of Antimicrobial Consumption, ESAC) surveillance. The Committee also founded the Croatian Chapter of the Alliance for the Prudent Use of Antibiotics (APUA). When EARSS and ESAC were transformed in 2010 and 2011 into EARS-Net and ESAC-Net of the European Surveillance System (Tessy), and European Center for Disease Control (ECDC) surveillance network, Croatia continued collaboration with ECDC Tessy program. Due to the political status of Croatia this collaboration does not include reporting of Croatian data at the moment. However, the Committee and the Referent Center continue data collection in EARSS and ESAC format and these data will be continuously reported in these yearly publications. As a contribution to the European Antibiotic Awareness Day (EAAD) an EAAD Symposium was held in Zagreb on 18 November 2010. As the European public campaign in 2010 was directed towards rationalization of antibiotic prescribing in hospitals the Symposium topics were adapted accordingly and adequate campaign material was delivered on that occasion. One of the important events in 2010 was the advent of the European standards for sensitivity testing. In order to help Croatian laboratories to adopt the European Committee for Antimicrobial Sensitivity Testing (EUCAST) standards the VI Teaching Course on Antibiotic Resistance was held in November at the University Hospital for Infectious Diseases. During the 10 days 75 participants took part at the Course.

Arjana Tambić Andrašević
President of the Committee for Antibiotic Resistance Surveillance in Croatia

POGLAVLJE/CHAPTER 1.

REZISTENCIJA BAKTERIJSKIH IZOLATA U 2010. GODINI
ANTIBIOTIC RESISTANCE IN 2010

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UVOD:

Već dugi niz godina Odbor za praćenje rezistencije bakterija na antibiotike Akademije medicinskih znanosti Hrvatske (AMZH) i Referentni centar za praćenje rezistencije bakterija na antibiotike Ministarstva zdravstva i socijalne skrbi (MZSS) pri Klinici za infektivne bolesti "Dr. Fran Mihaljević" provode praćenje rezistencije na antibiotike u Hrvatskoj. Donošenjem Nacionalnog programa za kontrolu otpornosti bakterija na antibiotike za razdoblje od 2009. do 2014. godine praćenje potrošnje antibiotika je postalo jednom od službenih nacionalnih aktivnosti koje koordinira Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike (ISKRA) Ministarstva zdravstva i socijalne skrbi. Praćenje rezistencije u Hrvatskoj se zasniva na mreži mikrobioloških laboratorija čiji su voditelji članovi Odbora. Na redovnim sastancima Odbora dogovaraju se načela i metodologija praćenja čime se osigurava visoka standardiziranost u radu hrvatskih laboratorija i jamči pouzdanost prikazanih rezultata. Nužnost kontinuiranog usuglašavanja među laboratorijima je naročito bitna u području interpretacije nalaza. S obzirom na stalno evoluiranje novih mehanizama rezistencije i pristup tumačenju *in vitro* dobivenih rezultata se stalno mijenja i ovisi o dogovoru stručnjaka. European Committee for Antimicrobial Sensitivity Testing (EUCAST) je uspio objediniti stavove različitih stručnih društava diljem Europe u jedinstvene europske standarde, što je Hrvatska spremno dočekala. Europski standardi za disk difuzijsku metodu donešeni su 2010.g., a Hrvatska ih službeno počinje primjenjivati u 2011.g. Provođenje redovite vanjske kontrole rada laboratorija u području testiranja osjetljivosti na antibiotike dodatno pospješuje standardizaciju rada i osigurava kvalitetu ovdje prikazanih rezultata. U ovom poglavlju iznose se podaci o stopama rezistencije za najčešće bakterijske patogene u pojedinim centrima u Hrvatskoj. Ovi podaci prvenstveno služe kao osnova za izradu nacionalnih i lokalnih smjernica za racionalnu primjenu antibiotika.

INTRODUCTION:

For many years antibiotic resistance data for Croatia are obtained through the collaboration of the Croatian Committee for Antibiotic Resistance Surveillance of the Croatian Academy of Medical Sciences (CAMS) and the Reference Center for Antibiotic Resistance Surveillance of the Croatian Ministry for Health and Social Welfare (MHSW) at the University Hospital for Infectious Diseases "Dr Fran Mihaljević". This surveillance program became one of the official national activities listed in the National program for antibiotic resistance control 2009 – 2014 and is a part of the whole strategy coordinated by the Croatian MHSW intersectorial coordination mechanism (ICM), the ISKRA (Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike). Antibiotic resistance surveillance system in Croatia is based on the network of microbiology laboratories whose heads are members of the CAMS Committee. At the regular Committee meetings principles and methodology of the resistance surveillance are discussed which guaranties high level of interlaboratory standardization and good quality of surveillance data. Continuous interlaboratory fine tuning is especially important when it comes to interpretation of the sensitivity testing results. As new resistance mechanisms keep emerging the approach to the interpretation of *in vitro* results is open for changes and presents consensus opinion of experts. The European Committee for Antimicrobial Sensitivity Testing (EUCAST) has united opinions of many national committees into unique European standards which was gladly welcomed by Croatia. The European standards for disk diffusion were issued in 2010 and will become official standards for Croatia in 2011. Regular external quality control further improves interlaboratory standardization and increases credibility of results published in this report. In this chapter we report the resistance rates for the most frequent bacterial pathogens in individual Croatian centers. These data are primarily intended for use as basis for the national and local guidelines for rational antibiotic prescribing.

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 31.12.2010.g. Rezultati za izolate streptokoka grupe A, salmonela, šigela i anaerobnih bakterija prikupljaju se, zbog malog broja izolata, tijekom cijele godine, od 1.1. do 31.12.2010. Podatke za 2010.g. podnjelo je 37 centara (popis u legendi za tablice), što obuhvaća >90% populacije u Hrvatskoj.

S obzirom da je tijekom 2010.g. došlo do spajanja nekih bolnica te nekih kadrovskih promjena došlo je do promjene u sastavu nekih centara u odnosu na prethodnu godinu. Promjene u 2010.g. uključuju sljedeće:
- OB Zabok i ZZJZ Krapinsko-zagorske županije prikazuju podatke zajedno
- Klinički bolnički centar „Zagreb" uključuje podatke i Klinike za plućne bolesti „Jordanovac"
- Klinička bolnica „Merkur" uključuje podatke i Sveučilišne klinike za dijabetes, endokrinologiju i bolesti metabolizma „Vuk Vrhovac"
- Klinička bolnica „Sestre milosrdnice" uključuje podatke i Klinike za traumatologiju te Instituta za tumore koji je prije bio uključen u podacima OB „Sveti Duh"
- Novi centri koji su se uključili u praćenje u 2010.g. su: ZZJZZŽ Ivanić Grad, Bolnica za plućne bolesti Klenovnik, OB Nova Gradiška

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. Za 2010.g. je dogovoreno da iznimka za ovo pravilo bude testiranje osjetljivosti *P. aeruginosa* na kolistin. Zbog skupoće testiranja preporuča se da kolistin testiraju samo laboratoriji koji imaju visoku rezistenciju psudomonasa 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 II i III generacije (engl. "beta-lactamase negative ampicillin resistant", BLNAR sojeve)

5. izolate *E.coli* i *K.pneumoniae* koji ne proizvode beta-laktamaze proširenog spektra (engl. "extended spectrum beta-lactamases", ESBL), a rezistentni su na jedan od cefalosporina III ili IV generacije
6. karbapenem rezistentne enterobakterije

Tijekom 2010.g. osjetljivost na antibiotike testirana je u svim laboratorijima disk difuzijskom metodom u skladu sa Clinical and Laboratory Standards Institute (CSLI) standardima (M100-S19 dokument). Iznimno, za enterobakterije usvojena je na proljetnom sastanku Odbora odluka da se od 1.6.2010. počnu primjenjivati EUCAST kriteriji za određivanje osjetljivosti enterobakterija na karbapeneme, kako se ne bi propustila pravovremena detekcija prvih sojeva koji proizvode karbapenemaze. Pneumokokima smanjene osjetljivosti na penicilin određivale su se minimalne inhibitorne koncentracije (MIK) penicilina kako bi se ti izolati razdvojili u umjereno i visoko rezistentne. MIK su određivane E-testom (AB, Biodisk, Sweden). Za 2010.g. koristili su se CLSI standardi za interpretaciju graničnih vrijednosti MIK-a tj. laboratoriji su svaki izolat pneumokoka smanjene osjetljivosti na penicilin svrstavali u kategoriju osjetljiv (S), umjereno (I) ili visoko rezistentan (R) po tri različita kriterija: penicilin oralni (S ≤0.06; I 0.12-1.0; R ≥2.0); penicilin parenteralni / bez meningitisa (S ≤2.0 I 4.0; R ≥8.0); penicilin parenteralni / meningitis (S ≤0.06; R ≥0.12).

Preporuka Odbora je da se izolati *A. baumanii* i *P. aeruginosa* rezistentni na jedan, ali ne i oba karbapenema retestiraju određujući MIK za imipenem i meropenem. Testiranje osjetljivosti pseudomonasa na kolistin vrši se također određivanjem MIK-a. Pri određivanju MIK-a korišteni su E-testovi (AB Biodisc, Sweden).

Osjetljivost anaerobnih bakterija testirana je određivanjem MIK-a koristeći E-test metodu ili mikrodiluciju u bujonu.

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

Ciljane studije

Kao i svake godine podaci o osjetljivosti *M.tuberculosis* su obrađivani u nacionalnom laboratoriju za tuberkulozu, Hrvatskog zavoda za javno zdravstvo. Izvješće o rezistenciji *M. tuberculosis* se nalazi u posebnom poglavlju ove publikacije.

U sklopu European Antimicrobial Resistance Surveillance System (EARSS) projekta prikupljali su se invazivni izolati (iz krvi i likvora) *S.pneumoniae*, *S.aureus, E.faecalis, E.faecium, E.coli*, *K.pneumoniae* i *P.aeruginosa*. S 1.1.2010. EARSS je prešao u EARS-Net, mrežu koja čini jedan segment The European Surveillance System (Tessy) Europskog centra za kontrolu bolesti (engl. "European Center for Disease Control", ECDC). Hrvatska je nastavila suradnju s ECDC Tessy programom, ali trenutno ta suradnja ne uključuje publiciranje hrvatskih podataka u sklopu Tessy rezultata. Hrvatska mreža mikrobioloških laboratorija okupljena oko Odbora AMZH i Referentnog centar MZSS nastavila je, međutim, i u 2010.g. prikupljati podatke o rezistenciji invazivnih izolata spomenutih bakterijskih vrsta te se i nadalje invazivni izolati enterokoka, stafilokoka i *P.aeruginosa* šalju u Zavod za kliničku i molekularnu mikrobiologiju Kliničkog bolničkog centra Zagreb, a invazivni izolati pneumokoka,

E.coli i *K.pneumoniae* u Zavod za kliničku mikrobiologiju Klinike za infektivne bolesti "Dr. F. Mihaljević". Podaci o rezistenciji invazivnih izolata izneseni su u posebnom poglavlju ove publikacije.

Podaci o potrošnji antibiotika u Hrvatskoj se prate preko podataka veledrogerija u sklopu European Surveillance of Antimicrobial Consumption (ESAC) projekta. Ti se podaci izražavaju u definiranim dnevnim dozama (ATC-5 klasifikacija) na 1000 stanovnika dnevno (DDD/TID) u skladu s naputcima ESAC-a te se mogu uspoređivati s podacima drugih europskih zemalja. Rezultati su prikazani odvojeno za ambulantnu i bolničku potrošnju. Predstavnici Hrvatske u ESAC projektu su prof.dr.sc. Arjana Tambić Andrašević i prof.dr.sc. Igor Francetić, a dr Marina Payerl Pal je urednik podataka. U sklopu APUA Croatia inicijative i u skladu s naputcima ISKRA-e Odbor prati bolničku potrošnju antibiotika i preko podataka dobivenih iz bolničkih ljekarni. Izvješće o potrošnji antibiotika nalazi se u posebnom poglavlju ove publikacije.

MATERIALS AND METHODS:

Global surveillance

All clinical isolates of designated bacterial species isolated from 1 October till 31 December, 2010 are included in surveillance with the exception of group A streptococci, salmonellae, shigellae and anaerobic bacteria. Data on these bacteria are collected throughout the year due to the small number of isolates. In 2010 a total of 37 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%.

During 2010 some hospitals merged and some staff transfer occurred so the data composition for some centers changed compared to previous year. The 2010 changes include the following:

- KA OB and KA ZZJZ report joint data
- ZG KBC data include data for ZG KBJ
- ZG KBM data include ZG VV data
- ZG KBSM data include ZG KTR data and also the Institute for carcinoma data that were previously included in ZG OBSD data
- The new centers that joined the network in 2010 are: ZZJZZŽ Ivanić Grad, Hospital for lung disease Klenovnik, OB Nova Gradiška

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. In 2010 the exception from this rule was made for *P. aeruginosa* and colistin. Because of the high cost for colistin testing it was decided that colistin should be tested only in laboratories that report high carbapenem resistance in pseudomonas.

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

c. during the study period a designated set of antibiotics is to be tested against all or at least 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 “Dr. F. Mihaljević”. 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 or linezolid
3. vancomycin resistant enterococci
4. *H.influenzae* resistant to co-amoxiclav, II or III generation cephalosporins (beta-lactamase negative ampicillin resistant, BLNAR strains)

5. *E.coli* and *K.pneumoniae* isolates that do not produce extended spectrum beta-lactamases (ESBL) but are resistant to one of the III or IV generation cephalosporins
6. carbapenem resistant enterobacteriaceae

During 2010 sensitivity to antibiotics was tested in all laboratories by disk diffusion method according to the Clinical and Laboratory Standards Institute (CSLI) standards (M100-S19 document). At the Committee's spring meeting an exception was made for enterobacteriaceae and carbapenem testing. Since 1.1.2010. EUCAST breakpoints for carbapenems were adopted as not to omit timely detection of first carbapenemase producing strains. In pneumococcal isolates with reduced sensitivity to penicillin low and high level resistance were distinguished based on minimal inhibitory concentration (MIC) values determined by the E-test method (AB, Biodisk, Sweden). In 2010 CLSI guidelines were used for interpretation of MIC breakpoints and sensitivity of pneumococcus to penicillin was reported respecting three different criteria: penicillin oral (S ≤0.06; I 0.12-1.0; R ≥2.0); penicillin parenteral / non meningitis (S ≤2.0 I 4.0; R ≥8.0); penicillin parenteral / meningitis (S ≤0.06; R ≥0.12).

The Committee recommendation is that for *A.baumanii* and *P.aeruginosa* isolates resistant to one but not to both carbapenems MICs of imipenem and meropenem should be determined. Sensitivity to colistin is also done by MIC method. MIC testing was done by E-test (AB Biodisc, Sweden).

Antibiotic sensitivity in anaerobic bacteria was determined by E-test or broth dilution method.

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

Focused studies

Same as every year data on *M. tuberculosis* sensitivity were processed in the National Laboratory for Tuberculosis at the Croatian Public Health Institute. Detailed report on resistance in *M.tuberculosis* is enclosed separately.

In the frame of the European Antimicrobial Resistance Surveillance System (EARSS) project invasive isolates (from blood and cerbrospinal fluid, CSF) of *S.pneumoniae*, *S.aureus, E.faecalis, E.faecium, E.coli*, *K.pneumoniae* and *P.aeruginosa* were collected. On 1.1.2010. EARSS was moved to EARS-Net, which is one segment of The European Surveillance System (Tessy), a global European Center for Disease Control (ECDC) surveillance network. Croatia continued collaboration with ECDC Tessy program which at present does not include reporting of Croatian resistance rates within Tessy data. However, the Croatian network of laboratories gathered around the CAMS Committee and the MHSW Referent Center continued data collection on invasive isolates in 2010. Same as in the previous years invasive isolates of enterococci, staphylococci and *P.aeruginosa* were sent to the Institute for Clinical and Molecular Microbiology, Clinical Hospital Centre Zagreb

and invasive pneumococci, *E. coli* and *K.pneumoniae* were sent to the Department of Clinical Microbiology, University Hospital for Infectious Diseases "Dr. F. Mihaljević". Data on invasive isolates are reported in a separate chapter of this publication.

Antibiotic consumption data are collected through wholesales reports as an activity of the European Surveillance of Antimicrobial Consumption (ESAC) project. Data are expressed as defined daily doses (ATC-5 classification) per thousand inhabitants daily (DDD/TID) according to the ESAC requirements and are therefore comparable with data from the other European countries. Results are presented separately for ambulatory and hospital consumption. National representatives for Croatia in the ESAC project are Prof. Arjana Tambić Andrašević and Prof. Igor Francetić and Dr. Marina Payerl Pal is the data manager. As a part of the APUA Croatia initiative and in line with ISKRA requirements the Committee also monitors hospital consumption based on the data from hospital pharmacies. Antibiotic consumption data are reported in a separate chapter of this publication.

REZULTATI

U praćenju rezistencije u 2010.g. sudjelovalo je 37 centara u Hrvatskoj. Prosječni rezultati za Hrvatsku 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 uključeni u zbirne rezultate za RH. Podaci o izolatima malo vjerojatnog fenotipa koji nisu potvrđeni u jednom od centralnih laboratorija ne smatraju se važećima.

Neki centri su zbog malog broja izolata u ispitivanom razdoblju ispitivanje proširili na cijelu godinu, a neki su zbog različitih razloga odstupali od predviđenog razdoblja praćenja. Odstupanja od predviđenog razdoblja praćenja uključuju:
- KA OB je za sve vrste prikazao rezultate za cijelu godinu
- GS ZZJZ je za sve vrste osim *E.coli*, *P.mirabilis* i *S.aureus* (MSSA) prikazao rezultate za cijelu godinu
- IG ZZJZ je za streptokok grupe A prikazao rezultate za razdoblje 1.10. do 31.12. 2010.
- ZG KIB je za streptokok grupe A prikazao rezultate za razdoblje 1.1. do 30.06. 2010.
- PU ZZJZ, SK ZZJZ, ŠI ZZJZ su za *A.baumanii* prikazali rezultate za cijelu godinu
- ZG KBM je za *H.influenzae* prikazao rezultate za cijelu godinu

Dvadesetpet laboratorija je usvojilo kategoriziranje na penicilin neosjetljivih pneumokoka po tri različita kriterija ovisno o tome radi li se o parenteralnoj ili oralnoj primjeni penicilina te infekciji koja zahvaća ili ne zahvaća središnji živčani sustav (SŽS). Svi laboratoriji su prikazali rezistenciju pneumokoka prema kategorizaciji za oralnu primjenu penicilina, što odgovara prijašnjoj jedinoj kategorizaciji za penicillin i sliči općoj kategorizaciji prema EUCAST-u (S $\leq$0.06; I 0.12-2.0; R >2.0), koja će se primjenjivati u 2011. Prema ovakvoj kategorizaciji stope iznose 4% rezistentno, 20% intermedijarno, 76% osjetljivo.

U 2010.g. izolaciju šigela prijavilo je sedam laboratorija: ČK ZZJZ *Sh.sonnei* (3), *Sh.flexneri* (1); RI NZZJZ *Sh.sonnei* (15); SB ZZJZ *Sh.sonnei* (1); SK ZZJZ *Sh.sonnei* (2); ZG KIB *Sh.sonnei* (1), *Sh.flexneri* (1); ZG ZZJZ *Sh.sonnei* (2). Ukupno je tijekom 2010.g. izolirano 26 šigela.

U 2010.g. podatke o anaerobnim bakterijama je podnjelo 14 centara. Ukupno je izolirano 162 *Bacteroides* spp., 61 *Clostridium* spp. i 100 anaerobnih gram-pozitivnih koka. Obrađeno je ukupno 323 anaerobnih bakterija iz četrnaest centara: BJ ZZJZ *Bacteroides* spp. (2); ČK ZZJZ *Bacteriodes* spp. (26), *Clostridium* spp. (7), gram-pozitivni koki (31); PU ZZJZ *Bacteriodes* spp. (8), *Clostridium* spp. (4); RI KBC gram-pozitivni koki (7); ŠI ZZJZ *Bacteroides* spp. (3), *Clostridium* spp. (3), gram-pozitivni koki (2); VK OB *Bacteroides* spp. (6), *Clostidium* spp. (2); VT ZZJZ *Bacteriodes* spp. (17); VŽ ZZJZ *Bacteroides* spp. (20), *Clostridium* spp. (11), gram-pozitivni koki (13); ZD ZZJZ *Bacteroides* spp. (26), *Clostidium* spp. (6), gram-pozitivni koki (6); ZG KBC *Bacteroides* spp. (4); ZG KBM *Bacteroides* spp. (7), *Clostidium* spp. (5); ZG KIB *Bacteroides* spp. (10), *Clostridium* spp. (2), gram-pozitivni koki (1); ZG KDB *Bacteriodes* spp. (29), *Clostridium* spp. (21), gram-pozitivni koki (35); ZG KBSD *Bacteriodes* spp. (4), gram-pozitivni koki (5).

RESULTS

In 2010 thirty-seven centers took part in antibiotic resistance surveillance in Croatia. Average data for Croatia 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 not considered representative for this laboratory but were included in the total number for Croatia. Isolates with a less probable phenotype that were not sent to a central laboratory for retesting were not considered valid.

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:
- KA OB reported data for the whole year for all species
- GS ZZJZ reported data for the whole year for all species except for *E.coli*, *P.mirabilis* and *S.aureus* (MSSA)
- IG ZZJZ reported data for group A streptococcus for period 1.10. till 31.12. 2010.
- ZG KIB reported data for group A streptococcus for period 1.1. till 30.06. 2010.
- PU ZZJZ, SK ZZJZ, ŠI ZZJZ reported data for *A.baumanii* for the whole year
- ZG KBM reported data for *H.influenzae* for the whole year

Twenty-five laboratories adopted the categorization of penicillin nonsusceptible pneumococci according to three different criteria depending on whether penicillin is administered orally or parenterally and whether central nervous system (CNS) is infected or not. All the laboratories reported resistance rates according to categorization valid for oral penicillin which corresponds to the former CLSI unique categorization and resembles general EUCAST categorization (S ≤0.06; I 0.12-2.0; R >2.0), which will be applied in 2011. According to this categorization rates are as follows: 4% resistant, 20% intermediate, 76% sensitive.

In 2010 seven laboratories reported isolation of shigella: ČK ZZJZ *Sh.sonnei* (3), *Sh.flexneri* (1); RI NZZJZ *Sh.sonnei* (15); SB ZZJZ *Sh.sonnei* (1); SK ZZJZ *Sh.sonnei* (2)*;* ZG KIB *Sh.sonnei* (1), *Sh.flexneri* (1); ZG ZZJZ *Sh.sonnei* (2).. Altogether 26 shigella isolates were isolated in Croatia in 2010.

In 2010 anaerobes were reported by 14 centers. Altogether there were 162 *Bacteroides* spp., 61 *Clostridium* spp. and 100 anaerobic gram-positive cocci. The 323 anaerobic bacteria were isolated in: BJ ZZJZ *Bacteroides* spp. (2); ČK ZZJZ *Bacteriodes* spp. (26), *Clostridium* spp. (7), gram-positive cocci (31); PU ZZJZ *Bacteriodes* spp. (8), *Clostridium* spp. (4); RI KBC gram-positive cocci (7); ŠI ZZJZ *Bacteroides* spp. (3), *Clostridium* spp. (3), gram-positive cocci (2); VK OB *Bacteroides* spp. (6), *Clostidium* spp. (2); VT ZZJZ *Bacteriodes* spp. (17); VŽ ZZJZ *Bacteroides* spp. (20), *Clostridium* spp. (11), gram-positive cocci (13); ZD ZZJZ *Bacteroides* spp. (26), *Clostidium* spp. (6), gram-positive cocci (6); ZG KBC *Bacteroides* spp. (4); ZG KBM *Bacteroides* spp. (7), *Clostidium* spp. (5); ZG KIB *Bacteroides* spp. (10), *Clostridium* spp. (2), gram-positive cocci (1); ZG KDB *Bacteriodes* spp. (29), *Clostridium* spp. (21), gram-positive cocci (35); ZG KBSD *Bacteriodes* spp. (4), gram-positive cocci (5).

DISKUSIJA

Rezistencija na penicilin u beta-hemolitičkog streptokoka grupe A (BHS-A) još nije zabilježena te je to prvi lijek izbora kod streptokoknih infekcija. Prema ISKRA hrvatskim nacionalnim smjernicama za grlobolju makrolidi predstavljaju osnovu terapije streptokokne grlobolje u pacijenata preosjetljivih na penicillin, a klindamicin se preporuča pri rekurirajućim streptokoknim infekcijama. Otpornost BHS-A na makrolide u 2010.g. (8%) i klindamicin (5%) je podjednaka kao i prethodne godine (9% i 6%) i još uvijek nešto niža negoli u 2008.g. (13% i 7%). Kao i prethodnih godina otpornost na klindamicin je pretežno konstitutivna.

U Hrvatskoj većina izolata pneumokoka i *Haemophilus influenzae* potječe iz briseva nazofarinksa, što velikim dijelom predstavlja kolonizaciju i nalaz koji ne zahtjeva primjenu antimikrobne terapije. U slučaju sumnje na akutnu bakterijsku upalu srednjeg uha lijek izbora za empirijsku antimikrobnu terapiju je amoksicilin. Otpornost *H.influenzae* na ampicilin kreće se zadnjih godina oko 10% (9% u 2006.g., 11% u 2007.g., 8% u 2008.g., 10% u 2009.g., 11% u 2010.g). U ispitivanju za 2010.g. još nisu uključeni novi EUCAST standardi za očitavanje osjetljivosti pneumokoka na amoksicilin disk difuzijskom metodom, no amoksicilin ima bolju učinkovitost od penicilina u slučaju otitisa. Većina pneumokoka je dobro osjetljiva na peroralnu primjenu, a gotovo svi na parenteralnu primjenu penicilina ako se ne radi o infekciji SŽS-a (R=0; I=1%). Ovi podaci podupiru primjenu parenteralnog penicilina pri empirijskoj terapiji pneumonija, ali ne i infekcija SŽS-a, pri kojima treba smatrati da otpornost na penicillin iznosi 28%. Nakon porasta otpornosti pneumokoka na makrolide u 2008.g. (40%) otpornost pneumokoka na makrolide nije nastavila rasti i u 2009. i 2010.g. iznosi 39% i 38%. Ove visoke stope otpornosti pneumokoka na makrolide ograničavaju empirijsku uporabu makrolida u liječenju pneumonija samo u slučajevima jasne sumnje na atipične bakterijske uzročnike. Otpornost pneumokoka na respiratorne kinolone je još uvijek ograničena na sporadične izolate.

Kao i prijašnjih godina *Staphylococcus aureus* osjetljiv na meticilin (MSSA) pokazuje dobru osjetljivost na druge grupe antibiotika. Udio meticilin rezistentnih stafilokoka (MRSA) u ukupnom broju *S aureus* izolata u 2010.g. iznosi 16%, što je najniža vrijednost zabilježena od početka praćenja 1997.g. i predstavlja značajan pad u okviru posljednjih pet godina (23% u 2006.g., 25% u 2007.g., 26% u 2008.g., 21% u 2009.g). Posebno ohrabruje značajan pad stopa MRSA u velikim centrima poput KBC Split (32% u 2008.g., 34% u 2009.g. te 24% u 2010.g.) i KB „Merkur" (57% u 2008.g. i 2009.g. te 32% u 2010.g.). MRSA je tipično u visokom postotku rezistentan i na druge grupe antibiotika osim na ko-trimoksazol i rifampicin (9%) te glikopeptide i linezolid, na koje rezistencija nije uočena. Početna rezistencija na mupirocin iznosi 38%, a prema podacima laboratorija koji su testirali i klinički značajniju visoku rezistenciju na mupirocin ona iznosi 12%. Razdvajanje izvanbolničkih od bolničkih MRSA je izvan dohvata ove studije.

Osjetljivost enterokoka je podjednaka kao prethodne godine, a vankomicin rezistentni *E.faecium* (VRE) je u 2010.g. registriran samo u dva centra (KBC Zagreb i KB Merkur).

E.coli je najčešći klinički značajan izolat u većini laboratorija što odgovara činjenici da su infekcije mokraćnog sustava (IMS) najčešće bakterijske infekcije odrasle dobi. Prema ISKRA nacionalnim smjernicama za IMS prvi lijek izbora za nekomplicirani cistitis je nitrofurantoin, na koji je rezistencija i nadalje niska (4%). U liječenju IMS od posebnog su interesa ko-trimoksazol i fluorokinoloni s obzirom da postižu odličnu eradikaciju uzročnika iz genitourinarnog trakta. Rezistencija na ko-trimoksazol kao i prethodnih godina iznosi 24% i prelazi 20% u većini centara, a rezistencija na ciprofloksacin iznosi 13%, što je nešto više negoli prethodne tri godine (11%) i ukazuje na postupan, ali stalan trend porasta rezistencije na kinolone. Rezistencija na ko-amoksiklav i aminoglikozide je i nadalje niska (<10%) te ovi antibiotici i nadalje mogu biti osnova parenteralnog liječenja IMS. Udio *E.coli* koje proizvode beta-laktamaze proširenog spektra (engl. „extended spectrum beta-lactamases", ESBL) je i nadalje nizak (5%), ali s uočljivim trendom porasta (2% u 2007.g, 3% u 2008.g., 4% u 2009.g.).

Udio izolata *K.pneumoniae* koji proizvode ESBL je jednak kao prethodne godine čime je zaustavljen trend porasta rezistencije na cefalosporine III. generacije (22% u 2006.g., 32% u 2007.g., 29% u 2008.g. i 34% u 2009.g. i 2010.g.). Rezistencija na cefalosporine III. generacije od 50% i više zabilježena je u Karlovcu (55%), Osijeku (50%), Vinkovcima (68%), KB Dubrava (51%), KB Merkur (52%) i KB Sveti Duh (51%). Otpornost na druge grupe antibiotika podjednaka je vrijednostima prethodne godine. Tijekom 2010.g. zabilježeno je nešto više izolata otpornih na karbapeneme (uglavnom samo na ertapenem) što je posljedica uvođenja oštrijeg EUCAST standarda u interpretaciji osjetljivosti enterobakterija na karbapeneme. Iako je prvi izolat *K.pneumoniae* koji proizvodi metalobetalaktamaze (NDM-1) u Hrvatskoj opisan 2009.g., u 2010.g. nije bilo novih izolata s metalobetalaktamazama među sojevima koji su poslani na retestiranje u Referentni centar za praćenje rezistencije. Posebno je važno da prisutnost izolata s KPC karbapenemazama, koji imaju značajan epidemijski potencijal, nije dokazana ni u 2010.g.

Otpornost ostalih enterobakterija, *P. mirabilis* te grupe *Enterobacter* spp. *, Serratia* spp.*, Citrobacter* spp. se nije bitno promijenila u odnosu na prethodnu godinu. Udio sojeva s derepresiranim inducibilnim cefalosporinazama u enterobakter grupi iznosila je 16%. Sporadični izolati rezistentni na karbapeneme zabilježeni su u šest centara, ali prisutnost karbapenemaze (IMI-1) je ustanovljena samo u jednog izolata *Enterobacter cloacae*.

Otpornost *P.aeruginosa* se nije bitno promijenila na nacionalnoj razini. Otpornost na karbapeneme i ove godine iznosi 12% za imipenem i 11% za meropenem s velikim odstupanjem među centrima. Dok je rezistencija na karbapeneme značajno pala u nekim centrima kao što su KBC Rijeka (26% u 2009.g. i 14% u 2010.g.) i Klinika za dječje bolesti Zagreb (33% u 2009.g. i 9% u 2010.g.) u KBC Zagreb otpornost na karbapeneme je u daljnjem porastu (17% u 2008.g., 33% u 2009.g. i 42% u 2010.g.). Stope rezistencije ispod 10% zabilježene su i nadalje za piperacilin/tazobaktam (7%), ceftazidim (6%), cefepim (5%) i kolistin (0%). Sporadični izolati otporni na kolistin zabilježeni su u Osijeku, Varaždinu i KBC Zagreb.

Trend porasta ukupnog broja *Acinetobacter baumanii* izolata se i dalje nastavlja (565 izolata u 2005.g., 800 izolata u 2007.g., 1097 izolata u 2009.g. i 1289 izolata u 2010.g.). Porast rezistencije na karbapeneme, koji je registriran 2009.g. se također

nastavlja (10% za meropenem i 4% za imipenem u 2008.g., 23% u 2009.g. i 34% u 2010.g.). Stope rezistencije na karbapeneme oko 50% i više zabilježene su u KBC Rijeka (71%), KBC Split (49%), KBC Zagreb (53%), KB Merkur (84%), Klinici za infektivne bolesti (74%) te KB Sveti Duh (53%). Otpornost na ampicilin/sulbaktam je također u porastu i iznosi 14% (9% u 2009.g.). Sporadični izolati otporni na kolistin zabilježeni su u Karlovcu, Splitu i HZZJZ.

Otpornost salmonela se nije bitno mijenjala. Otpornost na ampicilin u 2010.g. iznosi 11%, a na sve druge antibiotike je <5%. Sojevi koji proizvode ESBL nisu zabilježeni kao ni izolati rezistentni na ciprofloksacin. Početna otpornost na kinolone (nalidiksičnu kiselinu) uočena je u 1% izolata.

Tijekom 2010.g. prikupljeno je 26 izolata šigela. Rezistencija je bila visoka na ampicilin i ko-trimoksazol. Rezistencija na kinolone u 2010.g. nije zabilježena.

Među anaerobima zabilježena je visoka rezistencija na ampicilin u *Bacteroides* spp. (78%), ali ne i u klostridija (7%) i anaerobnih gram-pozitivnih koka (8%). Rezistencija na metronidazol je visoka u gram-pozitivnih koka (55%), a niska u klostridija (2%) i *Bacteroides* spp. (9%). Rezistencija na klindamicin je iznosila između 15% i 25% za sve tri vrste anaeroba.

DISCUSSION

Penicillin resistance in group A streptococcus (GAS) has not yet emerged and this is still the first line therapy for streptococcal infections. According to the ISKRA Croatian national guidelines for sorethroat macrolides are drugs of choice in patients with penicillin allergy and clindamycin is recommended in recurrent streptococcal infections. In 2010 resistance to macrolides (8%) and clindamycin (5%) was similar to the previous year rates (9% and 6%) and lower than in 2008 (13% and 7%). As recorded before clindamycin resistance was predominantly constitutive.

Most isolates of pneumococci and *Haemophilus influenzae* in Croatia originate from nasopharyngeal swabs and largely represent colonization that should not be treated by antimicrobial therapy. First line therapy for suspected acute otitis media (AOM) is amoxicillin. Ampicillin resistance in *H.influenzae* is around 10% for the past several years (9% in 2006, 11% in 2007, 8% in 2008, 10% in 2009, 11% in 2010). For the 2010 surveillance period the new EUCAST standards for amoxicillin disk diffusion testing in pneumococci were not yet adopted but amoxicillin is supposed to be more effective than penicillin in AOM. Judging by the penicillin rates the majority of pneumococci are sensitive to oral penicillin and almost all of them are well covered by parenteral penicillin therapy in cases when central nervous system (CNS) is not affected (R=0; I=1%). This data support the use of penicillin as the first line therapy of pneumonia but not in CNS infections. When using breakpoints for CNS infections penicillin resistance is 28%. Macrolide resistance rose significantly in 2008 (40%) but did not increase ever since (39% in 2009 and 38% in 2010). The high macrolide resistance rates in pneumococci restrict the use of macrolides in the treatment of pneumonia only in cases of clear infection by atypical bacteria. Pneumococcal resistance to respiratory quinolones is still sporadic.

Same as recorded in previous years methicillin sensitive *Staphylococcus aureus* (MSSA) shows good susceptibility to other groups of antibiotics. The rate of methicillin resistant staphylococci (MRSA) in 2010 is 16%, which is the lowest recorded value since the beginning of surveillance in 1997 and presents the significant decrease over the last five years (23% in 2006, 25% in 2007, 26% in 2008, 21% in 2009). It is encouraging that decrease in MRSA rates is recorded in some large centers like KBC Split (32% in 2008, 34% in 2009 and 24% in 2010) and KB „Merkur" (57% in 2008 and 2009, 32% n 2010). MRSA is typically highly resistant to other groups of antibiotics with the exception of co-trimoxazole and rifampicin (9%), glycopeptides and linezolid to which no resistance was recorded. The low level mupirocin resistance is 38% and clinically relevant high level resistance was tested in only some laboratories that report the rate of 12%. Differentiating community acquired from hospital acquired MRSA isolates is out of the scope of this study.

Sensitivity of enterococci is similar as reported previously and in 2010 vancomycin resistant *E.faecium* (VRE) is registered in only two centers (KBC Zagreb and KB Merkur).

E.coli is the most frequent clinically significant isolate in most laboratories which reflects the fact that urinary tract infections (UTI) are the most frequent bacterial

infections in adults. According to the ISKRA national guidelines for UTI nitrofurantoin is the first line therapy for uncomplicated cystitis. This is still supported by the fact that resistance to nitrofurantoin is still low (4%). Co-trimoxazole and the fluoroquinolones are the mainstay in UTI treatment as they achieve excellent eradication of bacteria from urogenital tract. Resistance to co-trimoxazole is 24% which is the same as in the previous years with rates higher than 20% in most centers. Ciprofloxacin resistance is 13% which is slightly higher than in the previous three years (11%) and suggests a slow but increasing trend in quinolone resistance. Resistance to co-amoxiclave and aminoglycozides is still low (<10%) suggesting that these antibiotics can still be the mainstay in parenteral treatment of UTI. The rate of *E. coli* isolates that produce the extended spectrum beta-lactamases (ESBL) is still low (5%) but the increasing trend is apparent (2% in 2007, 3% in 2008, 4% in 2009).

The rate of ESBL *K.pneumoniae* isolates is equal as in the previous year and this seems to be an end of the increasing trend in 3rd generation cephalosporin resistance (22% in 2006, 32% in 2007, 29% in 2008, 34% in 2009 and 2010). Resistance to 3rd generation cephalosporins of 50% and more is recorded in Karlovac (55%), Osijek (50%), Vinkovci (68%), KB Dubrava (51%), KB Merkur (52%) and KB Sveti Duh (51%). Resistance to other groups of antibiotics is similar as compared with the previous year. During 2010 somewhat higher number of carbapenem resistant isolates (mostly resistant to ertapenem only) were recorded which is a consequence of introducing more rigorous EUCAST standards in the interpretation of carbapenem resistance in enterobacteriaceae. Although the first metallo-beta-lactamase (NDM-1) producing isolate of *K.pneumoniae* in Croatia was described in 2009, during 2010 no further NDM-1 isolates were detected among the isolates sent for retesting to the Reference center for antibiotic resistance surveillance. It is of special importance to note that the presence of strains producing KPC carbapenemases, that have a significant epidemic potential, is still not yet detected in Croatia.

Resistance in other enterobacteriaceae, *P. mirabilis* and the *Enterobacter* spp*., Serratia* spp*., Citrobacter* spp. group did not change significantly compared with the previous year. The rate of derepressed mutants that hyperproduce inducible cephalosporinases in the enterobacter group is 16%. Sporadic isolates resistant to carbapenems were recorded in six centers but carbapenemase (IMI-1) production was detected in only one isolate of *Enterobacter cloacae*.

Resistance in *P.aeruginosa* did not change significantly at the national level. Resistance to carbapenems is still 12% for imipenem and 11% for meropenem with large variations among centers. While resistance has decreased significantly in some centers like KBC Rijeka (26% in 2009 and 14% in 2010) and Children's Hospital Zagreb (33% in 2009 and 9% in 2010) resistance to carbapenems in KBC Zagreb is still increasing (17% in 2008, 33% in 2009 and 42% in 2010). Resistance rates lower than 10% were still recorded for piperacillin/tazobactam (7%), ceftazidim (6%), cefepim (5%) and colistin (0%). Sporadic isolates resistant to colistin were recorded in Osijek, Varaždin and KBC Zagreb.

The increasing trend in total number of *Acinetobacter baumanii* isolates is still on (565 isolates in 2005, 800 isolates in 2007, 1097 isolates in 2009 and 1289 isolates

in 2010). Increase in carbapenem resistance which was recorded in 2009 is also ongoing (10% for meropenem and 4% for imipenem in 2008, 23% in 2009 and 34% in 2010). Carbapenem resistance rates of approx. 50% and more are recorded in KBC Rijeka (71%), KBC Split (49%), KBC Zagreb (53%), KB Merkur (84%), University Hospital for Infectious Diseases (74%) and KB Sveti Duh (53%). Resistance to ampicillin/sulbactam is also increasing (9% in 2009, 14% in 2010). Sporadic isolates resistant to colistin were recorded in Karlovac, Split and HZZJZ.

Antibiotic resistance in salmonellae did not change significantly. In 2010 resistance to ampicillin is 11%, and resistance to all the other antibiotics is <5%. ESBL producing or ciprofloxacin resistant isolates were not recorded. The first step quinolone resistance (as tested by nalidixic acid) was recorded in 1% of isolates.

During 2010 only 26 shigella isolates were recorded. Resistance was high for ampicillin and co-trimoxazole. Resistance to quinolones was not detected in 2010.

Among anaerobic bacteria high ampicillin resistance was recorded in *Bacteroides* spp. (78%), but not in clostridia (7%) and anaerobic gram-positive cocci (8%). Resistance to metronidazole is high in gram-positive cocci (55%) and low in clostridia (2%) and *Bacteroides* spp. (9%). Resistance to clindamycin is between 15% and 25% for all three groups of anaerobes.

Legenda za tablice */ Legend to tables:*

Šifra */ code*	USTANOVE */ CENTERS*
BJ ZZJZ	*ZZJZ Bjelovarsko-bilogorske županije, Bjelovar*
ČK ZZJZ	*ZZJZ Međimurske županije, Čakovec*
DU ZZJZ	*ZZJZ Dubrovačko-neretvanske županije, Dubrovnik*
GS ZZJZ	*ZZJZ Ličko-senjske županije, Gospić*
IG ZZJZ	*ZZJZ Zagrebačke županije Ivanić Grad*
KA OB	*Opća bonica Karlovac, Karlovačka županija*
KA ZZJZ	*ZZJZ Karlovačke županije, Karlovac*
KC ZZJZ	*ZZJZ Koprivničko-križevačke županije, Koprivnica*
KL BPB	*Bolnica za plućne bolesti i TBC, Klenovnik*
KR ZZJZ*	*ZZJZ Krapinsko-zagorske županije, Krapina*
NG OB	*Opća bolnica Nova Gradiška*
OG OB	*Opća bolnica Ogulin, Karlovačka županija*
OS ZZJZ	*ZZJZ Osječko-baranjske županije, Osijek*
PK OŽB	*Opća županijska bolnica Pakrac*
PU ZZJZ	*ZZJZ Istarske županije, Pula*
PŽ OŽB	*Opća županijska bolnica Požega, Požeško-slavonska županija*
RI KBC	*Klinički bolnički centar Rijeka, Rijeka*
RI NZZJZ	*NZZJZ 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	*NZZJZ Splitsko-dalmatinske županije, Split*
ŠI ZZJZ	*ZZJZ Šibensko-kninske županije, Šibenik*
VK OB	*Opća bolnica, Vinkovci*
VT ZZJZ	*ZZJZ Virovitičko-podravske županije, Virovitica*
VŽ ZZJZ	*ZZJZ Varaždinske županije, Varaždin*
ZD ZZJZ	*ZZJZ Zadarska županija, Zadar*
ZG KBC**	*Klinički bolnički centar «Zagreb», Zagreb*
ZG KBD	*Klinička bolnica «Dubrava», Zagreb*
ZG KBM***	*Klinička bolnica «Merkur», Zagreb*
ZG KBSM******	*Klinička bolnica «Sestre milosrdnice», Zagreb*
ZG KIB	*Klinika za infektivne bolesti «Dr. F. Mihaljević», Zagreb*
ZG ZZJZ	*Zavod za javno zdravstvo 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 BR	*Poliklinika za med. mikrobiologiju s parasitologijom «Dr. Brazda»*

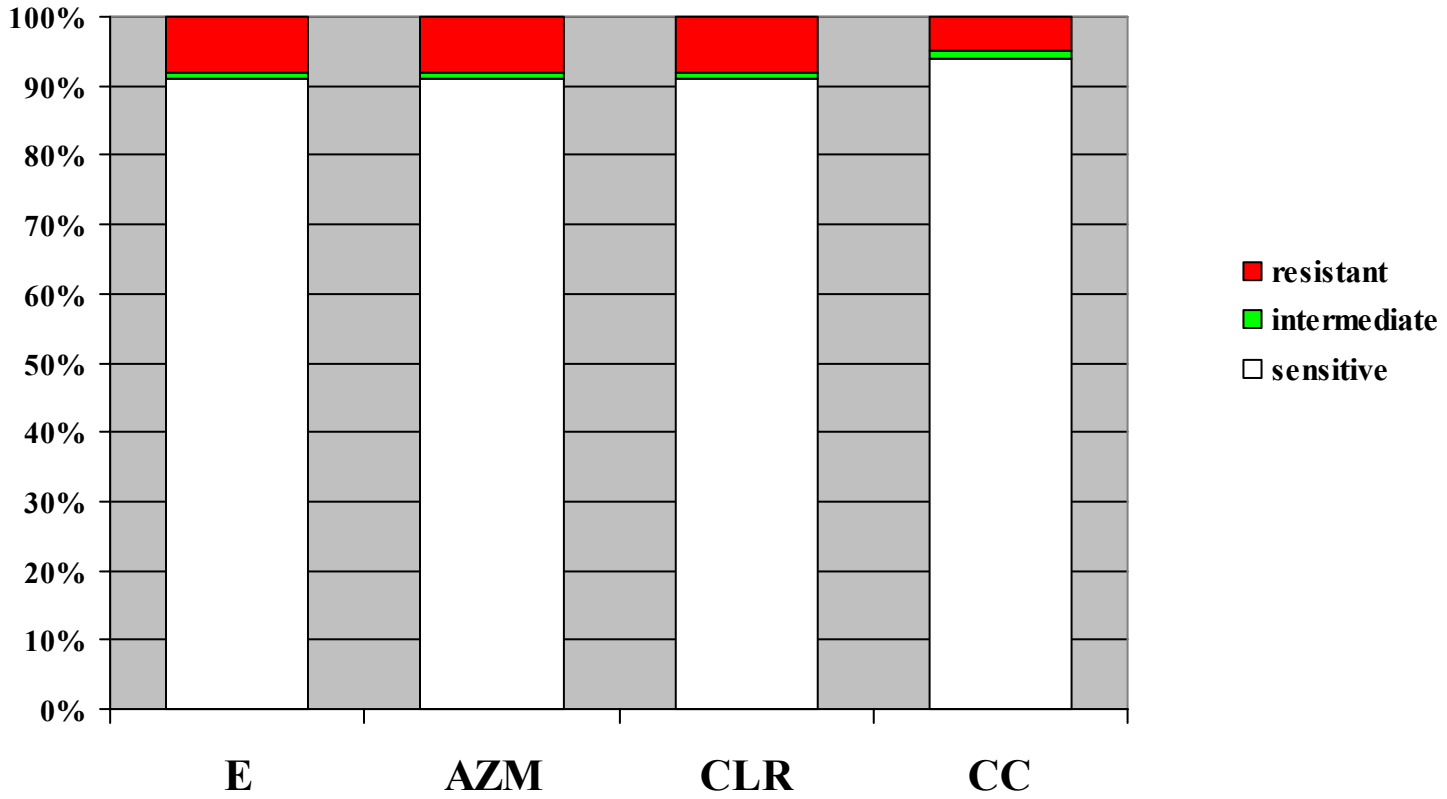
* uključuje podatke i za: Opću bolnicu Zabok
** uključuje podatke i za: Kliniku za plućne bolesti „Jordanovac", Zagreb
*** uključuje podatke i za: Sveučilišnu Kliniku za dijabetes, endokrinologiju i bolesti metabolizma „Vuk Vrhovac", Zagreb
**** uključuje podatke i za: Kliniku za traumatologiju i Institut za tumore, Zagreb

ANTIBIOTICI / ANTIBIOTICS:

P	penicillin
AMP	ampicillin
AMX	amoxicillin
AMC	amoxicillin + clavulanic acid
SAM	ampicillin + sulbactam
OX	oxacillin
CN	cefalexin (I. gen. cephalosporins)
CXM	cefuroxime (II. gen. cephalosporins)
CAZ	ceftazidime (III. gen. cephalosporins)
CRO	ceftriaxone (III. gen. cephalosporins)
CTB	ceftibuten (III. gen. cephalosporins)
CFM	cefixime (III. gen. cephalosporins)
CFP	cefoperazone (III. gen. cephalosporins)
CFEP	cefepime (IV. gen. cephalosporins)
PIP	piperacillin
PTZ	piperacillin/tazobactam
ERT	ertapenem
IMP	imipenem
MER	meropenem
E	erythromycin
AZM	azithromycin
CLR	clarythromycin
CC	clindamycin
CL	chloramphenicol
TEICO	teicoplanin
TE	tetracycline
SXT	co-trimoxazole
NF	nitrofurantoin
VA	vancomycin
RIF	rifampicin
CIP	ciprofloxacin
NOR	norfloxacin
GM	gentamicin
AN	amikacin
MUP 5	mupirocin 5
MUP 200	mupirocin 200
MTZ	metronidazole
MOX	moxifloxacin
LZD	linezolid
NA	nalidixic acid
COL	colistin

No = broj izolata / *number of isolates*
I% = % intermedijarnih izolata / % *of intermediate isolates*
R% = % rezistentnih izolata / % *of resistant isolates*
NS% = % neosjetljivih izolata / % *of nonsusceptible isolates*

Beta-hemolitički streptokok grupe A
Group A beta-hemolytic streptococcus
(1.01. - 31.12. 2010.) - osjetljivost na antibiotike u RH
- sensitivity to antibiotics in Croatia



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Croatian Committee for Antibiotic Resistance Surveillance

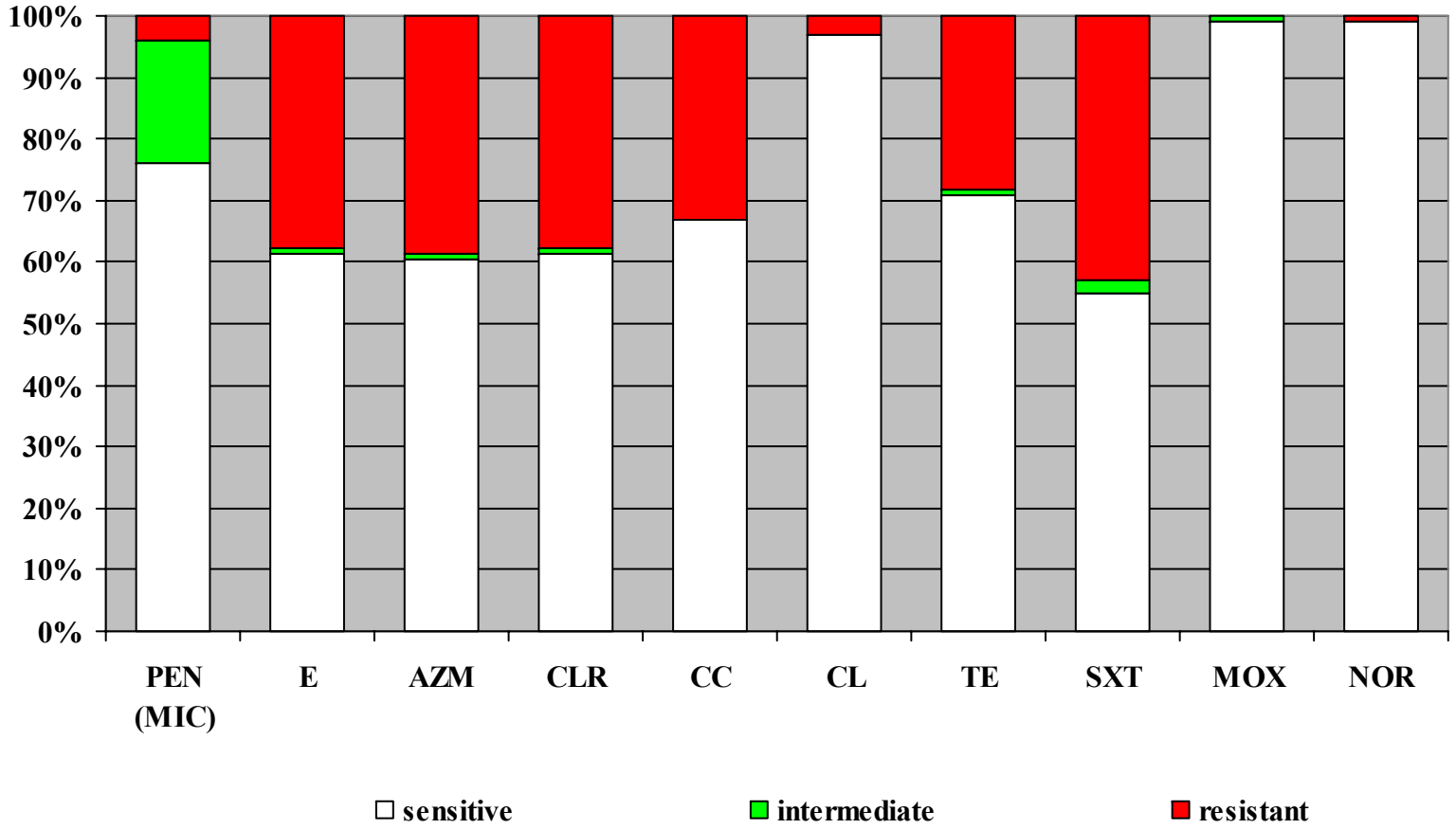
Beta-hemolitički streptokok grupe A
Group A streptococcus

- rezistencija na antibiotike u razdoblju od 1.01.- 31.12. 2010.
  zbirni prikaz izolata iz 37 centra u RH
- antibiotic resistance for the period 1.01. - 31.12. 2010.
  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	13 158	8 (1)	2 (0) - 27 (0)
Azithromycin	13 158	8 (1)	2 (0) - 27 (0)
Clarythromycin	13 158	8 (1)	2 (0) - 27 (0)
Clindamycin	12878	5 (1)	
constitutive		4	0 - 20
inducible		1	0 - 8

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

Streptococcus pneumoniae (1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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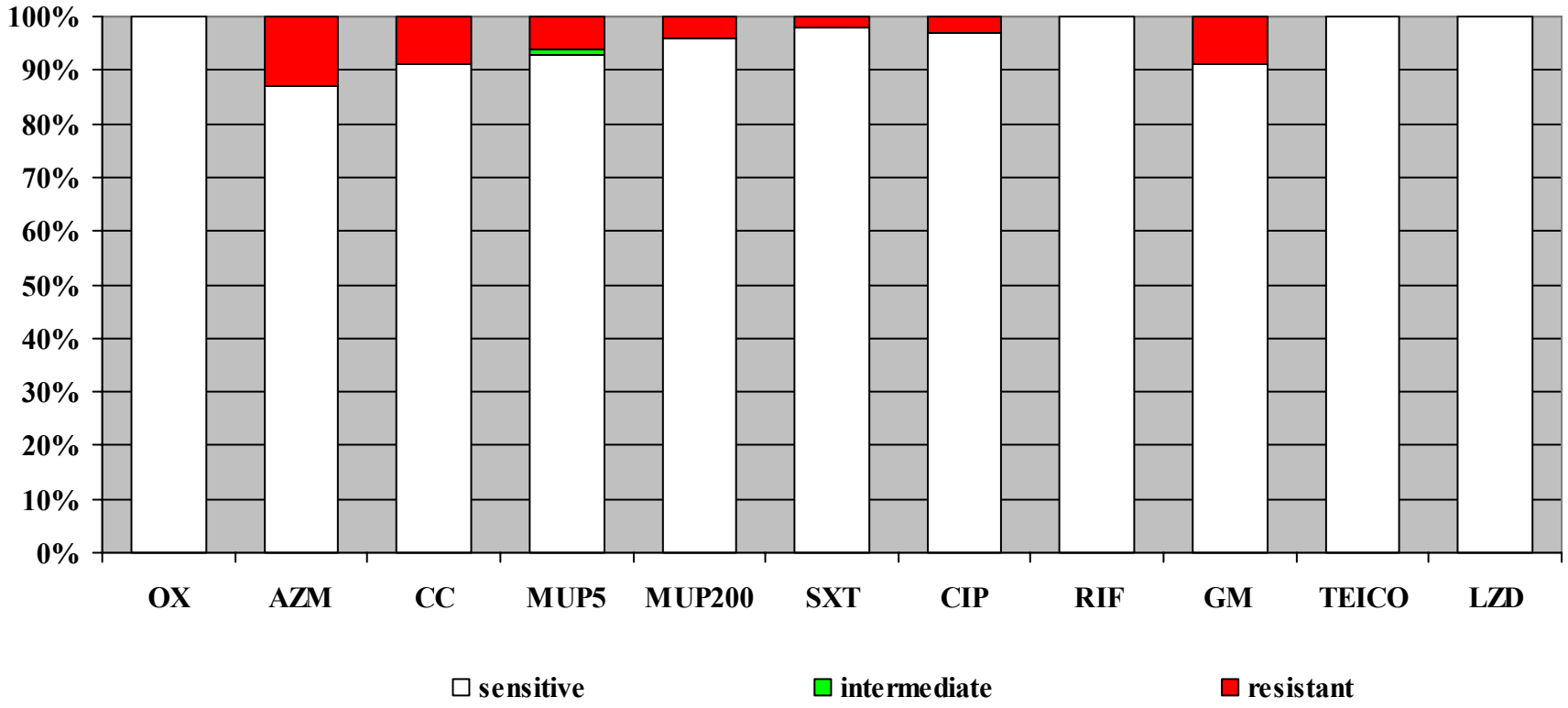
Streptococcus pneumoniae

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2010.
zbirni prikaz izolata iz 37 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2010.
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	4 107		
visoko rez. / high		4	0 - 20
umjereno rez. / low		20	0 - 54
Erythromycin	4 211	38 (1)	3 (0) - 66 (0)
Azithromycin	4 211	38 (1)	3 (0) - 66 (0)
Clarythromycin	4 211	38 (1)	3 (0) - 66 (0)
Clindamycin	4 137	33 (0)	7 (0) - 56 (0)
Chloramphenicol	4 004	3 (0)	0 (0) - 20 (0)
Tetracycline	4 008	28 (1)	7 (0) - 47 (0)
Co-trimoxazole	4 166	43 (2)	2 (0) - 86 (0)
Moxifloxacin	3 740	0 (1)	0 (0) - 3 (6)
Norfloxacin	4 023	1 (0)	0 (0) -12 (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 MSSA (1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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Staphylococcus aureus / MSSA

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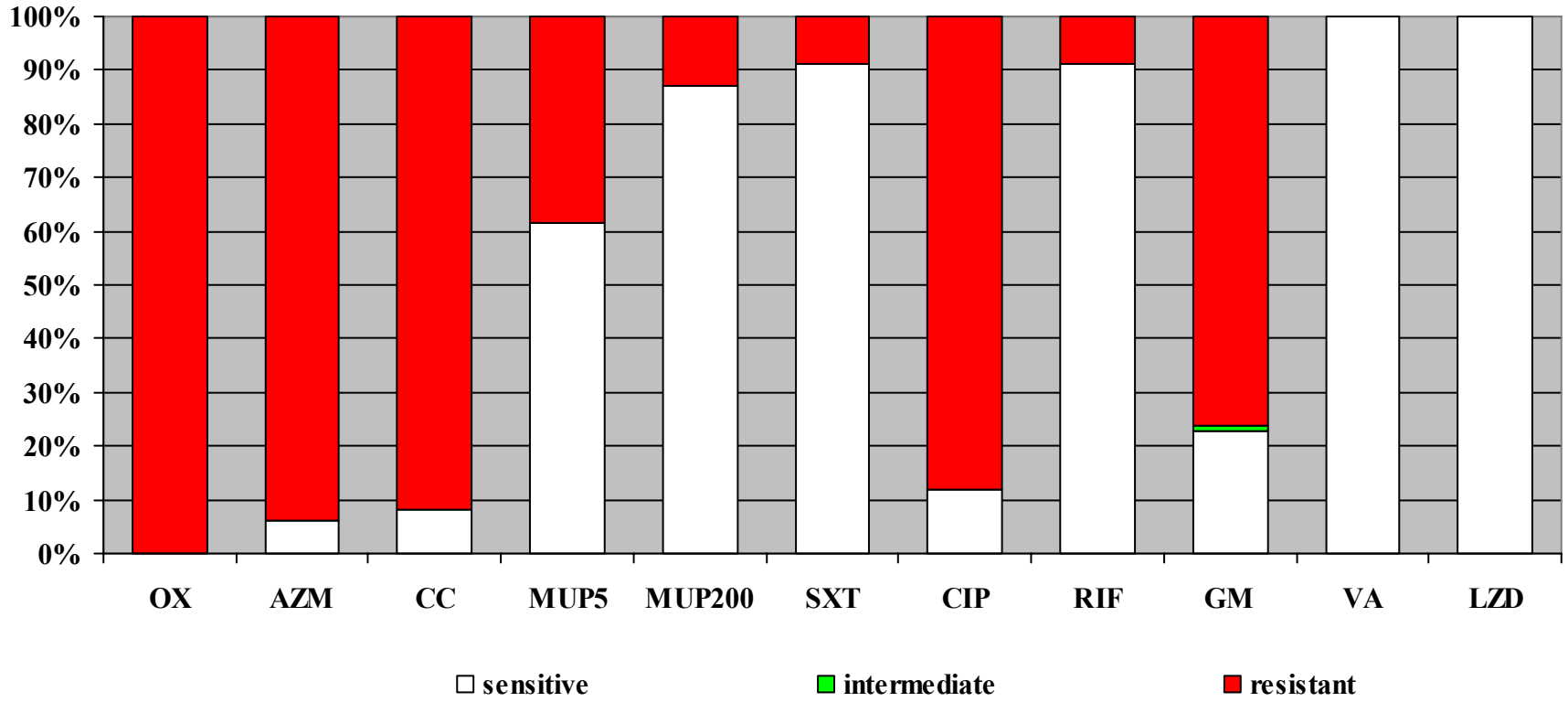
zbirni prikaz izolata iz 37 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2010.
summary results for the isolates from 37 centers in Croatia

ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Oxacillin	4 222	0	0
Azithromycin	4 014	13 (0)	5 (0) - 26 (0)
Clindamycin	4 213	9 (0)	2 (0) - 22 (0)
Mupirocin 5	3 651	6 (1)	0 (0) - 21 (0)
Mupirocin 200	2 385	4 (0)	0 (0) – 13 (0)
Co-trimoxazole	4 203	2 (0)	0 (0) - 9 (0)
Ciprofloxacin	4 189	3 (0)	0 (0) - 9 (0)
Rifampicin	4 051	0 (0)	0 (0) - 3 (0)
Gentamicin	4 218	9 (0)	0 (0) - 29 (0)
Teicoplanin	3 852	0 (0)	0 (0) - 0 (0)
Linezolid	3 783	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 (1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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Staphylococcus aureus / MRSA

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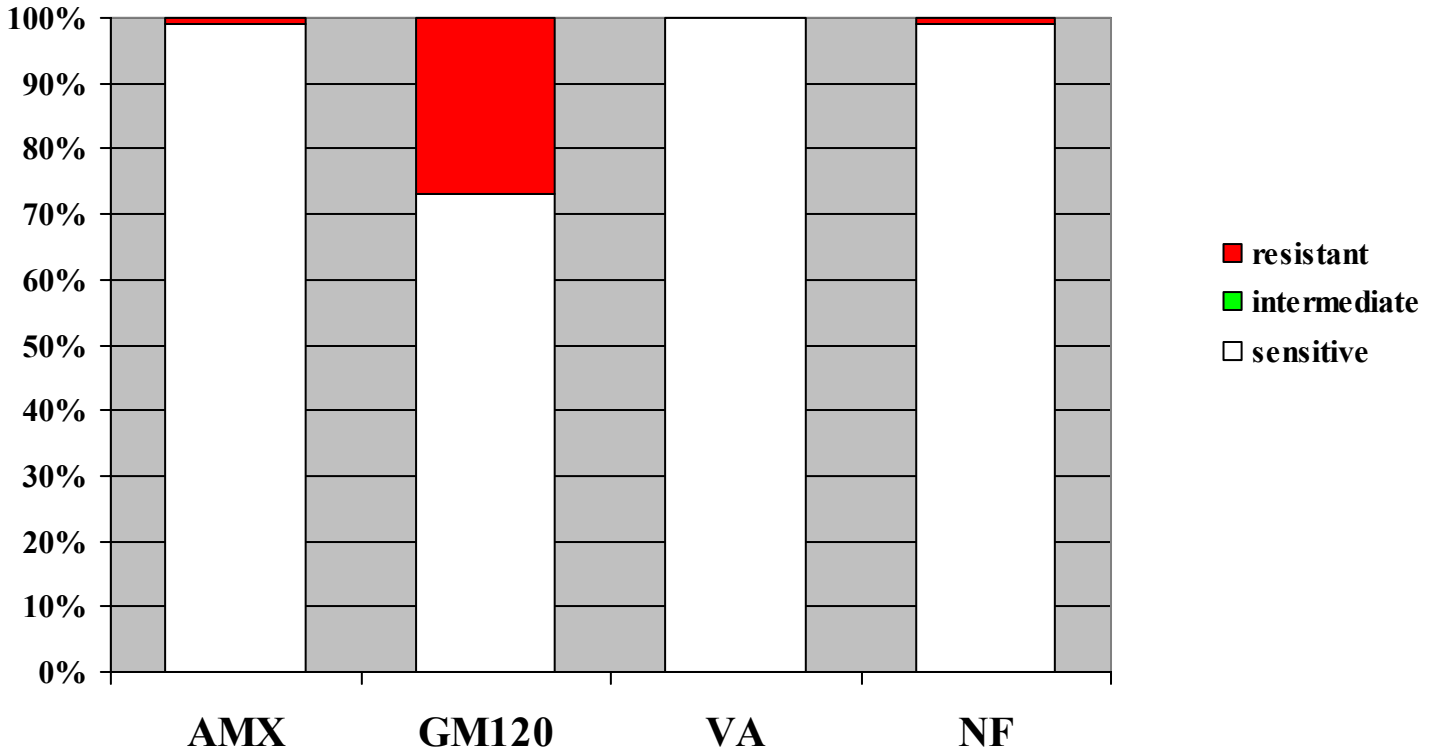
zbirni prikaz izolata iz 37 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2010.
summary results for the isolates from 37 centers in Croatia

ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Oxacillin	804	100 (0)	100 (0) - 100 (0)
Azithromycin	798	94 (0)	74 (0) - 100 (0)
Clindamycin	802	92 (0)	73 (0) - 100 (0)
Mupirocin 5	724	38 (0)	15 (0) - 60 (0)
Mupirocin 200	521	12 (0)	0 (0) - 22 (0)
Co-trimoxazole	803	9 (0)	0 (0) - 21 (0)
Ciprofloxacin	789	88 (0)	78 (2) - 98 (0)
Rifampicin	788	9 (0)	0 (0) - 25 (0)
Gentamicin	803	77 (1)	74 (0) - 93 (0)
Teicoplanin	732	0 (0)	0 (0) - 0 (0)
Linezolid	689	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

Enterococcus faecalis (1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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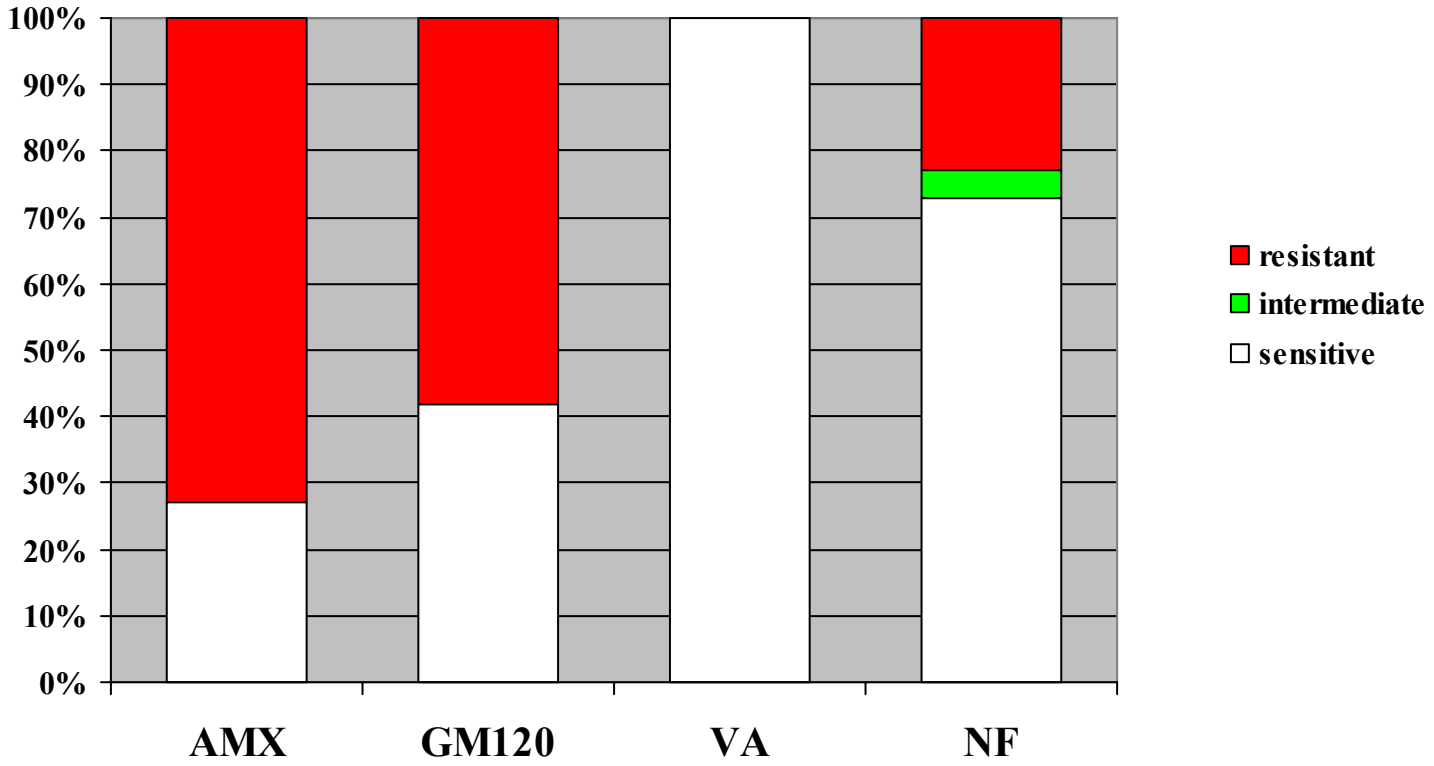
Enterococcus faecalis

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2010.
zbirni prikaz izolata iz 37 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2010.
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*
Amoxicillin	6 072	1 (0)	0 (0) - 13 (0)
Gentamicin 120	6 033	27 (0)	0 (0) - 80 (0)
Vancomycin	6078	0 (0)	0 (0) - 0 (0)
Nitrofurantoin	5 995	1 (0)	0 (0) - 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 into consideration

Enterococcus faecium (1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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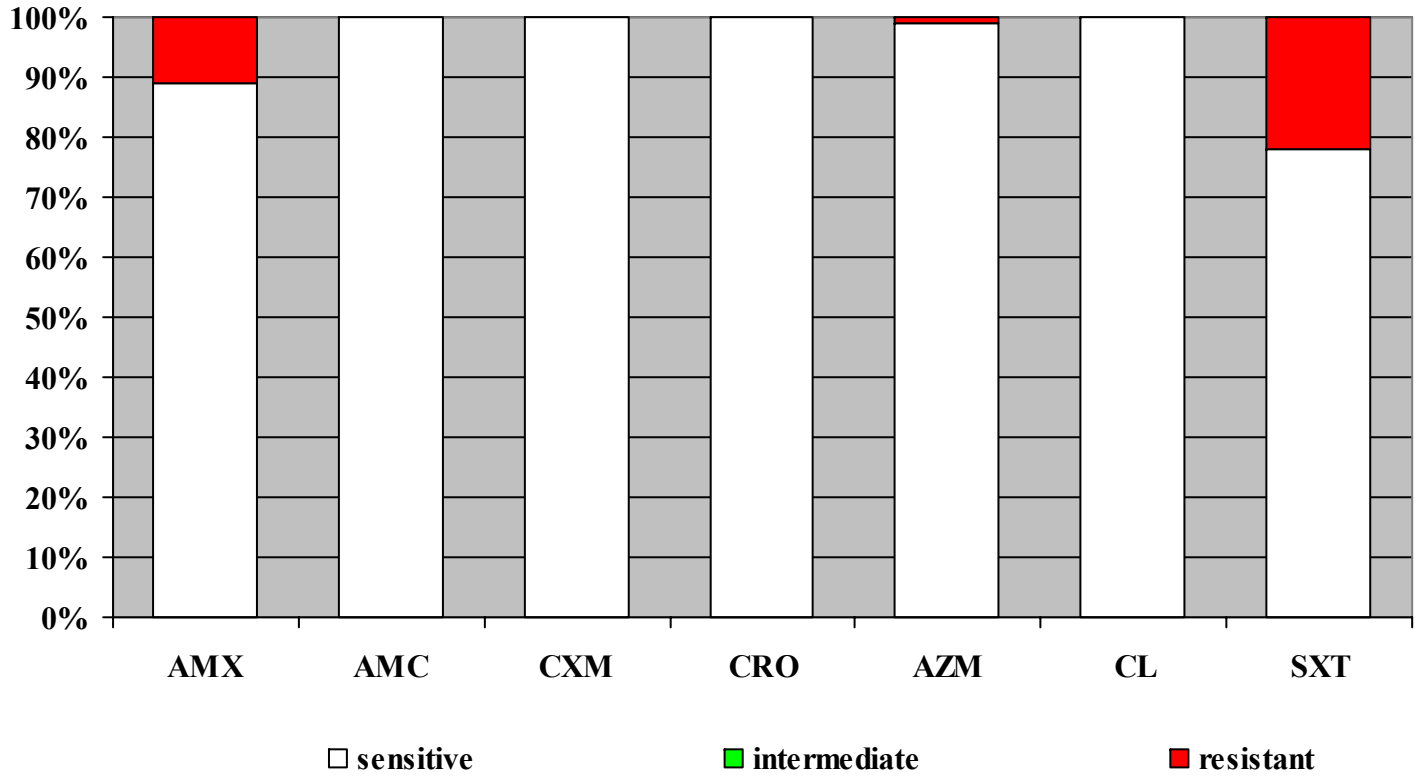
Enterococcus faecium

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2010.
zbirni prikaz izolata iz 37 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2010.
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*
Amoxicillin	412	73 (0)	58 (0) - 95 (0)
Gentamicin 120	409	58 (0)	14 (0) - 79 (0)
Vancomycin	413	0 (0)	0 (0) - 2 (0)
Nitrofurantoin	407	23 (4)	8 (5) - 45 (21)

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

Haemophilus influenzae (1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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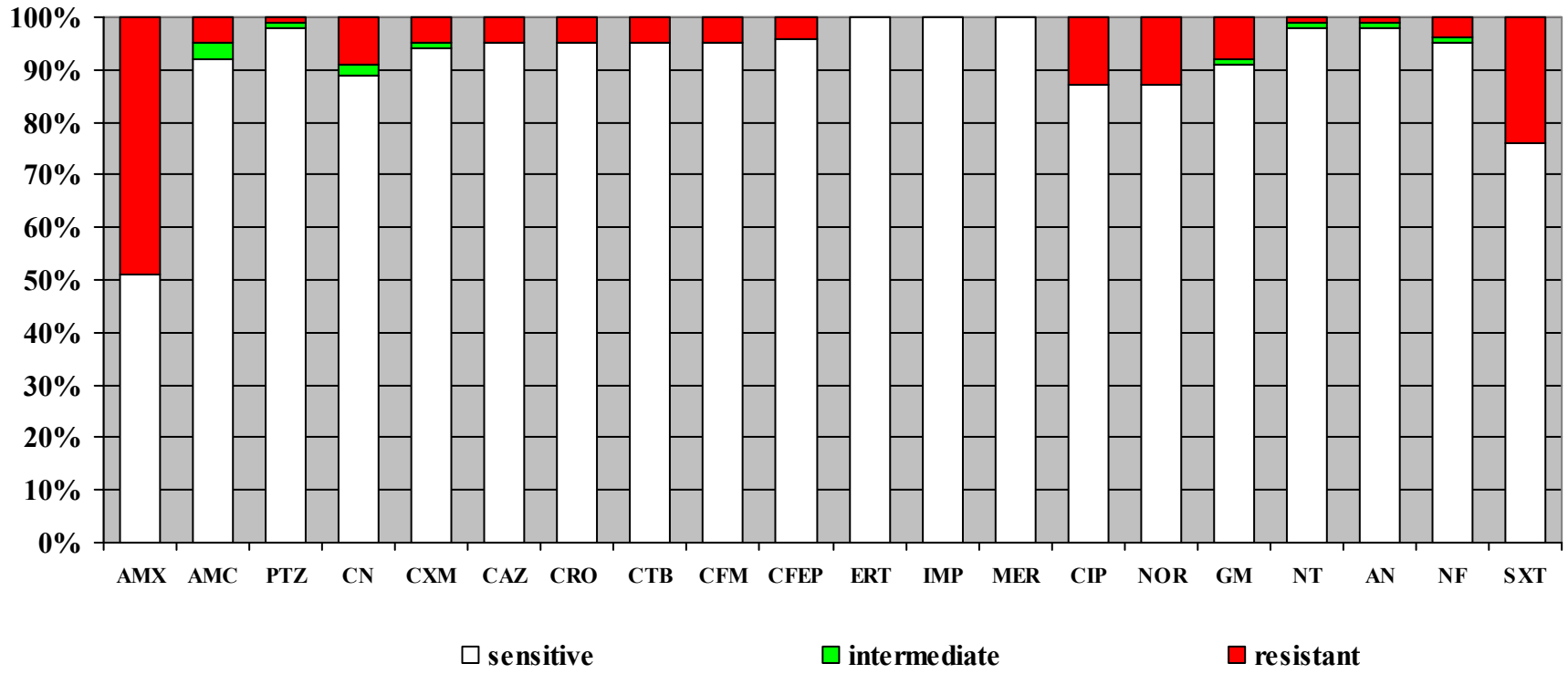
Haemophilus influenzae

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2010.
zbirni prikaz izolata iz 37 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2010.
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*
Amoxicillin	3 059	11 (0)	0 (0) - 28 (0)
Amoxicillin + clav. acid	3 058	0 (0)	0 (0) - 0 (0)
Cefuroxime	3 056	0 (0)	0 (0) - 0 (0)
Ceftriaxone	3 043	0 (0)	0 (0) - 0 (0)
Azithromycin	3 014	1 (0)	0 (0) - 14 (0)
Cloramphenicol	3 022	0 (0)	0 (0) - 0 (0)
Co-trimoxazole	2 373	22 (0)	2 (0) - 67 (1)

* 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 (1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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Escherichia coli

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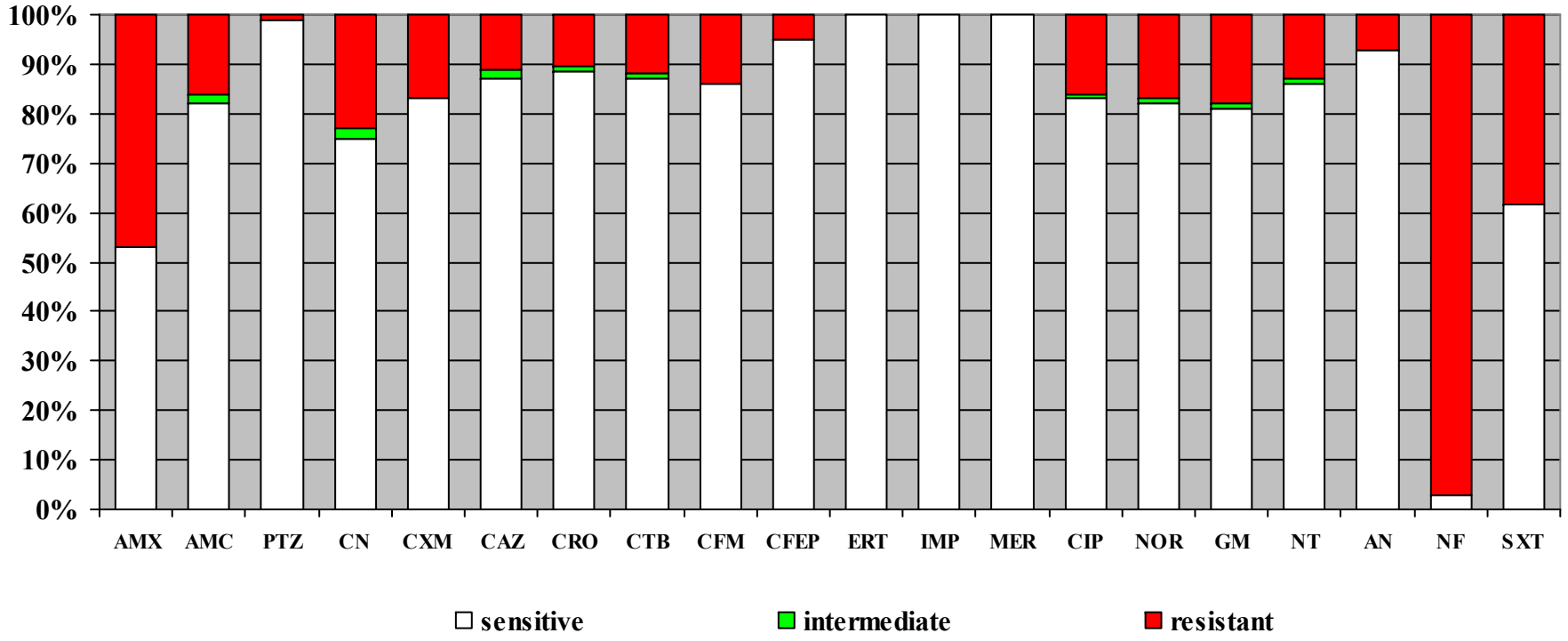
summary results for the isolates from 37 centers in Croatia

ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Amoxicillin	19 808	49 (0)	36 (0) - 68 (0)
Amoxicillin + clav. acid	19 811	5 (3)	0 (2) - 13 (0)
Piperacillin + tazobactam	19 507	1 (1)	0 (0) - 6 (0)
Cephalexin	19 191	9 (2)	3 (0) - 22 (0)
Cefuroxime	19 751	6 (1)	1 (1) - 16 (0)
Ceftazidime	19 789	5 (0)	0 (0) - 14 (0)
Ceftriaxone	19 716	5 (0)	0 (0) - 14 (0)
Cefepime	19 611	4 (0)	0 (0) - 14 (0)
Ceftibuten	18 695	5 (0)	1 (0) - 15 (1)
Cefiksime	18 910	5 (0)	1 (0) - 11 (0)
Ertapenem	18 340	0 (0)	0 (0) - 0 (0)
Imipenem	19 763	0 (0)	0 (0) - 0 (0)
Meropenem	19 730	0 (0)	0 (0) - 1 (0)
Ciprofloxacin	19 741	13 (0)	3 (0) - 29 (0)
Norfloxacin	19 571	13 (0)	3 (0) - 29 (0)
Gentamicin	19 742	8 (1)	2 (0) - 46 (0)
Amikacin	19 385	1 (1)	0 (0) - 16 (0)
Netilmicin	19 534	1 (1)	0 (0) - 6 (6)
Nitrofurantoin	19 296	4 (1)	0 (0) - 53 (0)
Co-trimoxazole	19 509	24 (0)	10 (0) - 50 (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 (1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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Proteus mirabilis

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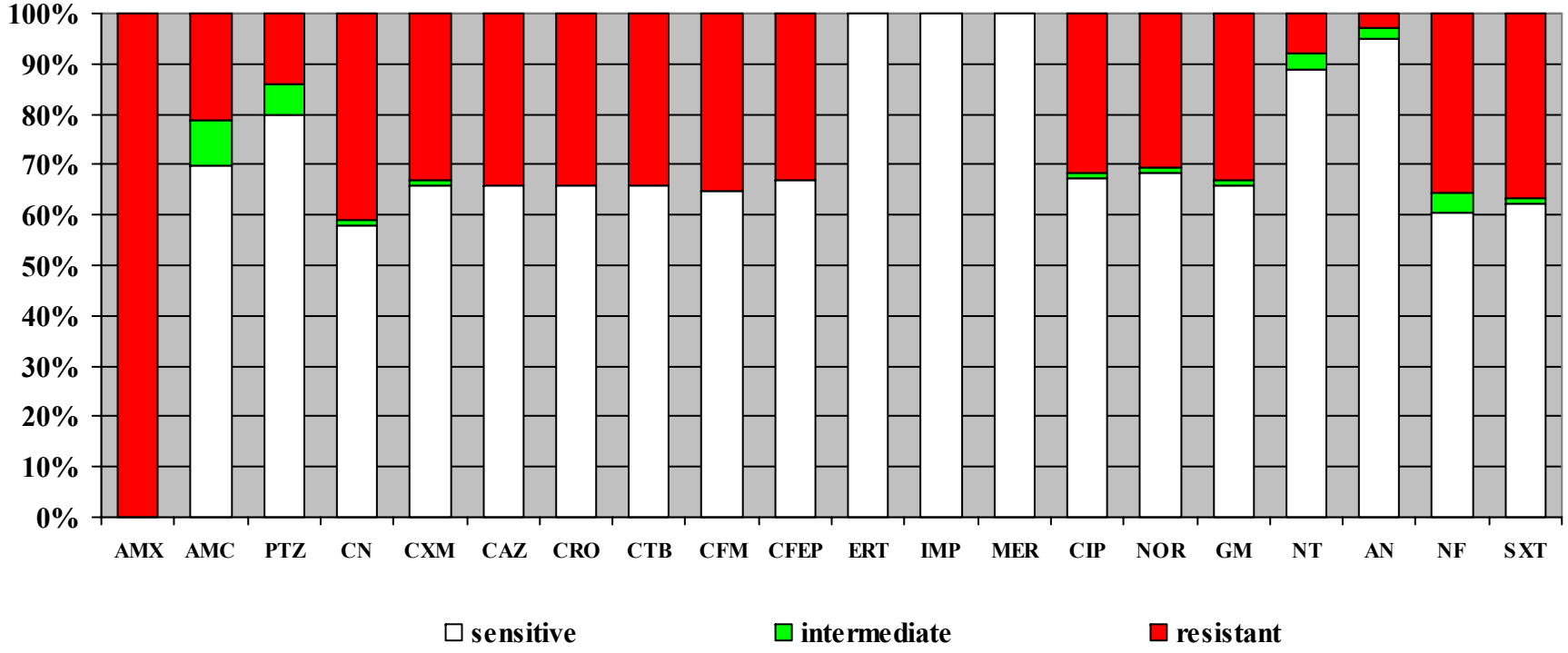
ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Amoxicillin	4 228	47 (0)	27 (0) - 67 (0)
Amoxicillin + clav. acid	4 232	16 (2)	0 (0) - 45 (0)
Piperacillin + tazobactam	4 163	1 (0)	0 (0) - 21 (1)
Cephalexin	4 143	23 (2)	0 (0) -55 (0)
Cefuroxime	4 225	17 (0)	0 (0) - 53 (0)
Ceftazidime	4 232	11 (2)	0 (0) - 43 (2)
Ceftriaxone	4 232	11 (1)	0 (0) - 44 (0)
Cefepime	4 000	5 (0)	0 (0) - 22 (0)
Ceftibuten	3 944	12 (1)	0 (0) - 43 (1)
Cefixime	3 981	14 (0)	0 (0) - 45 (0)
Ertapenem	3 981	0 (0)	0 (0) - 0 (0)
Imipenem	4 230	0 (0)	0 (0) - 0 (0)
Meropenem	4 222	0 (0)	0 (0) - 0 (0)
Ciprofloxacin	4 223	16 (1)	2 (3) - 45 (0)
Norfloxacin	4 123	16 (1)	0 (0) - 45 (0)
Gentamicin	4 223	18 (1)	4 (2) - 58 (0)
Amikacin	4 145	7 (0)	0 (0) - 38 (0)
Netilmicin	4 181	13 (1)	0 (0) - 89 (0)
Nitrofurantoin	4 088	97 (0)	0 (0) - 100 (0)
Co-trimoxazole	4 183	38 (0)	16 (1) - 63 (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 (1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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Klebsiella pneumoniae

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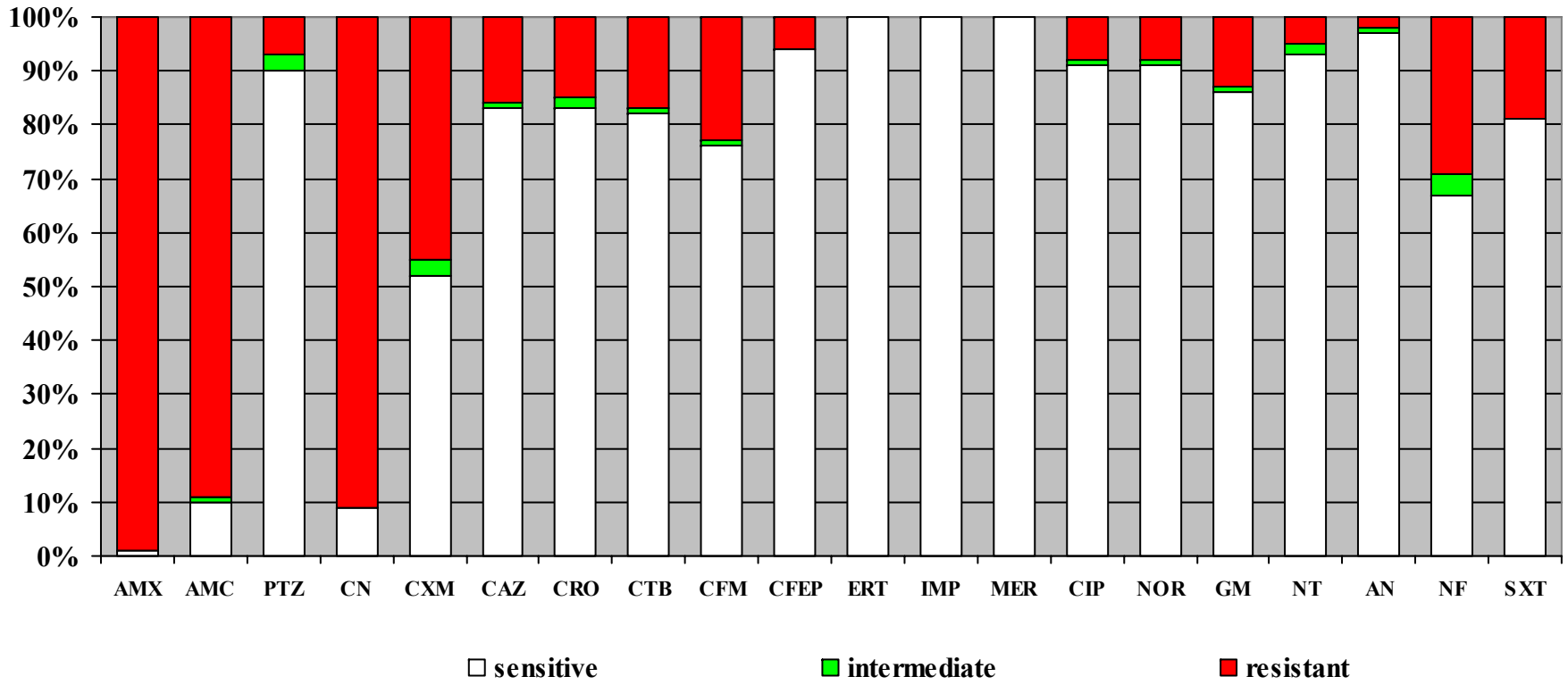
summary results for the isolates from 37 centers in Croatia

ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Amoxicillin	4 226	100 (0)	92 (0) - 100 (0)
Amoxicillin + clav. acid	4 226	21 (9)	0 (11) - 48 (2)
Piperacillin + tazobactam	4 170	14 (6)	0 (0) - 49 (6)
Cephalexin	4 108	41 (1)	10 (1) - 71 (0)
Cefuroxime	4 223	37 (1)	0 (0) - 70 (0)
Ceftazidime	4 226	34 (0)	0 (0) - 68 (0)
Ceftriaxone	4 196	34 (0)	0 (0) - 68 (0)
Cefepime	4 210	33 (0)	0 (0) - 68 (0)
Ceftibuten	3 853	34 (0)	8 (0) - 73 (0)
Cefixime	3 933	35 (0)	0 (0) - 89 (4)
Ertapenem	3 977	1 (0)	0 (0) - 23 (21)
Imipenem	4 225	0 (0)	0 (0) - 3 (4)
Meropenem	4 221	0 (0)	0 (0) - 2 (6)
Ciprofloxacin	4 199	30 (1)	5 (0) - 57 (3)
Norfloxacin	4 055	31 (1)	5 (0) - 57 (3)
Gentamicin	4 218	33 (1)	5 (3) - 62 (0)
Netilmicin	4 195	8 (3)	0 (0) - 41 (0)
Amikacin	4 151	3 (2)	0 (0) - 27 (2)
Nitrofurantoin	3 966	36 (4)	11 (18) - 58 (2)
Co-trimoxazole	4 139	37 (1)	13 (0) - 56 (1)

* 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

Enterobacter spp., *Serratia* spp., *Citrobacter* spp.
(1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH
- sensitivity to antibiotics in Croatia



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

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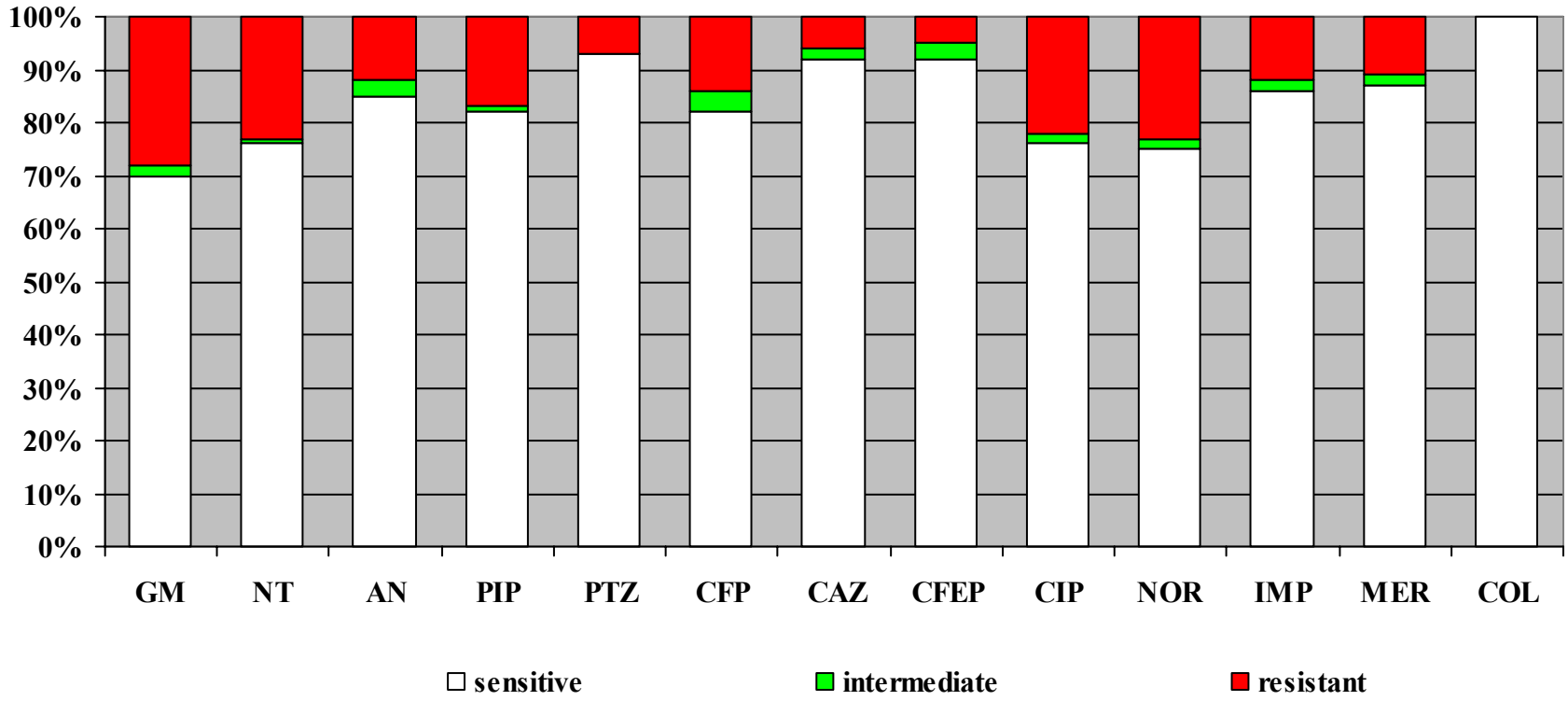
ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Amoxicillin	2 794	99 (0)	86 (4) - 100 (0)
Amoxicillin + clav. acid	2 795	89 (1)	56 (0) - 100 (0)
Piperacillin + tazobactam	2 741	7 (3)	0 (0) - 45 (2)
Cephalexin	2 710	91 (0)	65 (0) - 100 (0)
Cefuroxime	2 792	45 (3)	12 (0) - 84 (2)
Ceftazidime	2 798	16 (1)	4 (0) - 57 (0)
Ceftriaxone	2 777	15 (2)	4 (0) - 57 (0)
Cefepime	2 727	6 (0)	0 (0) - 23 (0)
Ceftibuten	2 602	17 (1)	6 (0) - 57 (0)
Cefixime	2 603	23 (1)	0 (0) - 30 (0)
Ertapenem	2 630	0 (0)	0 (0) - 4 (0)
Imipenem	2 796	0 (0)	0 (0) - 2 (0)
Meropenem	2 790	0 (0)	0 (0) - 2 (0)
Ciprofloxacin	2 795	8 (1)	0 (0) - 26 (0)
Norfloxacin	2 641	8 (1)	0 (0) - 16 (0)
Gentamicin	2 791	13 (1)	0 (0) - 48 (0)
Amikacin	2 763	2 (1)	0 (0) - 26 (0)
Netilmicin	2 765	5 (2)	0 (0) - 24 (8)
Nitrofurantoin	2 600	29 (4)	14 (0) - 71 (9)
Co-trimoxazole	2 748	19 (0)	3 (0) - 56 (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
s

Pseudomonas aeruginosa (1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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Pseudomonas aeruginosa

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zbirni prikaz izolata iz 37 centra u RH
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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*
Gentamicin	3 934	28 (2)	6 (4) - 63 (2)
Netilmicin	3 789	23 (1)	3 (0) - 61 (2)
Amikacin	3 869	12 (3)	3 (3) - 28 (2)
Piperacilin	3 527	17 (1)	4 (0) - 54 (0)
Piperacilin + tazobaktam	3 932	7 (0)	0 (0) - 24 (0)
Cefoperazon	3 432	14 (4)	1 (1) - 41 (10)
Ceftazidim	3 932	6 (2)	0 (0) - 29 (0)
Cefepim	3 865	5 (3)	0 (0) - 56 (10)
Ciprofloxacin	3 928	22 (2)	9 (0) - 49 (0)
Norfloxacin	3 591	23 (2)	6 (0) - 51 (0)
Imipenem	3 935	12 (2)	0 (0) - 41 (2)
Meropenem	3 936	11 (2)	0 (0) - 49 (5)
Colistin	2 021	0 (0)	0 (0) - 1 (1)

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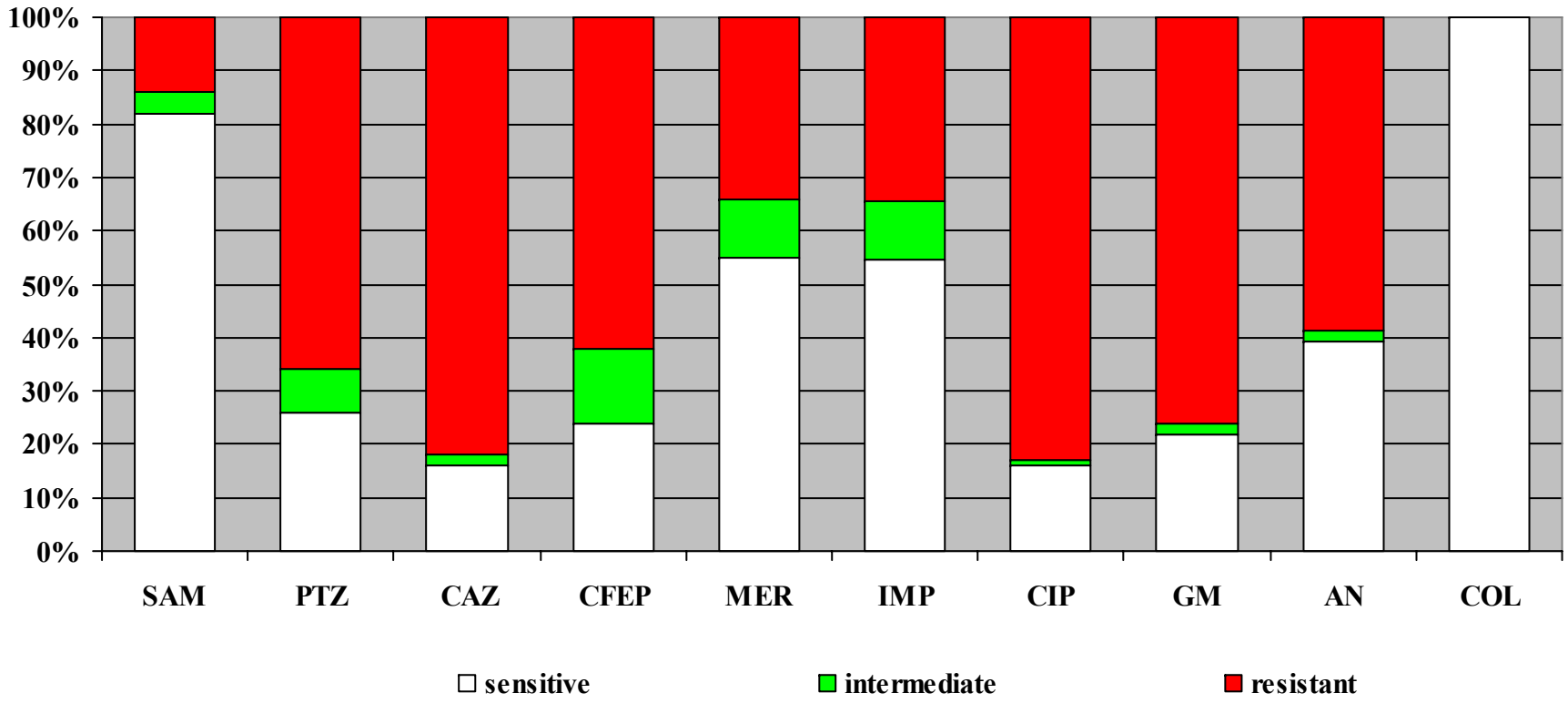
results from the centers with small number of isolates (<30) were not taken into consideration

Acinetobacter baumanii. (1.10. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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Acinetobacter baumanii

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zbirni prikaz izolata iz 37 centra u RH
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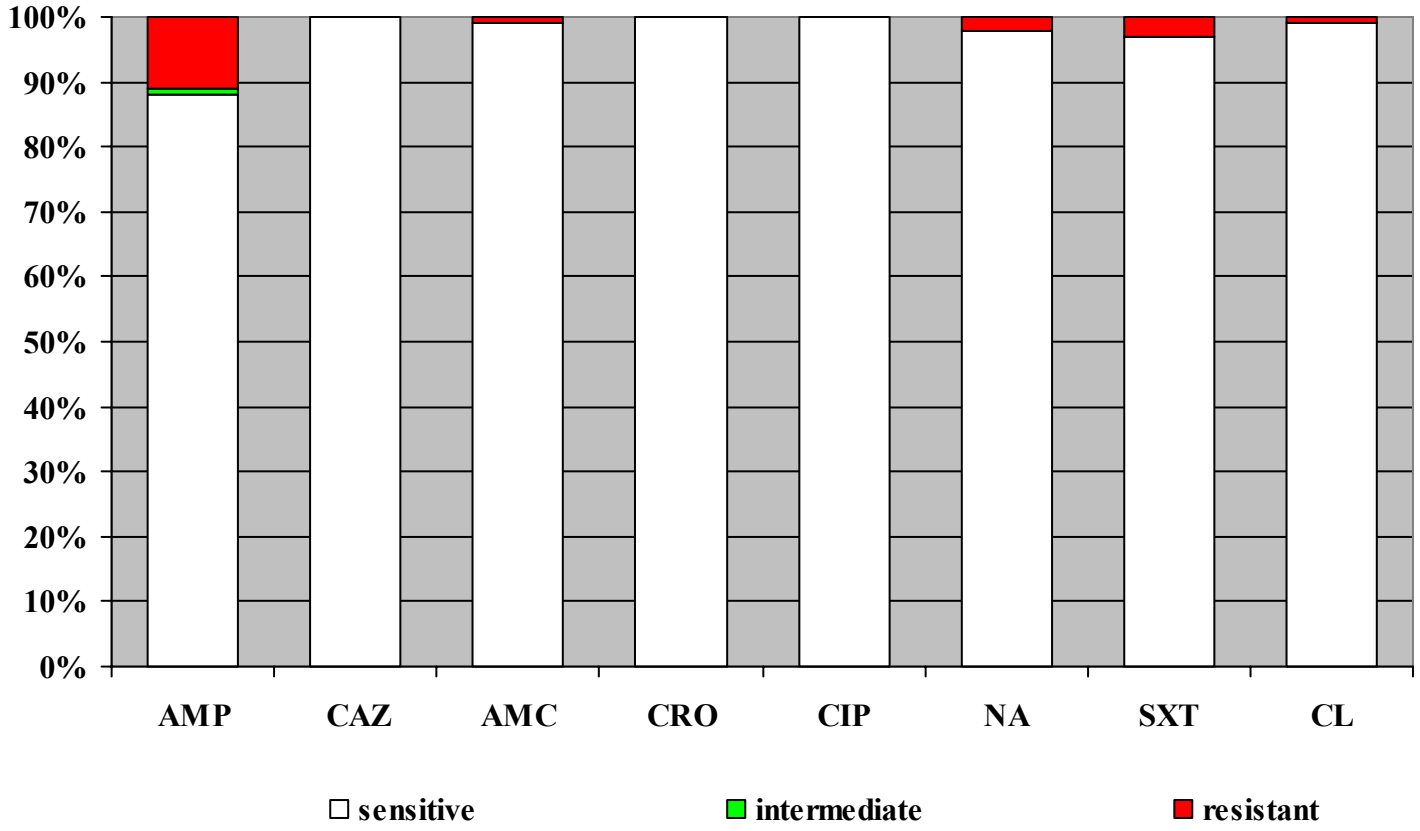
summary results for the isolates from 37 centers in Croatia

ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Ampicillin + sulbactam	1245	14 (4)	0 (0) - 58 (6)
Piperacillin + tazobactam	1 288	66 (8)	27 (17) - 100 (0)
Ceftazidime	1 290	82 (2)	60 (4) - 100 (0)
Cefepime	1 289	62 (14)	14 (35) - 100 (0)
Meropenem	1 289	34 (11)	14 (0) - 84 (0)
Imipenem	1 288	34 (11)	0 (0) - 89 (3)
Ciprofloxacin	1 286	83 (1)	57 (1) - 96 (0)
Gentamicin	1 289	77 (2)	29 (9) - 100 (0)
Amikacin	1 289	58 (2)	25 (5) - 91 (0)
Colistin	832	0 (0)	0 (0) - 3 (0)

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

Salmonella spp. (1.01. - 31.12. 2010.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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Salmonella spp.

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ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Amoxicillin	3 158	11 (1)	0 (0) - 38 (3)
Ceftazidim	3 021	0 (0)	0 (0) - 0 (0)
Amoxicillin + clav. acid	3 158	1 (0)	0 (0) - 10 (0)
Ceftriaxone	2 982	0 (0)	0 (0) - 0 (0)
Ciprofloxacin	3 019	0 (0)	0 (0) - 0 (1)
Nalidixic acid	2 719	1 (0)	0 (0) - 4 (0)
Co-trimoxazole	3 021	3 (0)	0 (0) - 19 (3)
Cloramphenicol	2 952	1 (0)	0 (0) - 4 (0)

* rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir
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***Shigella* spp.** - rezistencija na antibiotike u RH / antibiotic resistance in Croatia, 01.01 - 31.12.2010.

	AMP			AMC			TE			NOR			CL			SXT		
***Shigella* spp.**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**
Shigella sonnei*	24	0	**79**	24	0	**0**	24	0	**8**	23	0	**0**	24	0	**4**	24	0	**100**
Shigella flexneri*	2	0	**2**	2	0	**1**	2	0	**2**	1	0	**0**	1	0	**0**	1	0	**1**
UKUPNO* ***TOTAL***	26	0	**81**	26	0	**4**	26	0	**15**	24	0	**5**	25	0	**4**	25	0	**100**

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

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Anaerobne bakterije - rezistencija na antibiotike u RH / antibiotic resistance in Croatia, 01.01 - 31.12.2010.

Anaerobes

	AMP			AMC			PTZ			IMP			MTZ			CC		
	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**
***Bacteroides* spp.**	162	1	**78**	159	3	**2**	162	0	**0**	160	1	**0**	162	1	**9**	162	4	**25**
***Clostridium* spp.**	61	0	**7**	57	0	**0**	60	0	**0**	60	0	**3**	61	0	**2**	61	3	**15**
Anaerobni gram pozitivni koki	100	2	**8**	96	0	**1**	92	0	**1**	94	0	**1**	94	1	**55**	100	3	**16**
UKUPNO ***TOTAL***	323	1	**43**	312	1	**1**	314	0	**0**	314	0	**0**	317	1	**24**	323	3	**20**

POGLAVLJE/CHAPTER 2.

OSJETLJIVOST *M. TUBERCULOSIS* U HRVATSKOJ U 2010. GODINI
SENSITIVITY OF M. TUBERCULOSIS IN CROATIA, 2010

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Služba za mikrobiologiju
Odjel za dijagnostiku tuberkuloze
Croatian National Institute of Public Health
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Mycobacteriology Department

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Odjel za dijagnostiku tuberkuloze
Microbiology Service
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Prim. dr. Vera Katalinić-Janković
Dr. sc. Ljiljana Žmak
Mr. sc. Mihaela Obrovac, dipl. ing.

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hzzjz-tbc@zg.htnet.hr

Mikobakterije izolirane u Hrvatskoj u 2010. godini

Incidencija tuberkuloze u Hrvatskoj u 2010. godini je najniža do sada zabilježena i iznosila je 17/100 000 stanovnika. Broj TBC laboratorija se nije promijenio, dijagnostika se provodila u 14 laboratorija organiziranih na tri razine. Za analizu podataka o izoliranim sojevima *M. tuberculosis* koristio se „Upitnik o radu TB laboratorija u 2010. godini".

Ukupno je pregledano 53.300 kliničkih uzoraka na tuberkulozu. U 4,9% uzoraka kultivacijom su otkrivene mikobakterije. Ukupno je izolirano 2.712 sojeva mikobakterija, što je u odnosu na 2009. godinu iznosilo 7% manje izolata.

M. tuberculosis je i dalje dominantna mikobakterija s 2283 (84,2%) izolata, premda je taj postotak niži u odnosu na prethodne godine. Za razliku od manjeg broja izolata *M. tuberculosis*, udio NTM među izoliranim mikobaktrijama se povećao s 13,6% na 15,8%. I tijekom 2010. godine iz humanih kliničkih materijala nije bilo izolata *M. bovis* i *M. caprae*, a *M. bovis* – BCG soj je izoliran iz jednog uzorka (Tablica 1.).

Iako se mikobakterioze ne prijavljuju epidemiološkoj službi u Hrvatskoj, laboratorijski se podaci o osobama s višekratno izoliranim NTM sustavno bilježe od 1982. godine. Broj bolesnika s mikobakteriozom je relativno malen, no u promatranom razdoblju je apsolutni broj bolesnika u kontinuiranom porastu. Tako su 1995. godine registrirana samo 3 (0,07/100 000), a u 2009. godini 22 (0,48/100 000), dok je u 2010. zabilježeno 30 (0,68/100 000) bolesnika koji su zadovoljili mikrobiološke kriterije za dijagnozu mikobakterioze.

Saprofitna mikobakterija *M. gordonae* bila je i u 2010. najzastupljenija. Identificirana je u 37,3% NTM izolata. Najčešće se radilo o kontaminaciji uzoraka, slučajnim nalazima, a ponovo je registrirana i pseudoinfekcija u nekoliko zdravstvenih ustanova. Među uvjetno patogenim NTM u Hrvatskoj i dalje prevladava *M. xenopi* s 12,6% izolata, slijede *M. fortuitum* s 11,2% te *M. avium* i *M. intracellulare* s 7,9% izolata. *M. kansasii* je u Hrvatskoj i dalje rijedak i otkriven je u svega 1,2% izolata. Prvi je put u Hrvatskoj zabilježen izolat *M. insubricum*, a identifikacija je potvrđena sekvenciranjem u laboratoriju u Borstelu, Njemačka (Tablica 2.).

Broj rezistentnih sojeva *M. tuberculosis*, a time i bolesnika s rezistentnom tuberkulozom, nije pokazao znatniji porast. Od 2283 izoliranih sojeva *M. tuberculosis*, 2108 (92,3%) ih je bilo osjetljivo, a 175 (7,7%) rezistentno na prvu liniju antituberkulotika (Tablica 3.). Među rezistentnim sojevima njih 52,0% je bilo monorezistentno, dok je više od 40% izolata *M. tuberculosis* rezistentno na 3 i više antituberkulotika iz prve linije. Kod 28,6% izoliranih sojeva utvrđena je monorezistencija na izoniazid (H), kod 22,9% monorezistencija na streptomicin (S), a samo kod jednog soja (0,6%) monorezistencija na rifampicin (R). Ni tijekom 2010. godine nije zabilježena monorezistencija na etambutol (E) (Tablica 4.).

Rezistencija na antituberkulotike kod *M. tuberculosis* nastaje spontanim mutacijama u specifičnim regijama određenih gena. Oko 96% sojeva rezistentnih na R imaju mutaciju u regiji gena *rpoB* dugačkoj 81 pb, a rezistencija na H povezana je s brojnim mutacijama koje pogađaju jedan ili više gena od kojih su najznačajniji *katG* i *inhA*. Na našem Odjelu za dijagnostiku tuberkuloze za određivanje mutacija u genima *rpoB*, *katG* i *inhA* koriste se komercijalni test Genotype MTBDR*plus* (Hain Lifescience) i in-house metoda višestrukog PCR uz korištenje specifičnih početnica koje su načinjene tako da otkrivaju postojanje mutacija u genima *katG* (Ser315Thr) i *inhA* ($inhA^{C\text{-}15T}$). Navedenih metodama bilo je moguće odrediti molekularnu osnovu rezistencije na R svih sojeva izoliranih u bolesnika s multirezistentnom tuberkulozom u 2010. godini, a na H u 72,7% sojeva. U 2010. godini nisu izolirani polirezistentni sojevi čiji bi profil rezistencije uključivao rezistenciju na H. Mutacija u genu *katG*, čest prekursor multirezistencije, pronađena je u 40,0% multirezistentnih sojeva, a otkrivanje te mutacije u monorezistentnih sojeva predstavlja upozorenje o mogućem razvoju daljnje rezistencije kao i multirezistencije (Tablica 5.). Mutacija u genu *inhA* (uzrokuje nisku razinu rezistencije na H) češća je u monorezistentnih sojeva. Važno je napomenuti da je ta mutacija pronađena u nekoliko sojeva koji su fenotipskim testiranjem identificirani kao osjetljivi na ATL, a taj je propust uočen usporedbom genotipova sojeva izoliranih u novooboljelih bolesnika. Ipak, kako za 27,3% sojeva nije bilo moguće odrediti molekularnu osnovu rezistencije na H, još uvijek nije moguće u potpunosti zamijeniti fenotipsko ispitivanje osjetljivosti na ATL molekularnim testovima.

Mycobacteria isolated in Croatia in 2010

TB incidence hit an all time low in Croatia in 2010 with a rate of 17/100 000 inhabitants. The number of TB laboratories did not change, though, and the diagnostic was divided between 14 labs on three levels. To analyze data on isolated strains, a questionnaire on the work of TB laboratories in 2010 was used.

A total of 53,300 clinical samples were analyzed for tuberculosis. In 4.9% of samples, cultivation detected mycobacteria. A total of 2,712 mycobacterial strains were isolated, which was 7% less than in 2009.

M. tuberculosis remained the predominant mycobacterium with 2,283 (84.2%) isolates, though on a lower scale than the previous year. Unlike fewer *M. tuberculosis* isolates, the share of nontuberculous mycobacteria (NTM) grew from 13.6% to 15.8%. In 2010 there were no *M. bovis* or *M. caprae* isolates, while only one *M. bovis* BCG strain was isolated – (Table 1).

Mycobacterioses are not reported to the Epidemiology Service in Croatia. Lab data on cases with multiple NTM isolates have, still, been systematically documented since 1982. Though the number of mycobacterioses is relatively small, the absolute number of cases in the monitored period is continually on the rise. To illustrate, in 1995 only 3 (0.07/100 000) cases were registered; in 2009, 22 (0.48/100 000), while in 2010, 30 (0.68/100 000) cases fulfilling the microbiological criteria for mycobacteriosis were documented.

Saprophytic mycobacterium *M. gordonae* was most common in 2010. It was identified in 37.3% of NTM isolates. Most frequently, it was a case of sample contamination, accidental finding, but also pseudoinfection in several health facilities. Among the potentially pathogenic NTMs, Croatia is still predominated by *M. xenopi* with 12.6% isolates, followed by *M. fortuitum* with a share of 11.2%, and *M. avium* and *M. intracellulare* with 7.9%. *M. kansasii* remains rare in Croatia with mere 1.2% of isolates. Croatia has for the first time recorded an *M. insubricum* isolate. It was confirmed by sequencing in a laboratory in Borstel, Germany (Table 2).

The number of resistant *M. tuberculosis* strains and, by extension, cases of resistant TB has not demonstrated any significant increase. Of the 2,283 isolated *M. tuberculosis* strains, 2,108 (92.3%) were sensitive to first-line antitubercular agents, while 175 (7.7%) were resistant (Table 3). Fifty-two percent of the resistant strains were monoresistant, while over 40% of *M. tuberculosis* isolates were resistant to 3 or more first-line antituberculotics. Monoresistance to isoniazid (H) was established in 28.6% of isolated cases, monoresistance to streptomycin (S) in 22.9%, to rifampicin (R) in one strain only (0.6%). In 2010 no monoresistance to ethambutol (E) was documented (Table 4).

Resistance to antituberculotics in *M. tuberculosis* is caused by spontaneous mutation in specific regions of certain genes. Some 96% of strains resistant to R have a mutation in the 81-pb-long region of the *rpoB* gene, while resistance to H is related to the numerous mutations affecting one or more genes, most significant being *katG* and *inhA*. At the TB Diagnostics Department of the Croatian National Institute of Public Health, which determines mutation in the *rpoB*, *katG* and *inhA* genes, commercial Genotype MTBDR*plus* (Hain Lifescience) tests and an in-house multiplex PCR method are used, with specific primers designed for detecting mutation in genes *katG* (Ser315Thr) and *inhA* ($inhA^{C\text{-}15T}$). The molecular base of the resistance to R using said methods was determinable in all strains isolated in patients with multiresistant TB in 2010, while the resistance to H could be determined in 72.7% strains. In 2010 no poly-resistant strains were isolated with a profile of resistance to H. Mutation in the gene *katG*, a common precursor of multiresistance, was detected in 40.0% of multiresistant strains, while this finding in monoresistant strains warned about potential further development of (multi)resistance (Table 5). Mutation in the *inhA* gene (causing lower resistance to H) is more common in monoresistant strains. It is important to stress that said mutation was detected in several strains identified as sensitive to ATL by means of phenotypic testing. This error was noted by comparison of genotypes of strains isolated in new cases. Still, as for 27.3% of strains the molecular base of resistance to H could not be determined, phenotypic test of sensitivity to ATL can still not be substituted by molecular tests.

Tablica-*Table* **1.**
Mikobakterije izolirane u Hrvatskoj, 1998. –2010.
Mycobacteria strains isolated in Croatia, 1998-2010

Godina **Year**	**Ukupno mikobakterija** **Total**	**M. tuberculosis**		***M. bovis***		**Netuberkulozne mikobakterije** *Nontuberculous mycobacteria*	
		Broj ***No***	**%**	***M. bovis***	**BCG - soj**	**Broj** ***No***	**%**
1998	5878	5650	96,1	-	1	227	3,8
1999	5864	5664	96,6	-	6	194	3,3
2000	5136	4927	95,9	-	1	208	4,0
2001	5109	4888	95,6	-	1	220	4,3
2002	5450	5280	96,9	-	2	168	3,1
2003	4760	4516	94,8	-	1	243	5,1
2004	4170	3958	94,9	1	3	208	5,0
2005	4114	3904	94,9	-	-	210	5,1
2006	3959	3717	93,9	-	2	240	6,1
2007	3217	2920	90,8	1	4	292	9,1
2008	3665	3299	90,0	-	1	365	9,9
2009	3197	2763	86,4	-	-	434	13,6
2010	2712	2283	84,2	-	1	429	15,8

Tablica-*Table* **2.**
Netuberkulozne mikobakterije (NTM) izolirane u Hrvatskoj u 2010. godini
Nontuberculous mycobacteria (NTM) isolated in Croatia in 2010

	Vrsta	Broj	%
UVJETNO PATOGENE MIKOBAKTERIJE			
sporog rasta	*M. avium*	12	2,8
	M. intracellulare	22	5,2
	M. kansasii	5	1,2
	M. xenopi	54	12,6
	M. lentiflavum	8	1,9
brzog rasta	*M. fortuitum*	48	11,2
	M. chelonae	28	6,5
	M. peregrinum	12	2,8
	M. abscessus	7	1,6
	M. mucogenicum	2	0,5
	M. celatum	2	0,5
	M. insubricum	1	0,2
SAPROFITNE MIKOBAKTERIJE			
sporog rasta	*M. gordonae*	160	37,3
	M. terrae	27	6,3
	M. nonchromogenicum	13	3,0
	M. triviale	7	1,6
brzog rasta	*M. flavescens*	2	0,5
	M. vaccae	9	2,0
	M. thermoresistibile	1	0,2
	M. phlei	1	0,2
	M. parafortuitum	3	0,7
	Mycobacterium sp.	5	1,2
Ukupno		**429**	**100**

Tablica-*Table* **3.**
Osjetljivost sojeva *M. tuberculosis* na antituberkulotike u Hrvatskoj, 2010. g.
Drug Susceptibility Testing of M. tuberculosis strains in Croatia, 2010

Ustanova *Institution*	M. tuberculosis *strains*	Osjetljivi Sensitive	*Rezistentni* Resistant
ZJZ Čakovec	32	32	-
SB Klenovnik	652	570	82
OB Nova Gradiška	55	55	-
ZJZ Osijek	111	111	-
ZJZ Pula	78	78	-
ZJZ Rijeka	81	76	5
ZJZ Sl.Brod	78	78	-
KB Split	125	121	4
ZJZ Split	37	37	-
ZJZ Šibenik	84	84	-
ZJZ Virovitica	41	41	-
ZJZ Zadar	106	106	-
KB Jordanovac	334	319	15
HZJZ	469	400	69
Ukupno	**2283**	**2108**	**175**

Tablica-*Table* **4.**
Rezistentni sojevi M. tuberculosis *u Hrvatskoj, 2010. godina*
Drug resistant M. tuberculosis strains isolated in Croatia in 2010

1 ATL	**Broj sojeva (No.)**
S (streptomicin)	40 (22,9%)
H (izoniazid)	50 (28,6%)
R (rifampicin)	1 (0,6%)
Z (pirazinamid)	-
	91 (52,0**%)**
2 ATL	
S,E	5 (2,8%)
H,R	4 (2,3%)
	9 (5,1**%)**
3 ATL	
H,R,S	2
H,R,E	-
H,R,Z	-
S,R,Z	-
S,H,Z	-
	2 (1,1**%)**
4 i 5 ATL	
S,H,R,Z	13 (7,4%)
S,H,R,E,Z	60 (34,3%)
	73 (41,7%)
Ukupno - *Total*	**175 (**100,0**%)**

Legenda - *Key*: ATL – antituberkulozni lijekovi
antituberculotic drugs

Tablica-*Table* **5.**
Mutacije odgovorne za rezistenciju na rifampicin i izoniazid u 2010. godini
Mutations responsible for rifampicin and isoniazid resistance in 2010

	No of strains	***kat*G (%)**	***inh*A(%)**	**DT**	***rpo*B**
MDR	10	4 (40.0 %)	1 (10.0%)	5 (50.0%)	10 (100%)
Monoresistant	12	5 (41.7%)	6 (50.0%)	1 (8.3%)	-
Total	22	9 (40.9%)	7 (31.8%)	6 (27.3%)	

POGLAVLJE/CHAPTER 3.

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

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Sudjelovanje u European Antibiotic Surveillance System (EARSS) projektu

Praćenje rezistencije bakterija na antibiotike u Hrvatskoj, utemeljeno 1996.g. osnutkom Odbora za praćenje rezistencije na antibiotike pri Akademiji medicinskih znanosti Hrvatske zasniva se na praćenju podataka iz rutine za velik broj klinički značajnih bakterijskih vrsta. Takav oblik praćenja je sveobuhvatan i s obzirom da ne uključuje informacije vezane uz pacijente predstavlja zadatak prihvatljivog obima za laboratorije koji sudjeluju u praćenju.

Kad je u Europi 1999.g. pokrenuta inicijativa za paneuropsko praćenje rezistencije u okviru EARSS projekta, Hrvatska se s mrežom Odbora za praćenje rezistencije u RH spremno uključila 2001.g. u ovaj projekt i dosljedno pružala potrebne podatke sve do okončanja ovog projekta 2010.g. Predstavnici Hrvatske u EARSS projektu su bili prof. Smilja Kalenić i prof. Arjana Tambić Andrašević. U okviru EARSS projekta prikupljali su se podaci samo za invazivne izolate (iz krvi i likvora) ograničenog broja bakterijskih vrsta: isprva za *S.aureus, E.faecalis, E.faecium, S.pneumoniae* i *E.coli*, a potom od 2005.g. i za *K.pneumoniae* i *P.aeruginosa*. Prednost praćenja rezistencije u samo invazivnih izolata je u tome što su to zasigurno klinički značajni izolati, dok izolacija bakterija iz ostalih uzoraka (urina, briseva rana i sl.) može predstavljati i kolonizaciju fiziološkom mikrobiotom. Osim toga izolati iz hemokultura i likvora nisu masovni, komunikacija s odjelnim liječnikom i prikupljanje osnovnih podataka o pacijentu je dio rutinskog postupanja kod pozitivnih hemokultura i likvora pa prikupljanje dodatnih informacija o pacijentu za potrebe praćenja rezistencije ne predstavlja dodatni napor za laboratorije koji u praćenju sudjeluju. Nedostatak ograničenja praćenja na izolate iz hemokultura i likvora je da nije sveobuhvatno, što naročito dolazi do izražaja kod praćenja novih mehanizama rezistencije. Takvi izolati mogu se prvo zapaziti u drugim, masovnijim uzorcima kao što su urini ili brisevi rana. Osim toga laboratoriji orjentirani izvanbolničkoj populaciji nisu našli svoje mjesto u EARSS mreži s obzirom da se uzorci krvi i likvora rijetko uzimaju u okviru izvanbolničke skrbi. Kombinacija kontinuiranog masovnog praćenja rezistencije u svim kliničkim uzorcima i praćenja fokusiranog na invazivne izolate godinama je predstavljala optimalan način praćenja rezistencije u Hrvatskoj.

Kada je 2010.g. EARSS prešao u EARSS-Net koji je dio The European Surveillance System (Tessy) mreže Europskog centra za kontrolu bolesti (engl. ”European Center for Disease Control”, ECDC) Hrvatska je nastavila suradnju s ECDC Tessy programom, ali ova suradnja trenutno ne uključuje publiciranje hrvatskih podataka u sklopu Tessy rezultata. S obzirom na visoku vrijednost podataka dobivenih praćenjem rezistencije u invazivnih izolata i već dobro postavljenu infrastrukturu, prikupljanje ovih podataka se nastavlja i objavljuje u ovoj publikaciji.

Rezultati praćenja rezistencije u invazivnih izolata

Broj laboratorija koji su slali podatke o invazivnim izolatima je prikazan u Tablici 1.

Invazivne izolate *S.pneumoniae, E.coli* i *K.pneumoniae* prikuplja Referentni centar za praćenje rezistencije, a izolate *S.aureus, E.faecalis, E.faecium* i *P.aeruginosa* prikuplja Referentni Centar za bolničke infekcije. Tijekom 2010.g. prikupljeno je 103 izolata *S.pneumoniae,* 897 izolata *E.coli*, 286 izolata *K.pneumoniae* 363 izolata *S.aureus,* 126 izolata *E.faecalis,* 50 izolata *E.faecium* i 217 izolata *P.aeruginosa* (Tablica 1). Podaci su prikupljani na formularima i obrađeni u Referentnom centru za praćenje rezistencije na antibiotike.

Za većinu uzročnika stope rezistencije se nisu bitno promijenile (Tablica 2), no udio MRSA izolata (26,5%) je po prvi puta od početka praćenja pao ispod 30%. To odgovara uočenom padu stope MRSA u sklopu praćenja rezistencije uzročnika iz svih uzoraka (16% u 2010.g.).

Demografski podaci za pacijente inficirane rezistentnim uzročnicima prikazani su u tablici 3.

Zastupljenost rezistentnih izolata u pojedinim centrima prikazane su na slikama 1- 6.

Participation in the European Antibiotic Surveillance System (EARSS) project

The Croatian National Surveillance of Antimicrobial Resistance, established in 1996 with the foundation of the Croatian Committee for Antibiotic Resistance Surveillance of the Public Health Collegium of the Croatian Academy of Medical Sciences (CAMS), is based on monitoring data of all clinically important isolates collected from regional laboratories. This type of surveillance is comprehensive and considering the fact that it does not include patient information represents acceptable volume of employment for laboratories taking part in national surveillance system.

After EARSS issued the importance of Pan-European surveillance of antimicrobial resistance in 1999, Croatia with CAMS readily joined the EARSS project in 2001, participating and collaborating by submitting its reports from the national data collection until 2010, when the project ended. The Croatian representatives in EARSS project have been Prof. Smilja Kalenić and Prof. Arjana Tambić Andrašević. Within the EARSS project, only invasive isolates (from blood and cerebrospinal fluid) limited to specific strains were collected: at first for *S.aureus, E.faecalis, E.faecium, S.pneumoniae* and *E.coli*, and then from 2005 for *K.pneumoniae* and *P.aeruginosa* strains as well.

The advantage of collecting only invasive isolates data is the fact that invasive isolates are definitely of clinical importance, whereas the clinical importance of isolates taken from other specimens (urine, wound swabs, etc.) can be doubtful and they could represent the colonisation with normal microbiota. Additionally, the isolates taken from blood cultures and cerebrospinal fluid are sporadic so possible dilemmas concerning patient data can be resolved in everyday communication with the attending physician without any additional effort. The disadvantage of limiting the survey only to invasive isolates is that the coverage of strains is insufficient which can consequently be an obstacle in the surveillance of strains with new resistance mechanisms. Such strains can easily be observed only in mass sampling, which can not be performed by taking invasive specimens. Another disadvantage of collecting only invasive isolates is that we lack data from a number of laboratories orientated to outpatient population considering the fact that taking blood cultures and cerebrospinal fluid is rarely done in community care. A combination of continuous mass surveillance of antimicrobial resistance in all clinical specimens and focusing only on invasive ones represented the optimal approach to surveillance of antimicrobial resistance throughout the years in Croatia.

When EARSS was transformed in 2010 into EARS-Net which is a subunit of the European Surveillance System (Tessy), the European Center for Disease Control (ECDC) surveillance network, Croatia continued collaboration with ECDC Tessy program, but due to the political status of Croatia this collaboration does not include reporting of Croatian data at the moment. However, the Committee and the Reference Centre are continuing with data collection in EARSS and ESAC format and these data will be continuously reported in these yearly publications.

Results of the antibiotic resistance surveillance in invasive isolates

Number of laboratories reporting data on invasive isoltes for 2010 is shown in Table 1.

The Reference Centre for Antimicrobial Resistance Surveillance collects forms and strains of *S.pneumoniae*, *E.coli and K.pneumoniae,* while the Reference Centre for Hospital Infections collects forms and strains of *S.aureus, E.faecalis, E.faecium* and *P.aeruginosa.* During 2010 we have collected 103 isolates of *S.pneumoniae,* 897 isolates of *E.coli*, 286 isolates of *K.pneumoniae*, 363 isolates of *S.aureus,* 126 isolates of *E.faecalis,* 50 isolates of *E.faecium* and 217 isolates of *P.aeruginosa* (Table 1). All data was collected on forms and analyzed at the Reference Centre for Antimicrobial Resistance Surveillance.

The percentage of antibiotic non-susceptible isolates has not significantly changed (Table 2) for most of the isolates, but the proportion of MRSA isolates (26,5%) has reached the level beneath 30% for the first time since surveillance started. It correlates with the observed trend of MRSA isolates decrease in all specimens (16% in 2010).

Demographic data of patients infected with resistant strains is shown in Table 3.

Proportion of resistant strains by laboratory centres is shown in Figures 1- 6.

Tablica-*Table **1.***

Broj laboratorija i izolata prijavljenih u razdoblju od 2001.-2010.
Number of laboratories and number of isolates reported for the period 2001-2010

Godina	*S. pneumoniae*		*S. aureus*		*E. coli*		*Enterococcus* spp.		*K. pneumoniae*		*P. aeuroginosa*	
	Lab	Izolati / Isolates	Lab	Izolati/ Isolates	Lab	Izolati/ Isolates	Lab	Izolati/ Isolates	Lab	Izolati/ Isolates	Lab	Izolati/ Isolates
2001	10	20	14	149	13	182	7	33	0	0	0	0
2002	14	90	14	279	15	490	13	96	0	0	0	0
2003	12	88	14	360	16	570	11	101	0	0	0	0
2004	12	103	13	392	14	535	11	115	0	0	0	0
2005	15	129	17	354	16	638	11	120	14	112	10	72
2006	14	116	17	391	17	780	16	178	15	205	15	170
2007	15	136	15	375	17	852	13	174	17	279	16	189
2008	13	100	18	474	17	915	16	232	17	333	14	221
2009	14	100	14	463	16	911	20	223	16	318	15	212
2010	11	103	15	363	16	897	12	176	16	286	15	217

Tablica-*Table 2.*

Udio izolata smanjene osjetljivosti na antibiotike izražen u postocima
Proportion of antibiotic non-susceptible isolates in percent

PATOGEN / PATHOGEN	ANTIBIOTICI/ Antimicrobial classes	2001 %	2002 %	2003 %	2004 %	2005 %	2006 %	2007 %	2008 %	2010 %
S. pneumoniae	Penicillin R	1	1	1	3	1	1	1	4	7
	Penicillin I+R	15	19	20	17	17	18	18	17	21
	Macrolides I+R	15	23	18	19	17	16	8	14	29
S. aureus	Oxacillin/Met R	32	37	37	38	37	36	38	35	27
E. coli	Aminopenicillins R	51	47	46	45	46	51	51	53	55
	Aminoglycosides R	6	7	7	6	5	6	6	6	6
	Fluoroquinolones R	5	5	7	8	9	15	13	15	17
	3. gen Cef R	2	3	4	3	1	1	3	4	8
E. faecalis	Aminopenicillins I+R	13	5	4	5	6	3	2	5	5
	HL Aminoglycosides R	50	40	28	35	31	37	37	46	37
	Glycopeptides R	3	<1	<1	<1	<1	<1	<1	<1	<1
E. faecium	Aminopenicillins I+R	100	56	47	69	82	69	78	79	82
	HL Aminoglycosides R	100	67	41	63	62	59	59	65	60
	Glycopeptides R	<1	22	6	3	6	3	2	6	12
K. pneumoniae	Aminoglycosides R					38	33	38	51	49
	Fluoroquinolones R					18	23	34	44	48
	3. gen Cef R					46	34	40	54	56
P. aeuroginosa	Piperacillin R					25	38	30	34	23
	Piperacllin/Tazobactam R									16
	Ceftazidime R					6	11	14	13	12
	Carbapenems R					24	25	26	30	26
	Aminoglycosides R					35	47	40	39	26
	Fluoroquinolones R					34	35	30	33	27

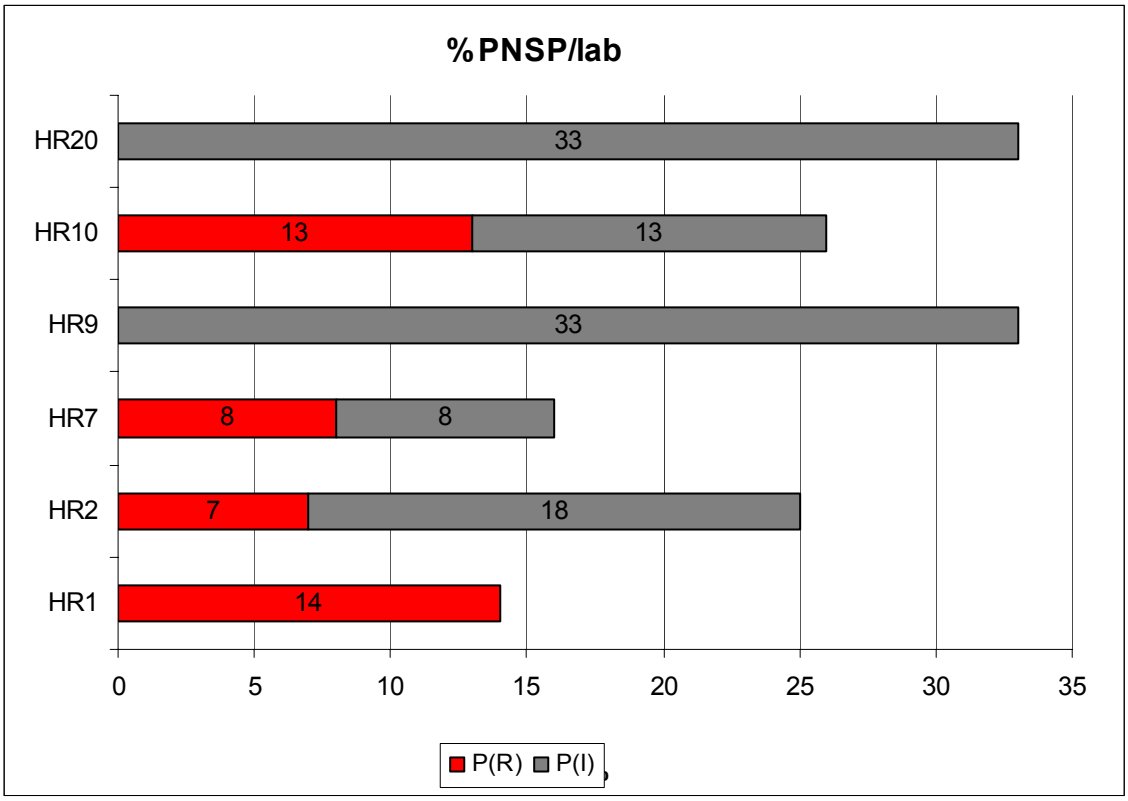
Tablica-*Table 3.*

Prikaz invazivnih izolata u 2010. prema demografskim podacima pacijenata
Selected details on invasive isolates from the reporting period 2010

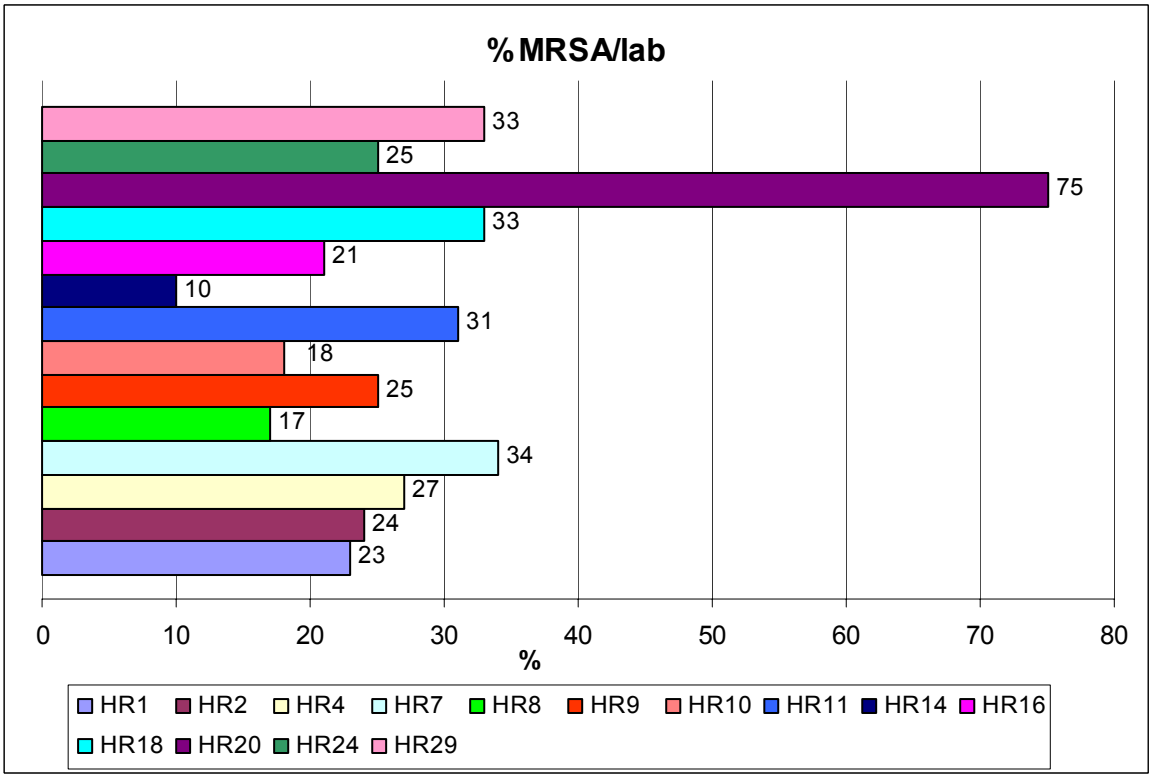
	S. pneumoniae		*S. aureus*		*E. coli*			*Enterococcus* spp.		*K. pneumoniae*		*P. aeuroginosa*	
	n=103		n=363		n=897			n=176		n=286		n=217	
	% tot	% PNPS	% tot	% MRSA	% tot	% FREC	% CREC	% tot	%VRE	% tot	%CRKP	% tot	%CRPA
UZORAK SAMPLE													
Krv / Blood	85	22	99	26	99	16	8	99	3	100	56	99	26
Likvor / CSF	15	19	<1	100	<1	50	0	1	0	0	0	1	0
SPOL													
M	56	22	68	28	43	21	9	58	3	61	60	67	25
Ž / F	43	21	32	21	56	13	6	40	4	37	50	25	27
Nepoznato / Unknown	1	0	0	0	<1	0	0	2	0	2	0	8	0
DOB AGE													
0-4	34	34	6	5	5	8	6	10	0	10	70	5	36
5-19	9	22	2	25	1	0	9	1	0	3	25	4	44
20-64	33	25	45	29	35	16	6	36	4	42	60	41	32
>65	24	8	46	25	59	19	9	45	4	40	47	46	16
Nepoznato / Unknown	0	0	1	0	0	0	0	8	0	5	0	4	0
ODJEL DEPARTMENT													
Intenzivna / ICU	16	25	12	58	7	30	19	15	0	16	76	29	23
Interna / Medical	84	21	71	15	81	15	6	70	5	63	45	53	29
Kirurgija / Surgery	0	0	13	53	6	30	14	13	0	19	81	16	21
Ostalo / Other	0	0	3	50	6	100	50	2	0	<1	14	1	0
Nepoznato / Unknown	0	0	0	0	0	0	0	0	0	2	0	1	0

PNSP=Penicillin Non-Susceptible *S. pneumoniae* MRSA=Methicillin Resistant *S.aureus* FREC=Fluoroquinolone Resistant *E.coli*
VRE=Vancomycin Resistant Enterococcus CRKP=3rd gen. Cepfalosporine Resistant *K. pneumoniae* CRPA=Carbapenem Resistant *P. aeruginosa*

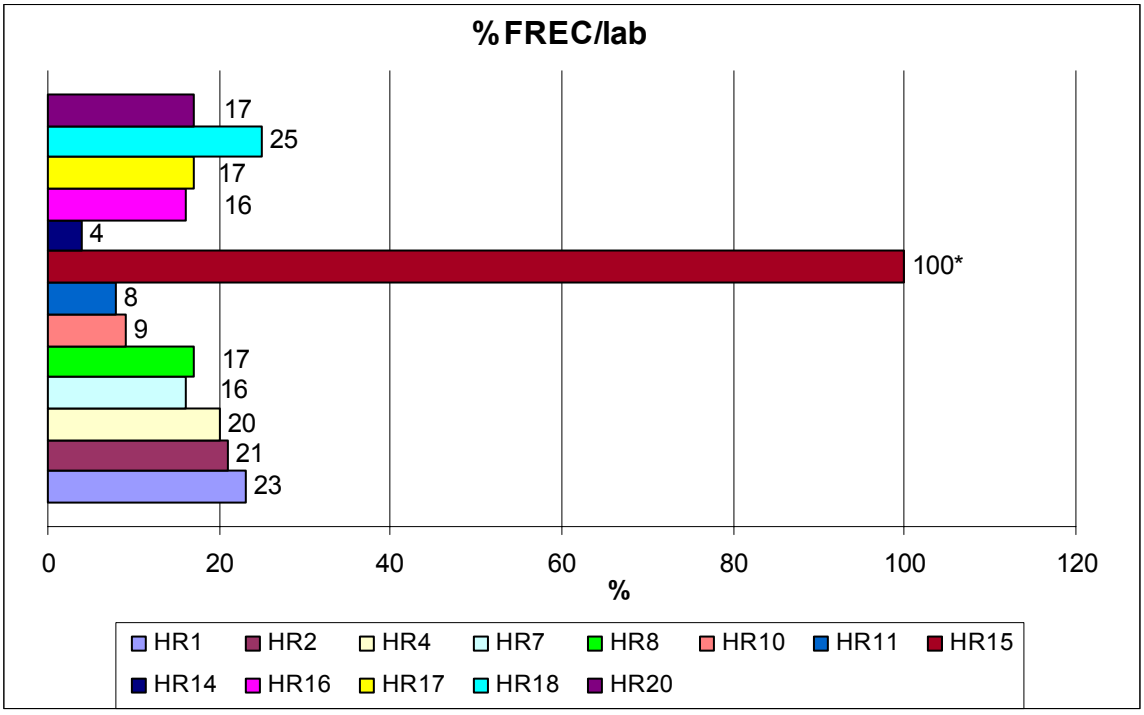
Slika-*Figure 1.*
Udio (%) izolata *S. pneumoniae* smanjene osjetljivosti na penicilin (PNSP) po laboratorijima
Proportion (%) of penicillin non-susceptible S. pneumoniae (PNSP) by laboratory



Slika-*Figure 2.*
Udio (%) MRSA izolata po laboratorijima
Proportion (%) of MRSA isolates by laboratory

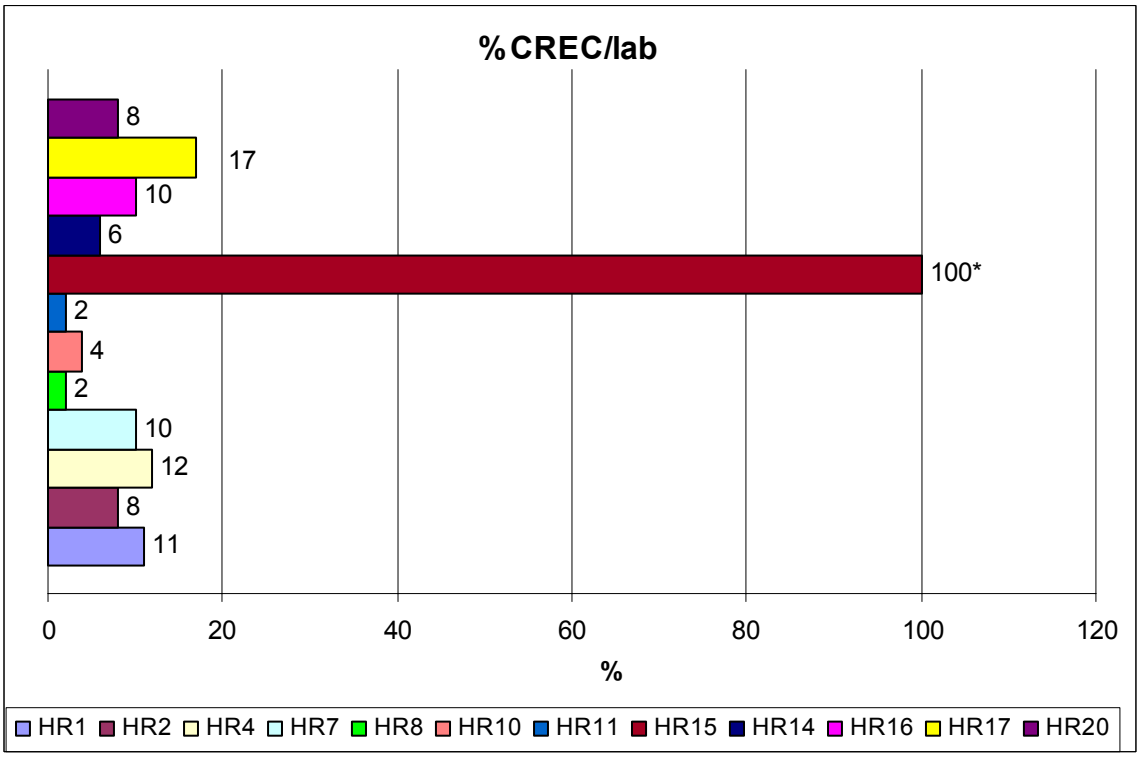


Slika-*Figure 3.*
Udio (%) fluorokinolon rezistentnih izolata *E. coli* (FREC) po laboratorijima
Proportion (%) of fluoroquinolone resistant E.coli isolates (FREC) by laboratory



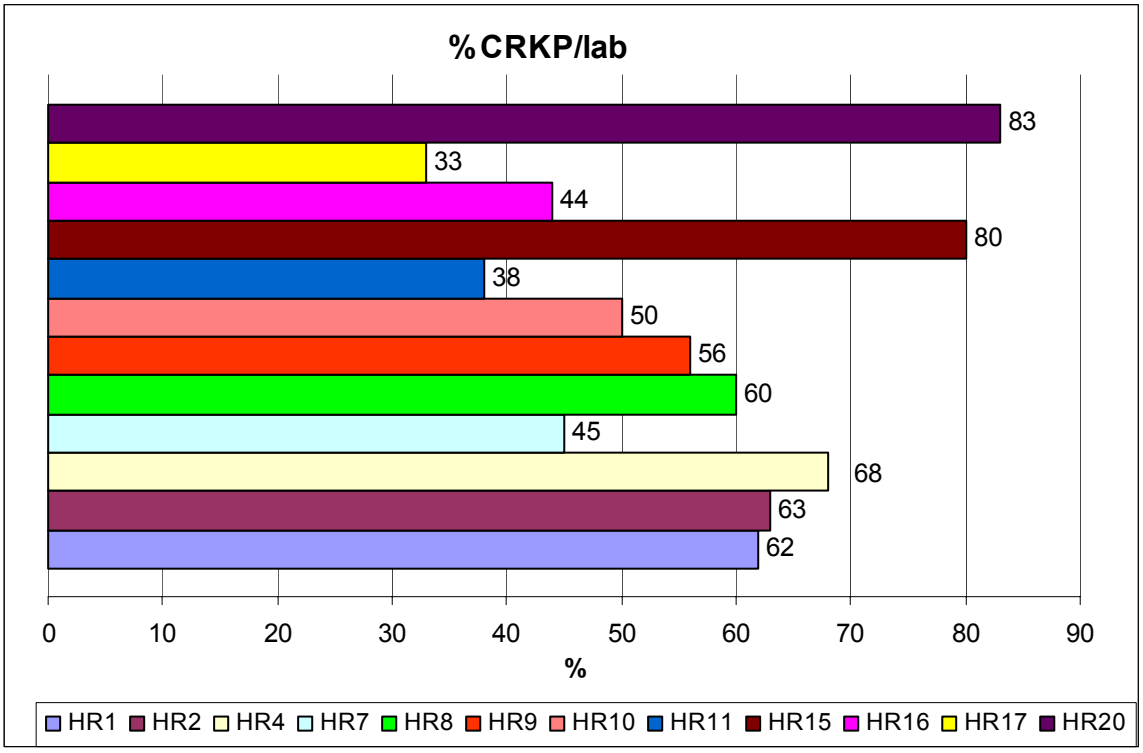
*samo jedan izolat / *only one isolate reported*

Slika-*Figure 4.*
Udio (%) ceftazidim rezistentnih izolata *E. coli* (CREC) po laboratorijima
Proportion (%) of ceftazidime resistant E. coli isolates (CREC) by laboratory

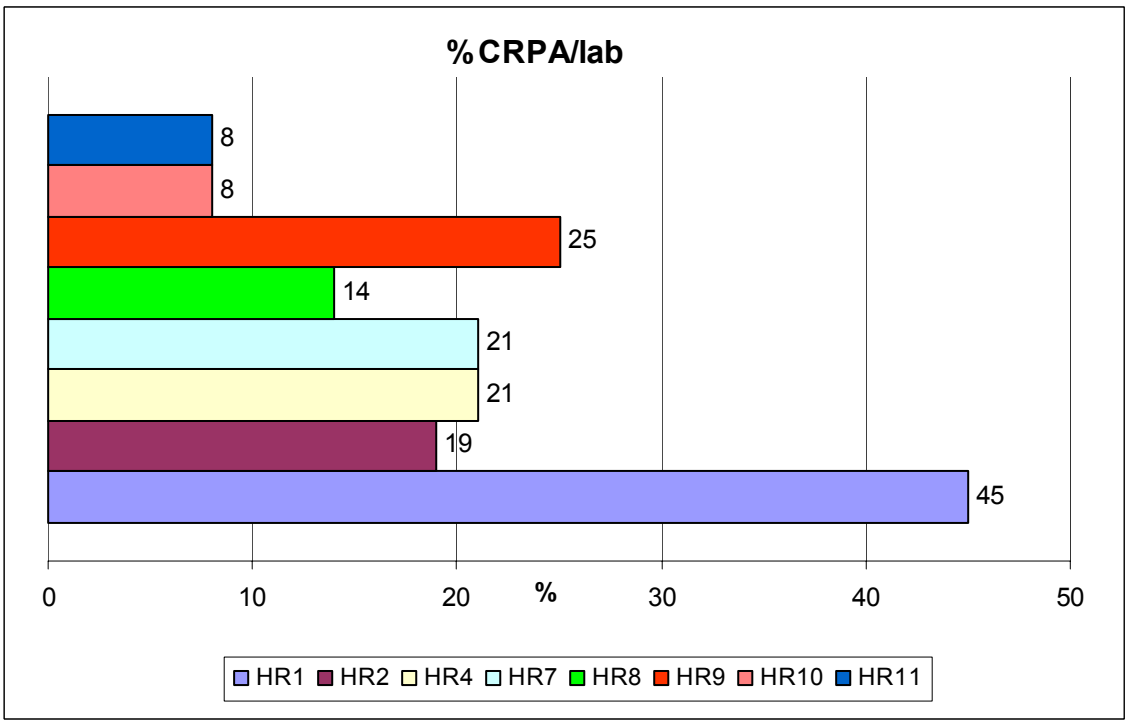


*samo jedan izolat / *only one isolate reported*

Slika-*Figure 5.*
Udio (%) ceftazidim rezistentnih izolata *K. pneumoniae* (CRKP) po laboratorijima
Proportion (%) of ceftazidime resistant K. pneumoniae (CRKP) by laboratory



Slika-*Figure 6.*
Udio (%) karbapenem rezistentnih izolata *P. aeruginosa* (CRPA) po laboratorijima
Proportion (%) of carbapenem resistant P. aeruginosa (CRPA) by laboratory



POGLAVLJE/CHAPTER 4.

POTROŠNJA ANTIBIOTIKA U HRVATSKOJ
ANTIBIOTIC CONSUMPTION IN CROATIA

European Surveillance of Antibiotic Consumption (ESAC)

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Potrošnja antibiotika u Hrvatskoj
Antibiotic consumption in Croatia

Podaci o potrošnji antibiotika u Hrvatskoj prikupljeni u okviru ESAC programa

Odbor za praćenje rezistencije bakterija na antibiotike Akademije medicinskih znanosti Hrvatske uključio se 2001.g. u program the European Surveillance of Antibiotic Consumption (ESAC) 2001.g. te je Hrvatska tada počela pratiti potrošnju antibiotika izraženu kao broj definiranih dnevnih doza na tisuću stanovnika dnevno (DDD/TID). Ovakvo izražavanje potrošnje i mtodologija praćenja razrađena kroz ESAC program omogućilo je Hrvatskoj uspoređivanje s drugim europskim državama koje sudjeluju u ESAC-u. Rezultati o potrošnji antibiotika koji se prikupljaju u okviru ESAC programa zasnivaju se na podacima veleprodaje antibiotika u Hrvatskoj. Odvojeno se prikazuju bolnička i izvanbolnička potrošnja (tablice 1 i 2). Podaci se prikupljaju na petoj, a objavljuju na četvrtoj razini WHO ATC/DDD klasifikacije. Kao i prethodne godine izvanbolnička potrošnja čini 94% ukupne potrošnje antibiotika. Kako je uhodavanje novog informatičkog sustava Hrvatskog zavoda za zdravstveno osiguranje (HZZO) još uvijek u tijeku detaljnija analiza izvanbolničke potrošnje prema vrsti pacijenata i pojedinim dijagnozama još nije moguća.

Izvanbolnička potrošnja pokazuje trend smanjenja potrošnje, naročito od 2008.g. U 2010. godini uočeno je smanjenje potrošnje amoksicilina (JO1CA) i cefalosporina svih generacija, pa je time zaustavljen nepoželjan trend porasta potrošnje cefalosporina III. generacije. Nažalost, penicilini rezistentni na beta-laktamaze (semisintetski penicilini) još uvijek nisu dostupni na hrvatskom tržištu, osim preko interventnog uvoza, te se blaže izvanbolničke stafilokokne infekcije vjerojatno liječe šire spektralnim antibioticima. Jedina klasa antibiotika u kojoj je registrirana povećana potrošnja su penicilini u kombinaciji s inhibitorima.

Metodologija izražavanja potošnje u DDD/TID, koja je u skladu s ESAC programom je pogodna za uočavanje promjena potrošnje u izvanbolničkoj sredini, no nedovoljno precizna za uočavanje pomaka u bolničkoj potrošnji. Stoga je Odbor na inicijativu APUA Croatia odjeljka započeo 2004.g. skupljanje podataka o potrošnji antibiotika u individualnim bolnicama pri čemu se 100 bolničkih dana (BOD) koristi kao denominator. Osnutkom Interdisciplinarne sekcije za kontrolu rezistencije na antibiotike (ISKRA) dostavljanje podataka o potrošnji antibiotika preko bolničkih ljekarni je postalo obveza svih bolnica što je omogućilo preciznije praćenje bolničke potrošnje u Hrvatskoj. Kroz četiri godine usporedno su se prikupljali podaci iz veledrogerija i preko bolničkih ljekarni. Praćenje bolničke potrošnje preko podataka dobivenih iz bolničkih ljekarni pruža vjerodostojnije podatke te omogućava detaljniju analizu podataka i opširnije je prikazana u daljnjem tekstu.

U okviru ESAC 3 projekta od 2007. g. pokrenut je niz podprojekata koji se bave detaljnijom analizom potrošnje antibiotika u bolnicama, domovima za umirovljenike, izvanbolničkoj sredini te analizom socioekonomskih čimbenika koji utječu na potrošnju antibiotika. Hrvatska se uključila u podprojekte o potrošnji antibiotika u bolnicama, o potrošnji u domovima za umirovljenike te u podprojekt o socioekonomskim čimbenicima. Rezultati ovih projekata su objavljeni ili će biti objavljeni kroz niz publikacija. Detaljnije informacije o ESAC podprojektima su dostupne na www.esac.ua.ac.be. 2010. godina je posljednja godina ESAC projekta. Od 2011.g. ESAC prelazi u ESAC-Net koji je dio The European Surveillance System (Tessy), mreže Europskog centra za kontrolu bolesti (engl. "European Center for Disease Control", ECDC).

Antibiotic consumption data for Croatia collected through the ESAC programme

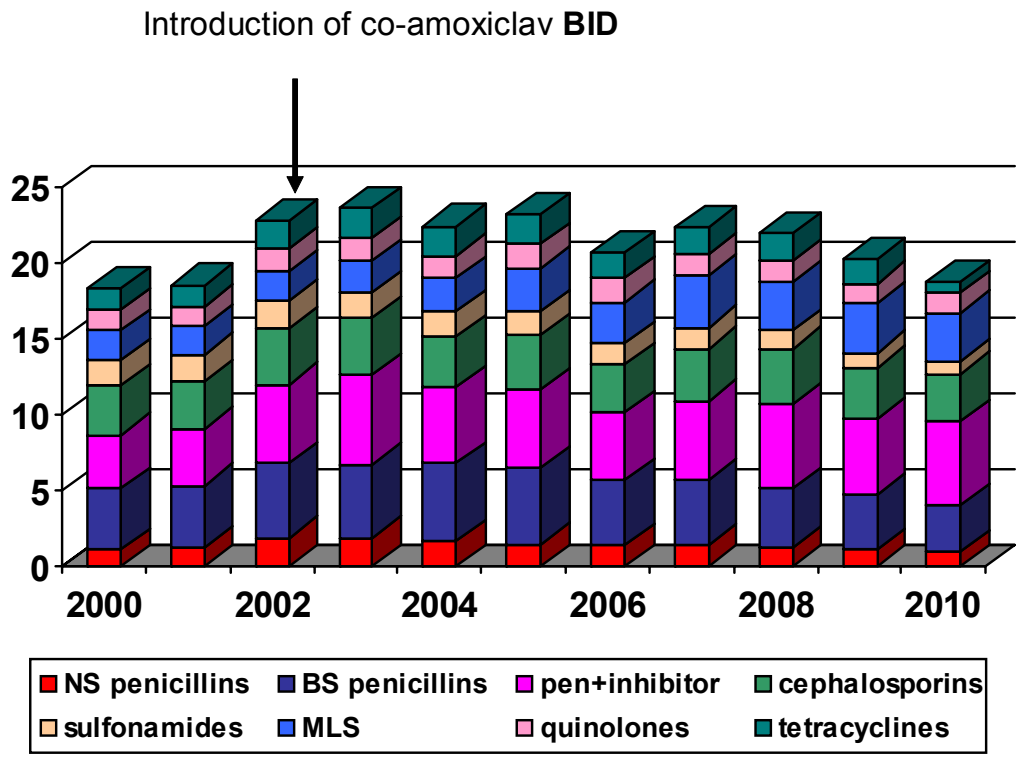
The Croatian Committee for Antibiotic Resistance Surveillance of the Croatian Academy of Medical Sciences has joined the European Surveillance of Antibiotic Consumption (ESAC) in 2001 and this when collection of antibiotic consumption data expressed as defined daily doses per thousand inhabitants daily (DDD/TID) began. Collecting data by using ESAC surveillance methodology and measurement units gave Croatia an opportunity to compare national consumption with the one in other European countries that take part in ESAC. Antibiotic consumption data collected through ESAC programme are based on the Croatian wholesales data. Hospital and ambulatory antibiotic consumption data are presented separately (table 1 and 2). Antibiotic consumption data are collected at the 5th level and presented at the 4th level of the WHO ATC/DDD classification. Same as in the previous year ambulatory care consumption presents 94% of total antibiotic consumption. As the implementation of the new informatization system at the Croatian Health Insurance Institute (CHII) is still in progress the more detailed analysis of antibiotic consumption in ambulatory care related to patient population and diagnosis is still not feasible.

There is a decreasing trend in ambulatory care consumption, especially after the year 2008. In 2010 a decrease in amoxicillin (JO1CA) and all classes of cephalosporins was recorded and this way an undesirable trend of increasing 3rd generation cephalosporin consumption was stopped. Unfortunately penicillins resistant to beta-lactamases (semisyntetic penicillins) are still not available at the Croatian market and therefore mild community acquired staphylococcal infections are probably treated with broad spectrum antibiotics. Penicillins in combination with beta-lactamase inhibitors are the only class of antibiotics that is increasing in consumption.

Antibiotic consumption data expressed in DDD/TID, which is in line with ESAC methodology are suitable for recording changes in ambulatory care consumption but are not sufficiently sensitive to record shifts in hospital consumption. Therefore, in 2004 the Committee accepted the initiative of the APUA Croatia Chapter to start collecting antibiotic consumption data from individual hospitals using 100 bed days (BD) as a denominator. When Interdisciplinary Section for Antibiotic Resistance Control (ISKRA) was founded, providing antibiotic consumption data from hospital pharmacy records became an obligation for all hospitals in Croatia and this greatly improved antibiotic consumption surveillance. Over the four years wholesales data were collected in parallel with hospital pharmacy data. Hospital pharmacy data provide more reliable results and enable more detailed data analysis which is presented further in the text.

Several of ESAC 3 subprojects were initiated in 2007. These subprojects are dealing in more details with antibiotic consumption in hospitals, nursing homes, ambulatory care and with the influence of socioeconomic factors on antibiotic consumption. Croatia got involved in hospital, nursing home and socioeconomic subprojects. Results of these subprojects are published or will be published in several publications. Further information on ESAC subprojects is available at www.esac.ua.ac.be. The year 2010 is the last year of the ESAC project. In 2011 ESAC will be transferred to ESAC-Net which is a part of the European Surveillance System (Tessy), the European Center for Disease Control (ECDC) surveillance network.

Slika-*Figure 1.*
Izvanbolnička potrošnja antibiotika 2000 – 2010.
Ambulatory antibiotic consumption 2000 – 2010



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

ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2002	2003	2004	2005	2006	2007	2008	2009	2010
JO1AA	Tetraciklini Tetracylines	1.82	1.90	1.91	2.01	1.74	1,81	1,73	1,57	1,46
JO1CA	Penicilini širokog spektra Broad spectrum penicillins	4.95	4.82	5.10	5.07	4.30	4,31	3,86	3,60	3,09
JO1CE	Penicilini uskog spektra Narrow spectrum penicillins	1.78	1.85	1.71	1.42	1.41	1,34	1,24	1,07	0,91
JO1CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0.06	0.06	0.06	0.05	0.05	0,05	0,04	0,00	0,00
JO1CR	Kombinacije s beta-laktamaza inhibitorima	5.21	5.9	5.04	5.21	4.43	5,26	5,61	5,06	5,55
JO1DA	Cefalosporini I gen. I gen. cephalosporins	1.99	1.94	1.87	1.85	1.66	1,88	1,56	1,21	1,05
	Cefalosporini II gen. II gen. cephalosporins	1.34	1.37	1.19	1.29	1.15	1,02	1,55	1,59	1,50
	Cefalosporini III gen. III gen. cephalosporins	0.35	0.44	0.39	0.42	0.42	0,56	0,55	0,61	0,59
JO1EE	Sulfonamides + trimethoprim	1.85	1.72	1.64	1.57	1.35	1,4	1,17	0,98	0,87
JO1F	Macrolides, lincosamides	1.92	2.07	2.27	2.82	2.73	3,40	3,24	3,24	3,19
JO1G	Aminoglycosides	0.04	0.01	0.01	0.01	0.01	0,01	0,01	0,01	0,01
JO1MA	Fluoroquinolones	1.52	1.53	1.47	1.57	1.56	1,41	1,41	1,33	1,31
JO1XE	Nitrofurantoin						0,47	0,63	0,68	0,69
UKUPNO TOTAL		**22.86**	**23.61**	**22.66**	**23.29**	**20,81**	**22,92**	**22,60**	**20,95**	**20,22**

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

ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2002	2003	2004	2005	2006	2007	2008	2009	2010
JO1AA	Tetracylines	0.12	0.15	0.08	0.09	0.07	0,06	0,06	0,06	0,05
JO1CA	Penicilini širokog spektra Broad spectrum penicillins	0.30	0.33	0.15	0.15	0.12	0,09	0,08	0,05	0,04
JO1CE	Penicilini uskog spektra Narrow spectrum penicillins	0.24	0.35	0.20	0.14	0.12	0,10	0,06	0,01	0,01
JO1CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0.04	0.04	0.03	0.03	0.03	0,04	0,02	0,00	0,00
JO1CR	Kombinacije s beta-laktamaza inhibitorima	0.64	0.79	0.40	0.36	0.27	0,22	0,25	0,23	0,22
JO1DA	Cefalosporini I gen. cephalosporins	0.20	0.17	0.09	0.11	0.10	0,11	0,09	0,10	0,09
	Cefalosporini II gen. cephalosporins	0.28	0.19	0.27	0.25	0.22	0,22	0,19	0,15	0,21
	Cefalosporini III + IV gen. cephalosporins	0.09	0.12	0.09	0.12	0.11	0,13	0,14	0,16	0,16
JO1DH	Carbapenems	0.02	0.02	0.02	0.02	0.02	0,04	0,04	0,04	0,04
JO1EE	Sulfonamides + trimethoprim	0.14	0.20	0.09	0.08	0.07	0,07	0,06	0,06	0,05
JO1F	Macrolides, lincosamides	0.14	0.16	0.10	0.12	0.10	0,11	0,11	0,12	0,11
JO1G	Aminoglycosides	0.15	0.12	0.10	0.11	0.10	0,09	0,10	0,10	0,09
JO1MA	Fluoroquinolones	0.18	0.22	0.15	0.18	0.17	0,19	0,19	0,21	0,21
JO1XA	Glycopeptides	0.02	0.02	0.02	0.02	0.02	0,03	0,03	0,03	0,03
JO1XD	Metronidazole	0.06	0.06	0.01	0.06	0.05	0,06	0,06	0,07	0,07
JO1XE	Nitrofurantoin						0,01	0,01	0,01	0,01
UKUPNO TOTAL		**2.52**	**2.94**	**1.80**	**1.84**	**1.57**	**1,57**	**1,49**	**1,40**	**1,39**

Potrošnja antibiotika u hrvatskim bolnicama u 2010.

Osnutkom Interdisciplinarne sekcije za kontrolu rezistencije na antibiotike (ISKRA) 2006. godine započelo je praćenje bolničke potrošnje antibiotika temeljeno na podacima dobivenim iz bolničkih ljekarni. Do tada se praćenje potrošnje antibiotika zasnivalo na podacima iz veledrogerija. Usporedbom bolničke potrošnje antibiotika koji su dobiveni putem veledrogerija i putem bolničkih ljekarni uočava se razlika u potrošnji. Veća potrošnja bilježi se prema podacima dobivenim iz bolničkih ljekarni. Razlika tijekom godina praćenja postaje sve veća, tako da je u 2010. godini uočeno najveće odstupanje. Prema podacima veleprodaje potrošeno je 1,39 DDD na 1000 stanovnika po danu (TID), dok je prema podacima bolničkih ljekarni potrošnja iznosila 1, 85 TID (tablica 3, slika 3).

Uočena razlika u potrošnji leži u činjenici da se neki antibiotici dostavljaju direktno u bolničke ljekarne, a ne putem veledrogerija. To se naročito odnosi na klasu antibiotika J01C (penicilini) koja je ujedno i najzastupljenija klasa antibiotika u ukupnoj potrošnji (30% ukupne potrošnje), kod koje je razlika ovisno o izvoru podataka iznosila 0,27 TID-a.
Nešto manja odstupanja se uočavaju i kod drugih klasa, makrolid-linkozamid-streptogramin (J01F) te klase ostali (J01X) glikopeptidi, polimiksin, metronidazol, nitrofurantoin.
Ova razlika potvrđuje opravdanost praćenja bolničke potrošnje putem podataka iz bolničkih ljekarni, koji preciznije i točnije oslikavaju potrošnju antibiotika u bolnicama. Iako podaci o potrošnji antibiotika putem veledrogerija ukazuju na trend smanjenja potrošnje antibiotika u zadnje četiri godine, podaci dobiveni iz bolničkih ljekarni ne potvrđuju to isto.
Analizirajući potrošnju antibiotika po klasama prema podacima iz bolničkih ljekarni uočava se kontinuirano visoka potrošnja penicilina (klasa J01C), trend porasta potrošnje cefalosporina (klasa J01D), klase makrolid-linkozamid-streptogramin (J01F), kinolona (J01M) te klase ostali (J01X) koja uključuje glikopeptidi, polimiksin, nitrofurantoin, metronidazol (slika 4).

Podatke o bolničkoj potrošnji antibiotika za 2010. godini dostavile su sve bolničke ustanove, ukupno njih 67.
Uhodanom metodologijom dostavljaju se podaci o potrošnji antibiotika koji pripadaju skupini J01 (antimikrobni lijekovi za sistemsku upotrebu) u ABC kalkulatoru koji je prilagođen za hrvatsko tržište. Sve manji broj bolnica (4 kliničke bolnice, 1 opća bolnica, 1 psihijatrijska, 3 specijalne bolnice) dostavlja podatke o potrošnji izražene u paketićima, ampulama ili bočicama upisanim u formular, što je moguće koristiti kao alternativnu metodu za slanje podataka. I nadalje se potiču sve bolnice da svoje podatke o bolničkoj potrošnji antibiotika dostavljaju u ABC kalkulatoru, kao standardiziranom alatu za jednoobrazno prikupljanje i obradu podataka o potrošnji antibiotika.

Podaci o potrošnji J01 skupine prikupljaju se na 5. razini, a rezultati se prikazuju na na 3. razini u skladu s WHO ATC/DDD klasifikacijom. Usprkos četverogodišnjem iskustvu u prikupljanju podataka o potrošnji antibiotika neka odstupanja od preporuka i dalje su prisutna. Jedan od nedostataka je nepopunjavanje formulara (1 klinička ustanova, 1 specijalna bolnica) s neophodno potrebnim podacima (broj bolničkoopskrbnih dana, broj primitaka), što u konačnici onemogućava završnu obradu podataka. Sljedeći propust je nenavođenje osobe za kontakt u pojedinoj bolnici što otežava rješavanje određenih nejasnoća, dilema i slično. Pet kliničkih ustanova i dvije opće bolnice nisu poslale podatke o potrošnji antibiotika odvojeno i za jedinice intenzivnog liječenja.

Ukupan broj **klinika** povećao se u odnosu na prethodnu godinu, jer je jedna opća bolnica dobila status kliničke ustanove. Analizirajući potrošnju antibiotika u 15 kliničkih ustanova, ona se kreće od 28,6 DDD/100 BOD do 143,7 DDD/100 BOD. Razlika u potrošnji antibiotika odražava veliku raznolikost među kliničkim ustanovama, Jedan od razloga su i različiti profili kliničkih ustanova (tablica 4).
U četiri kliničke bolnice uočava se trend smanjenja potrošnje antibiotika (K01; K02; K13; K14), dok je trend porasta potrošnje uočljiv kod tri bolnice. (K03; K04; K05). Posebno je uočljiv porast potrošnje u kliničkim ustanovama K 04 i K07, kod kojih je potrošnja je porasla za 20 DDD/100 BOD-a u zadnjoj godini praćenja u odnosu na 2007. godinu. Kod ostalih kliničkih ustanova se ne prate pravilnosti u kretanju potrošnje (slika 5).

Iz skupine **općih bolnica**, opća bolnica 6* je premještena u skupinu specijalnih bolnica, dok je bolnica 16** premještena u skupinu kliničkih bolnica. Skupini općih bolnica je u praćenju potrošnje antibiotika pridružena još jedna opća bolnica u Hrvatskoj.
U skupini koja je najhomogenija, a čine ju opće bolnice, potrošnja se kreće od 34,6 do 82 DDD/100 BOD. Najveći broj općih bolnica (9) ima potrošnju između 51 i 60 DDD/100 BOD. Samo 4 opće bolnice bilježe potrošnju manju od 50 DDD/100 BOD, dok 4 bolnice odskaču u potrošnji antibiotika iznad 70 DDD/100 BOD. Pet bolnica bilježi potrošnju između 61 i 70 DDD/100 BOD (tablica 5). Posebno zabrinjava trend koji se uočava kod općih bolnica, a to je porast potrošnje antibiotika u deset općih bolnica (O01; O02; O04; O05; O08; O11; O19; O20; O21:O23 dok je u svega jednoj bolnici (O10) zabilježen trend pada potrošnje antibiotika (slika 6).

Psihijatrijske ustanove kojih je 8 čine skupinu s najmanjom potrošnjom antibiotika. Raspon se kreće od 2,6 do 14,7 (tablica 6).
Usprkos niskoj potrošnji antibiotika u toj skupini bolnica, čak kod četiri se bilježi trend porasta potrošnje (P02; P05; P07; P08), dok svega u dvije bolnice taj trend pada (P03; P06) (slika 7).

Skupina **specijalnih bolnica** je najheterogenija skupina u kojoj se nalaze različite specijalizirane ustanove kroničnog tipa, specijalizirane kirurške bolnice, lječilišta, toplice, što se odražava i u velikom rasponu u potrošnji, koji se kreće od 0 do 61,6 DDD/100 BOD (tablica 7).
Tri bolnice iz skupine specijalnih bolnica pokazuju trend smanjenja potrošnje antibiotika
(S07; S15; S19), dok pet iz te skupine bilježe trend porasta potrošnje (S05; S09; S11; S14; S16) (slika 8).

U praćenju bolničke potrošnje antibiotika putem podataka dobivenih iz bolničkih ljekarni u posljednjoj godini učestvovale su sve bolnice u Hrvatskoj.

Paralelno praćenje bolničke potrošnje antibiotika iz dva izvora (veledrogerije, bolničke ljekarne) pokazalo se korisnim i vrijednim. Utvrđena je razlika u potrošnji ovisno o izvoru podataka, s tim da su podaci iz bolničkih ljekarni cjelovitiji i pouzdaniji, a što je posljedica distribucije nekih antibiotika direktno u bolnice, a ne putem veledrogerija. Utvrđena razlika u podacima utječe na divergenciju trendova u potrošnji antibiotika, pa prema podacima dobivenim putem veledrogerija potrošnja antibiotika u Hrvatskoj pada, međutim rezultati dobiveni iz bolničkih ljekarni ne pokazuju isti trend.
Nastavit će se praćenje bolničke potrošnje antibiotika s podacima dobivenim iz bolničkih ljekarni.

Uz podatke o kretanju rezistencije bakterija u svakoj bolničkoj ustanovi, podaci o potrošnji antibiotika upotpunjuju sliku temeljem koje je moguće nastaviti, odnosno pokrenuti potrebne promjene i intervencije u smjeru racionalne antibiotske terapije.

Antibiotic Consumption in Croatian Hospitals in 2010

Monitoring of hospital consumption of antibiotics based on the data obtained from hospital pharmacies began with the foundation of the Interdisciplinary Section for Antibiotic Resistance Control (ISKRA) in 2006. Until then monitoring consumption of antibiotics was based only on wholesales data. When comparing hospital consumption of antibiotics obtained through wholesaler and the data obtained through hospital pharmacies we can see a clear difference in results. Records obtained from hospital pharmacies showed much higher values of consumption. Over the years this difference is getting greater and greater. In year 2010 the largest deviation in consumption depending on the source data was recorded. According to wholesale data 1.39 DDD per 1000 inhabitants a day was spent (TID), while the data of hospital pharmacy showed the number of 1, 85 DDD per 1000 people a day (table3, figure 3).
The observed difference in consumption lies in the fact that some of the antibiotics were delivered directly into hospital pharmacy and not through the wholesalers. This particularly applies to the class of antibiotics J01C (Penicillin) which is the most common class of antibiotics in total consumption (30% total consumption) and in which the difference depending on the source of data totaled 0.27 TID. Smaller deviations were observed in other classes such as macrolides-lincosamides-streptogramin (J01F) and class other (J01X), such as glycopeptides, polymyxin, metronidazole, nitrofurantoin. This difference confirms the validity and importance of monitoring the hospital consumption by data from hospital pharmacies, which precisely and accurately depicts the consumption of antibiotics in hospitals. Although data on antibiotic consumption by drug wholesalers indicated a trend of reduced consumption of antibiotics in the last four years, the data obtained from hospital pharmacies did not show the same results. When analyzing the use of antibiotics by class according to data from hospital pharmacies throughout four years, a continuing high consumption of penicillins can be seen (J01C class), as well as higher consumption of cephalosporins (J01D class), of class macrolide-lincosamides-streptogramin (J01F) quinolones (J01M) and of the class J01X including glycopeptide, polymyxin, nitrofurantoin, metronidazole (figure 4).
Hospital antibiotic consumption data was submitted by all 67 hospital facilities in 2010. Data regarding the group J01 (antimicrobial drugs for systemic use) in the ABC calculator, tailored for Croatian market, was submitted with the established methodology. Fewer hospitals (4 clinical hospital, 1 general hospital, a psychiatric hospital, and 3 specialized hospitals) provided data on consumption that are expressed in packets, ampoules or bottles and filled out the form which can be used as an alternative method for sending data. All hospitals are continually encouraged to submit their data on hospital antibiotic consumption delivered through ABC calculator, which is a standardized tool for unified collection and processing of data on antibiotic consumption.
Data on consumption of J01 group were collected at the 5th level, and the results are displayed on the 3rd level in accordance with the WHO ATC / DDD classification. Despite four years experience in collecting data on antibiotic consumption some deviations from the recommendations are still present. One of the drawbacks is the lack of filled out the forms (1 clinical facility, 1 special hospital) with the necessary data required (number of bed days of care, hospital admissions), which ultimately prevents processing of the final data. Also, one of the main flaws is that hospitals do not identify a person in charge of collecting data which makes it difficult to deal with and resolve certain ambiguities, dillemas, etc. Five clinical facilities and two general hospitals did not send separate data on antibiotic consumption and for the intensive care units.
The total number of **clinics** has increased over the previous year, as one general hospital received a status of clinical hospital. Analyzing the use of antibiotics in 15 clinical

institutions, one can see that it ranges from 28.6 DDD/100BD to 143,7 DDD/100BD. The difference in antibiotic consumption reflects the great diversity among clinical institutions. One of the reasons is different profiles of clinical facilities (figure 4). In four clinical hospitals a trend of reduced consumption of antibiotics can be seen, while the trend of increased consumption is detected in five hospitals. There is no regularity in the movement of consumption observed in others (figure 5).

From the group of **general hospitals**, general hospital number 6* has been transferred to the group of specialized hospitals, while hospital number 16** transferred to the group of clinical hospitals. Another one general hospital has been added to the group of general hospitals in monitoring of antibiotic consumption. In the most homogenous group, made of general hospitals, consumption ranges from 34.6 DDD/100 BD to 82 DDD/100 BD. The largest number of general hospitals (9) has consumption between 51 DDD/100 BD and 60 DDD/100 BD . Only 4 general hospitals reported spending less than 50 DDD/100BD, while 4 hospitals diverge in antibiotic consumption over 70 DDD/100 BD. Five hospitals reported consumption between 61 DDD/100BD and 70 DDD/100 BD (table 5). In eight general hospitals particularly worrisome trend can be observed and that is the increase of the antibiotic consumption (O01; O02; O05; O08; O11; O19; O20; O21; O23), while only one hospital (O10) reported decrease of the antibiotic consumption (figure 6).

Eight of the **psychiatric institutions** are a group with the lowest consumption of antibiotics. The range moves from 2.6 DDD/100BD to 14.7 DDD/100BD (table 6). Despite the low consumption of antibiotics in this group of hospitals, in four hospitals a trend of increased consumption was reported (P02; P05; P07; P08), while only in two hospitals that trend is in a downward trajectory (P03, P06) (figure 7).

A group of **special hospitals** is the most heterogeneous group in which there are: different specialized institutions of chronic type, specialized surgical hospitals, health resorts and spas. The heterogeneity is reflected in the wide range of consumption, which ranges from 0 DDD/100 BD to 61.6 DDD/100 BD (table 7). Three hospitals in the group of specialized hospitals showed a trend of reduced consumption of antibiotics (S07; S15; S19), while five recorded a trend of increased consumption (S05; S09; S11; S14; S16) (figure 8).

All hospitals in Croatia participated in the monitoring of hospital antibiotic consumption by data obtained from hospital pharmacies in the last year.

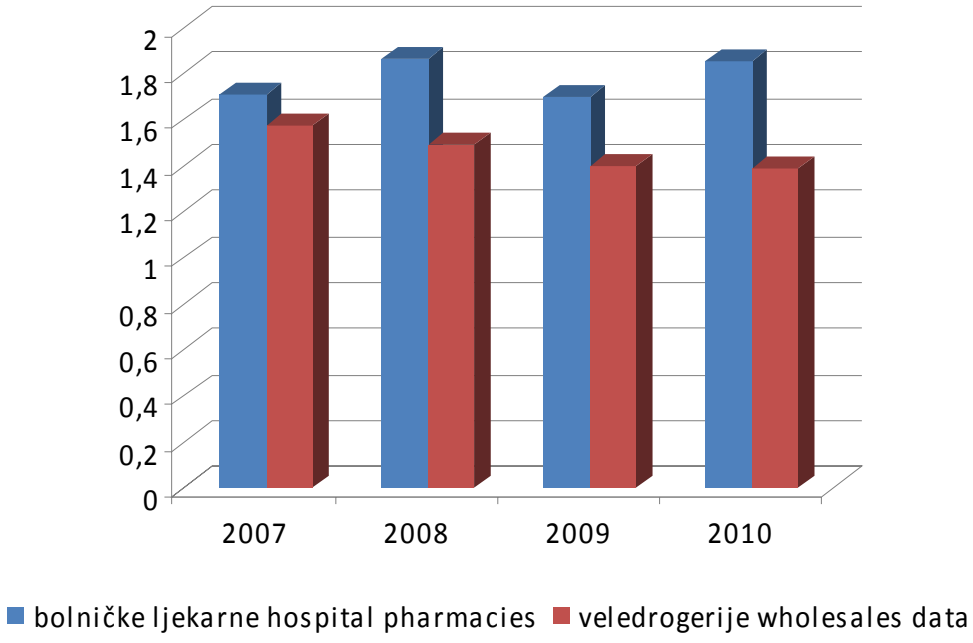
As such, parallel monitoring of hospital consumption of antibiotics from two sources (wholesales data and hospital pharmacies) has proven useful and valuable. A difference was detected in the consumption data depending on the source of data. Data from hospital pharmacies were comprehensive and more reliable, which was a result of the distribution of some antibiotics directly to hospitals rather than through a wholesaler. Deviation seen in the data thus affects the divergence of trends in antibiotic consumption. Data obtained through wholesalers showed that the consumption of antibiotics in Croatia tends to fall; however, the results obtained from hospital pharmacies do not show the same trend. Monitoring of the hospital antibiotic usage data obtained from hospital pharmacies will be continued.

Continuous four year monitoring of hospital antibiotic consumption provides a good survey of the consumption of antibiotics at the Croatian level and gives us a possibility to compare its consumption with other countries. Each hospital is given an opportunity for its own analysis of trends in consumption and the consumption pattern of antibiotics. Data on the movement of bacterial resistance joined with data of antibiotic consumption complete the picture according to which it is possible to start intervention or to continue with it in the direction of rational antibiotic therapy.

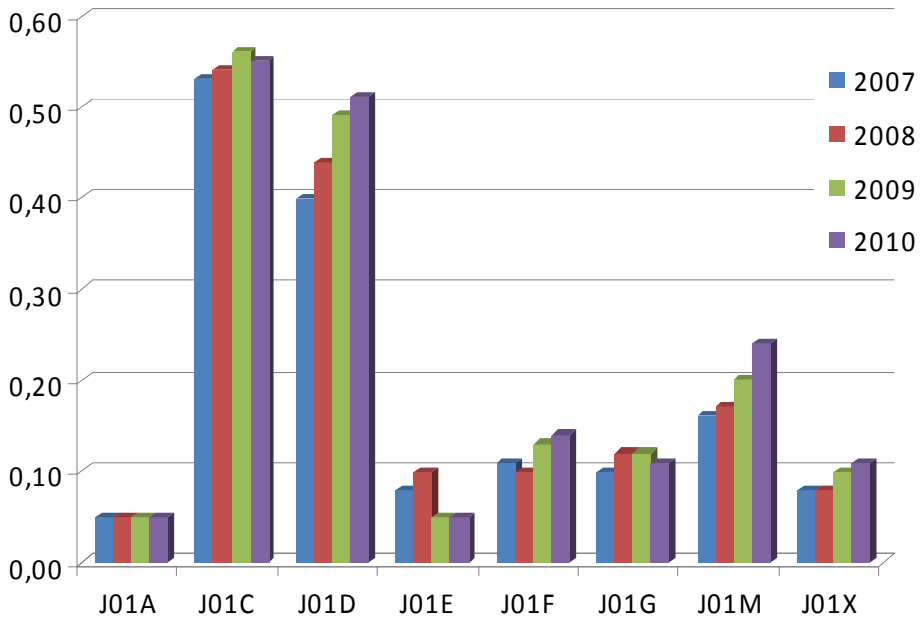
Tablica-*Table 3.*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija
Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales data

godina year	bolničke ljekarne hospital pharmacies	veledrogerije wholesales data
2007	1,71	1,57
2008	1,86	1,49
2009	1,70	1,40
2010	1,85	1,39

Slika-*Figure 3*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija
Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales data



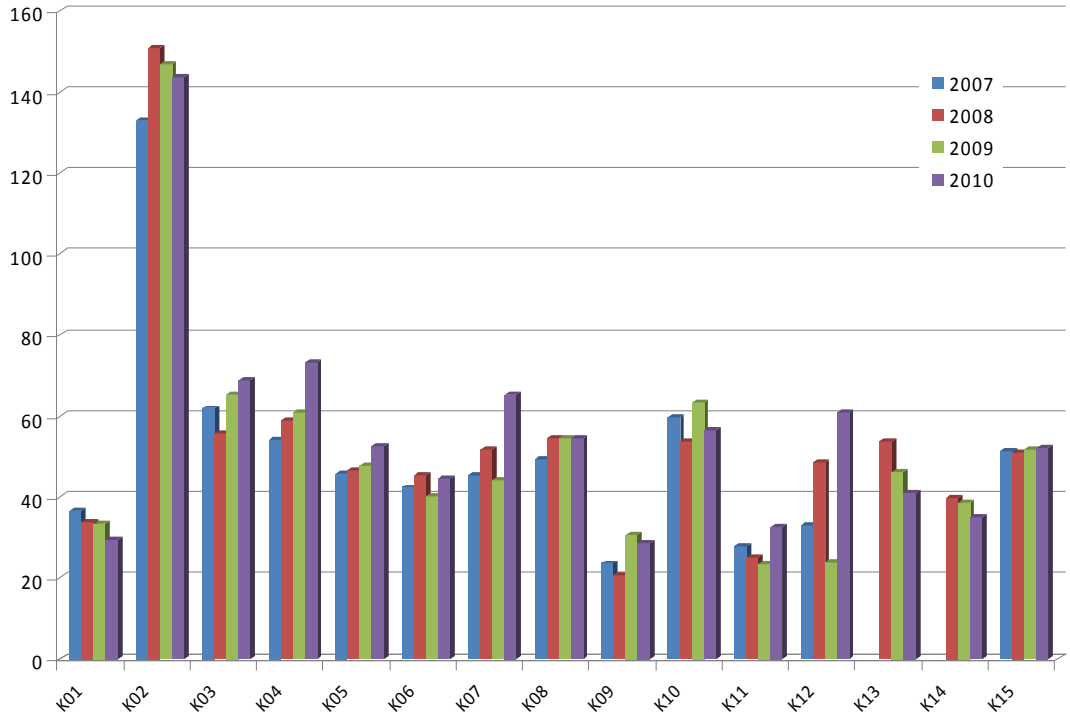
Slika-*Figure 4.*
Bolnička potrošnja antibiotika (DDD/TID) po klasama, izvor podataka - bolničke ljekarne
Hospital antibiotic consumption (DDD/TID) by class, origin of data - hospital pharmacies



Tablica-*Table 4.*
Kliničke ustanove - potrošnja antibiotika u 2010.
Clinical insitutions - antibiotic consumption in 2010

USTANOVA INSTITUTION	DDD/100 BOD DDD/100 BD	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
K 01	29,5	0,1	6,5	8,3	1	6,2	3,8	1	2,5
K 02	143,7	3,3	54,7	42,6	3	12,5	4,4	13,2	10
K 03	68,9	0	26,1	21,2	1,5	3,2	3,9	6,6	6,3
K 04	73,4	0,9	25,7	20,6	2,5	4,3	3	9,7	6,8
K 05	52,5	1,6	17,8	12,4	1,2	4,6	3,6	8,2	3,1
K 06	44,6	0,7	9,9	18,5	0,9	2,7	2,2	5,4	4,4
K 07	65,3	0,7	15,1	18,1	2,1	4,5	3,4	16,2	5,2
K 08	54,4	2,2	13,1	17,6	1,8	3,8	2,1	8,9	4,9
K 09	28,6	0,1	1	24,1	0	0,3	1,1	1,5	0,5
K 10	56,7	0,7	19,8	14,5	0	7,5	2,8	10,4	1
K 11	32,5	2,3	7,2	12	0,7	0,5	1	6	2,9
K 12	61	0,3	15,1	3,6	0,4	13,9	0,3	11,2	16,1
K 13	41,1	0	12,3	12,4	2,6	2,9	2,9	4,6	3,3
K 14	35,2	0,2	8,2	16,5	1,7	3	2,6	0,7	2,3
K 15	52	0,9	19,7	14,1	0	3	3,4	7,5	3,7

Slika-*Figure 5.*
Kliničke ustanove - potrošnja antibiotika u 2010.
Clinical insitutions - antibiotic consumption in 2010

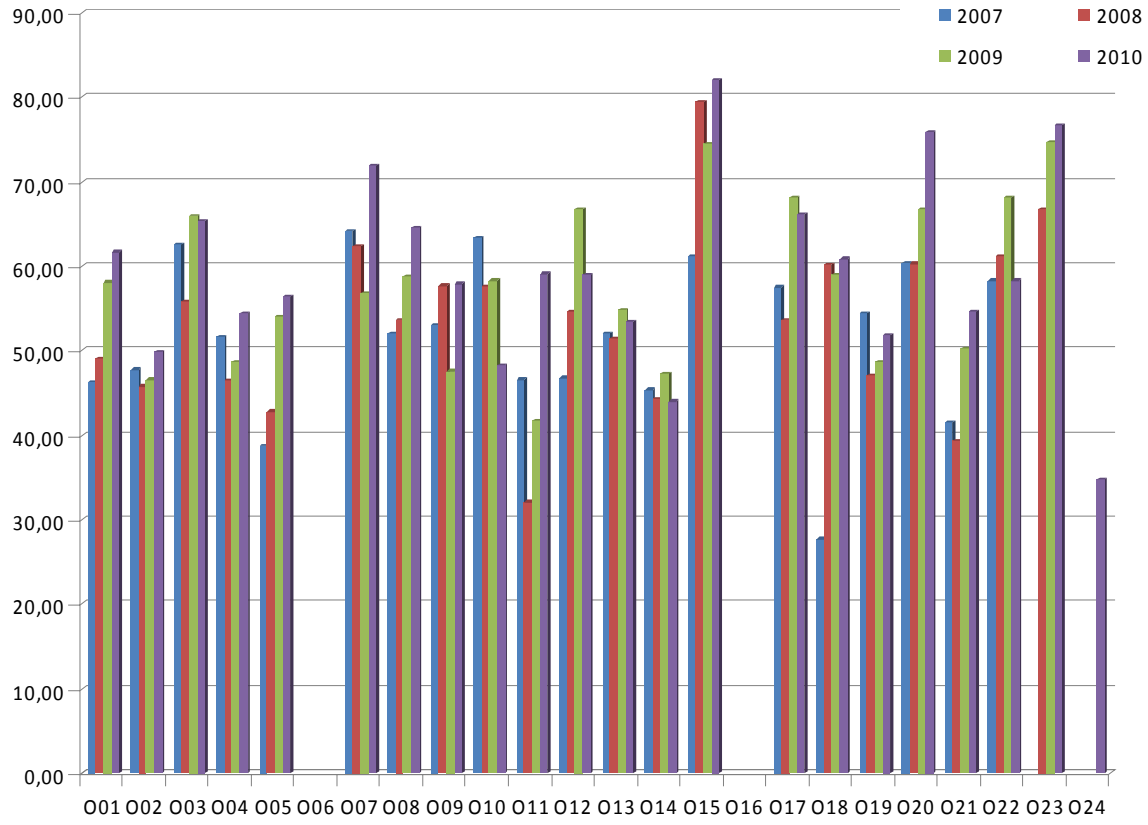


Tablica-*Table **5.***
Opće bolnice - potrošnja antibiotika u 2010.
General hospitals - antibiotic consumption in 2010

USTANOVA INSTITUTION	DDD/100 BOD DDD/100 BD	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
O 01	61,7	0,1	25,7	14,6	0,7	5,5	6,9	4	4,3
O 02	49,8	1,1	27	11,1	0,4	2	2,9	3,4	1,9
O 03	65,4	5,3	12,5	25,5	1	11,4	3,2	3,1	3,4
O 04	54,5	3,1	7,9	16,9	2,6	5,5	6,2	9,6	2,7
O 05	56,5	4,2	22,1	7	0,7	9,9	5,7	5,6	1,4
O 06*									
O 07	71,9	0,6	21,5	24,5	1,7	8,6	7,6	5,4	2
O 08	64,6	1,9	23,6	12,3	3	4,1	6,3	8,6	4,8
O 09	57,9	0,3	16,7	18,8	1,3	2,6	7,5	7,1	3,8
O 10	48,3	0,4	12,5	21,3	0,6	3,6	3,3	2,3	4,2
O 11	59,1	1,7	18	14,4	2,5	4	9,8	6,6	2,1
O 12	59	4	19	15,8	1	4,9	2,2	10	2,3
O 13	53,5	0,4	12,9	23,7	1,7	6,6	2,5	4,5	1,3
O 14	44	0	18,4	10,7	2,4	2,8	3,4	3,4	2,9
O 15	82	3,9	26	25,1	1	5,8	6,7	7,5	6
O 16**									
O 17	66,1	2,3	21,1	23,4	0,6	4,6	5,1	4,3	4,8
O 18	60,9	3,3	26,8	14,4	0,7	2,6	2,8	7,2	3
O 19	51,8	1,2	20,6	12,1	1,2	3	4,8	6,3	2,6
O 20	75,9	2,4	11,4	36,4	0,5	6,2	4,6	11,3	3
O 21	54,8	0,8	18,6	12,6	1,8	5,4	5,6	6,7	3,4
O 22	58,3	0,9	14	20,2	1,2	4,2	4,1	10,6	3,1
O 23	76,7	2,4	30,7	20,6	0,7	6,4	5,9	5	5
O 24	34,8	0	18,1	6,4	2,4	1	2,5	2,5	1,9

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

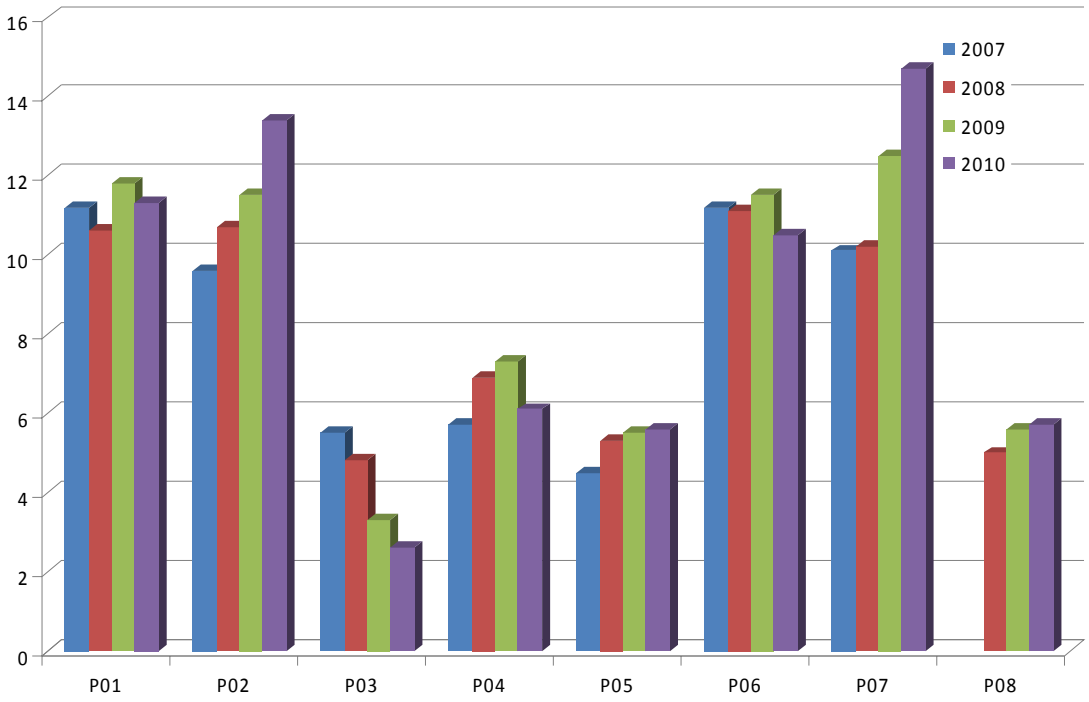
Slika-*Figure **6.***
Opće bolnice - potrošnja antibiotika 2007.-2010.
General hospitals - antibiotic consumption 2007-2010



Tablica-*Table **6.***
Psihijatrijske ustanove - potrošnja antibiotika u 2010.
Psychiatric institutions - antibiotic consumption in 2010

USTANOVA INSTITUTION	DDD/100 BOD DDD/100 BD	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
P 01	11,3	0,6	4,9	2,2	0,9	1,1	0,2	1	0,4
P 02	13,4	0,1	6,9	2,3	0,6	0,7	0,3	2,1	0,3
P 03	2,6	0	2,1	0,3	0	0,2	0	0	0
P 04	6,1	0,8	2,8	0,8	0,4	0,6	0,1	0,7	0
P 05	5,6	0,3	2,8	1,1	0,1	0,4	0,1	0,8	0
P 06	10,5	0,4	5,8	0,7	0,4	0,8	0,5	1,8	0,2
P 07	14,7	0,1	3,5	6,3	0,1	0,8	1,3	2	0,7
P 08	5,7	0,2	2,6	1,2	0,3	0,2	0,3	1	0,1

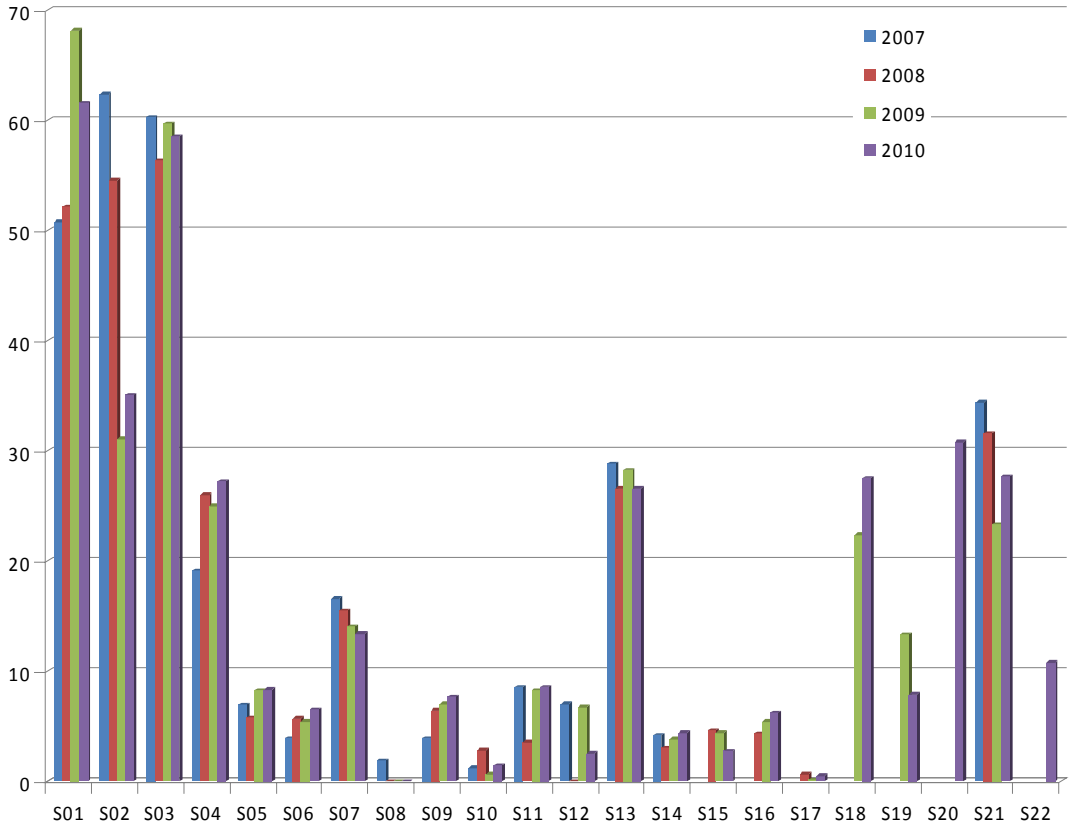
Slika-*Figure 7.*
Psihijatrijske ustanove - potrošnja antibiotika 2007.-2010.
Psychiatric institutions - antibiotic consumption 2007-2010



Tablica-*Table 7.*
Specijalne bolnice - potrošnja antibiotika u 2010.
Specialised hospitals - antibiotic consumption in 2010

USTANOVA INSTITUTION	DDD/100 BOD DDD/100 BD	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
S 01	61,6	0,2	27,8	1,9	1,3	2,7	8,9	16,9	1,8
S 02	35,1	0,1	9,2	10	0,3	13,6	0,8	0,6	0,5
S 03	58,6	2,3	23,7	9,1	2,6	3,4	7,3	9,5	0,7
S 04	27,2	0,4	11,8	4,7	3	0,3	2,2	2,9	1,9
S 05	8,3	0,1	4,4	1,3	0,3	0,5	0,3	1,1	0,3
S 06	6,5	0	2,4	0,7	1	0,2	0,2	1,9	0,2
S 07	13,4	0	3,7	2,8	0,6	1,5	0,8	3,4	0,5
S 08	0	0	0	0	0	0	0	0	0
S 09	7,7	0,3	3,7	1	0,8	1,5	0	0,5	0
S 10	1,4	0	0,4	0,1	0,3	0,1	0,1	0,2	0
S 11	8,5	0,1	2,6	2,2	0,2	0,4	0,6	2,2	0,2
S 12	2,5	0,7	1,2	0,1	0,2	0,5	0	0	0
S 13	26,6	9,7	6,1	2,8	2	0,3	0,3	2,5	2,9
S 14	4,4	0,3	1,8	1,2	0	0,6	0	0,5	0
S 15	2,7	0	1,3	0,8	0	0,1	0	0	0,4
S 16	6,2	0,4	2,7	1,4	0,4	0,4	0	0,6	0,2
S 17	0,5	0	0,3	0,1	0	0	0	0	0
S 18	27,5	1,9	11	6,9	0,4	0,6	0,3	6	0,3
S 19	7,9	0	4	2,6	0,3	0,1	0,1	0,3	0,5
S 20	30,8	0	23,4	2,6	0	2,8	0,7	1,3	0,1
S 21	27,7	0	9,6	6,3	0	3,9	0,4	5,1	2,5
S 22	10,8	0	0,9	7,9	0	0,6	1	0	0,5

Slika-*Figure* ***8.***
Specijalne bolnice - potrošnja antibiotika 2007.-2010.
Specialised hospitals - antibiotic consumption 2007-2010



ATK KLASIFIKACIJA ANTIBIOTIKA:
ATC CLASSIFICATION OF ANTIBIOTICS

J01A – TETRACIKLINI / *TETRACYCLINES*

J01B – AMFENIKOLI / *AMPHENICOLS*

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

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

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

J01G – AMINOGLIKOZIDI / *AMINOGLYCOSIDES*

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

POGLAVLJE/CHAPTER 5.

VANJSKA KONTROLA KVALITETE, 2010.
EXTERNAL QUALITY CONTROL, 2010

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Vanjska kontrola kvalitete
External Quality Control

Opis sojeva za kontrolu: proljeće 2010.

Test soj 01 / 10 je *Klebsiella pneumoniae* (196/08) rezistentna na cefuroksim, ko-amoksiklav, ampicilin/sulbaktam, te intermedijarno osjetljiva na piperacilin/tazobaktam. Soj je osjetljiv na karbapeneme. Po disk difuziji soj je osjetljiv na ceftazidim, ali intermedijarno rezistentan na ceftriakson. Minimalne inhibitorne koncentracije za ceftriakson (6.0 ug/mL) i ceftazidim (4.0 ug/mL) su unutar granica osjetljivosti prema CLSI 2009, ali u kategoriji rezistentno i intermedijarno prema EUCAST 2010 standardima. Soj ne proizvodi beta-laktamaze proširenog spektra (engl. „extended spectrum beta-lactamases“, ESBL) niti inducibilne AmpC beta-laktamaze. Soj, međutim, proizvodi metalo-beta-laktamazu VIM-2. Jedan laboratorij je soj opisao kao ESBL pozitivan, a 15 laboratorija je naznačilo da soj proizvodi AmpC beta-laktamazu. Od 35 laboratorija koji su sudjelovali u kontroli 34 laboratorija su točno identificirali izolat. Većina laboratorija (30) je u disk difuziji za ceftriakson dobila intermedijaran ili rezistentan rezultat što ne odgovara interpretaciji MIK-a za ceftriakson prema CLSI 2009 standardu, ali je bliska interpretaciji MIK-a prema EUCAST 2010. Sedam laboratorija je izdalo rezistentan ili intermedijaran rezultat za jedan od karbapenema. Do nedavno nije bilo jasno kako izdavati soj koji je *in vitro* osjetljiv na karbapeneme, ali koji proizvodi karbapenemaze. EUCAST standardi jasno naznačuju da se takvi sojevi izdaju kao osjetljivi na karbapeneme, jer klinički učinak ovisi o MIK-u, a ne o prisutnosti karbapenemaza. Detekcija karbapenemaza ukazuje, međutim, na nužnost primjene mjera kontaktne izolacije pri kontroli bolničkih infekcija.

Test soj 02 / 10 je *Pseudomonas aeruginosa* (MDR29/08) rezistentan na sve antipseudomonasne antibiotike osim na piperacilin/tazobaktam, karbapeneme i kolistin. Soj proizvodi beta-laktamazu proširenog spektra (engl. „extended spectrum beta-lactamases“, ESBL) PER-1. S obzirom da se radi o klasi A beta-laktamaza tipičan antibiogram pokazuje rezistenciju na piperacilin, ali osjetljivost na piperacilin/tazobaktam. Proizvodnja ESBL nije čest mehanizam rezistencije u *P. aeruginosa*, no od 1990-tih se opisuju rijetke PER (engl. „Pseudomonas extended resistant“) beta-laktamaze koje se, iako rijetko, mogu naći i u ostalih bakterijskih vrsta. Od 35 laboratorija koji su sudjelovali u kontroli svi su točno identificirali izolat. Četiri laboratorija su izdala rezistentan / intermedijaran rezultat za piperacilin/tazobaktam, a tri laboratorija su izdala soj kao osjetljiv na piperacilin. Dvanaest laboratorija je izdalo rezistentan / intermedijaran rezultat za meropenem, što predstavlja grešku prema CLSI 2009 interpretaciji. Kad bi se primjenila EUCAST 2010 interpretacija izolat bi bio intermedijarno osjetljiv na meropenem te i dalje osjetljiv na imipenem.

Challenge strains: spring 2010

Test strain 01 / 10 is *Klebsiella pneumoniae* (196/08) resistant to cefuroxim, co-amoxiclav, ampicillin/sulbactam and intermediately resistant to piperacillin/tazobactam. The strain is sensitive to carbapenems. The strain is sensitive to ceftazidim and intermediately resistant to ceftriaxone by disk diffusion. Minimal inhibitory concentrations (MICs) for ceftriaxone (6.0 ug/mL) and ceftazidim (4.0 ug/mL) are interpreted as sensitive according to CLSI 2009, but are categorized as resistant and intermediate according to EUCAST 2010. The strain does not produce extended spectrum beta-lactamases (ESBL) or inducible AmpC beta-lactamases. However, the strain produces metallo-beta-lactamase VIM-2. One laboratory described the strain as an ESBL producer and 15 laboratories reported it as an AmpC producer. Out of 35 laboratories that took part 34 laboratories identified the strain correctly. The majority of laboratories (30) reported the strain as intermediate or resistant to ceftriaxone by disk diffusion which is not in accordance with ceftriaxone MIC if it is interpreted by CLSI 2009 but is close to the MIC interpretation by EUCAST. Seven laboratories reported the strain to be resistant or intermediate to one of the carbapenems. Until recently it was not quite clear how to report isolates that are carbapenemase producers but are sensitive *in vitro* to carbapenems. EUCAST clearly states that these isolates should be reported as they test because the clinical outcome is depended on MIC level and not on the presence or absence of carbapenemases. Carbapenemase detection indicates, however, that the patient should be placed in contact isolation.

Test strain 02 / 10 is *Pseudomonas aeruginosa* (MDR29/08) resistant to all antipseudomonal antibiotics except to piperacillin/tazobactam, carbapenems and colistin. The strain produces extended spectrum beta-lactamase (ESBL) PER-1. As this is a class A beta-lactamase the antibiogram typically demonstrates resistance to piperacillin and sensitivity to piperacillin/tazobactam. ESBL production is not a frequent resistance mechanism in *P. aeruginosa*, but since the 1990s rare PER („Pseudomonas extended resistant“) beta-lactamases are being described in pseudomonas but also in other bacterial species. All the 35 laboratories that took part in this quality control challenge identified the strain correctly. Four laboratories reported the strain as resistant / intermediate to piperacillin/tazobactam and three laboratories reported the strain as sensitive to piperacillin. Twelve laboratories reported the strain as resistant / intermediate to meropenem which is a major mistake according to CLSI 2009 interpretation. According to EUCAST 2010 the isolate is intermediately sensitive to meropenem and fully sensitive to imipenem.

Tablica-*Table **1.***
Rezultati za kontrolu: proljeće 2010.
Rresults for the Quality Control: spring 2010

Lab.	01 / 10 *K.pneumoniae*					02 / 10 *P.aeruginosa*	
	ID	CEFALOSPORINI	KARBAPENEMI	OSTALI	ampC	ID	ATB
1	+	CRO* CAZ**	+	PTZ* FOX**	-	+	PTZ** MEM**
2	+	CFP* CTB*	****	PTZ*	-	+	MEM**
3	+	CFP* CTB*	+	FOX**	-	+	CFP* FEP*
4	+	CFP*	+	FOX**	-	+	+
5	+	CAZ* CFP* CTB*	****	PTZ* FOX**	-	+	MEM** CFP*
6	+	CRO*	ERTA**	PTZ* FOX**	-	+	+
7	+	CRO* CAZ**CFP**CTB**	ERTA**	FOX**	-	+	PTZ** MEM**
8	+	CFP** CTB**	MEM*	PTZ* FOX**	-	+	MEM**
9	+	CFP* CTB*	+	FOX**		+	+
10	+	CFP** CTB*	+	PTZ* FOX**	-	+	MEM**
11	+	CAZ* CFP*	+	PTZ* FOX*		+	+
12	+	CRO*	+	FOX**	-	+	CFP*
13	+	CTB*	+	PTZ* FOX**		+	+
14	+	+	+	+		+	+
15	+	CFP* CTB*	+	PTZ*		+	MEM*
16	+	CRO* CFP*	+	PTZ* FOX*		+	AN*** CIP* COL* PIP*** CFP* FEP*
17	+	CFP* CTB*	+	FOX**		+	CFP*
18	+	CRO* CTB*	+	PTZ* FOX**		+	PTZ*
19	+	CFP*	+	PTZ* FOX**		+	FEP*** AN*** NT* CFP*
20							
21	+	CRO* CAZ** CFP**CTB**	+	FOX**	-	+	+
22	+	CFP*	+	FOX**	-	+	+
23	+	CRO* CAZ** CTB**	****	FOX**		+	AN***
24	+	+	ND	+		+	+
25	+	CFP* CTB*	+	PTZ* FOX**		+	MEM**
26	+	CAZ*	+	FOX*		+	+
27	+	CFP*	ERTA**	FOX**		+	+
28	+	CRO*	+	PTZ* FOX**		+	AN*** PIP***
29	+	CTB* CFP**	+	PTZ* FOX**	-	+	MEM**
30	+	CRO* CTB* CFP**	+	PTZ* FOX**		+	MEM** FEP*
31	-	CFP*	+	PTZ* FOX**		+	GM*** AN***PIP*** FEP*** NT* PTZ* CFP* CIP* NOR*
32	+	CRO* CAZ** CFP** CTB**	+	FOX**		+	+
33	+	CFP* CTB*	+	PTZ* FOX*	-	+	+
34	+	CRO* CAZ**	+	FOX**	-	+	IMI** MEM**
35							
36	+	CRO* CAZ** CFP** CTB** FEP**	+	PTZ**** FOX**		+	AN*** CIP*** NOR***
37	+	CAZ* CFP* CTB*	+	FOX*+		+	MEM*

* manja greška/*minor error*, ** velika greška/*major error*, *** vrlo velika greška/*very major error*, **** greška u interpretaciji/*error in interpretation*, ND = nije učinjeno/*not done*

Opis sojeva za kontrolu: jesen 2010.

Kao jesenska kontrola testiranja osjetljivosti na antibiotike obrađeni su podaci za sojeve koji su testirani u okviru EARS-Net projekta ljeto 2010. godine, distribucija 2785 .Rezultati su interpretirani prema CLSI 2009 standardima, s obzirom da su to bili službeni standardi za Hrvatsku u 2010. godini.

Soj 0243: ***Klebsiella pneumoniae**:* soj je osjetljiv na cefepim i karbapeneme, ne producira ESBL ali izlučuje plazmid posredovanu AmpC beta-laktamazu (CIT-tip). Dva hrvatska laboratorija imala su problema s točnom identifikacijom soja. Samo sedam laboratorija od 24 su točno odredili osjetljivost ovog soja na sve antibiotike. Četiri laboratorija su ovaj soj proglasili osjetljivim na seftriakson (vrlo velika greška), a jedan laboratorij pogrešno je utvrdio produkciju ESBL-a.

Soj 0244: ***Escherichia coli**:* soj je osjetljiv na sve antibiotike ali pokazuje graničnu osjetljivost na amikacin. Svi laboratoriji su točno identificirali soj. Točnu osjetljivost ovog soja na antibiotike odredilo je dvanaest od 24 laboratorij. Dva su laboratorija imala veliku grešku, a jedan je pogrešno utvrdio produkciju ESBL-a. Naglasak kod ovog soja je bio na različitoj interpretaciji disk difuzije primjenom EUCAST ili CLSI preporuka, što je vidljivo kod granično osjetljivih sojeva.

Soj 0245: ***Streptococcus pneumoniae**:* soj je rezistentan na kinolone i eritromicin. Naglasak je bio na primjeni diska norfloksacina od 10 μg za provjeru osjetljivosti soja, te primjeni diska ciprofloksacina od 1 ili 5 μg. Osamnaest hrvatskih laboratorija točno je odredilo osjetljivost ovog soja. Četiri laboratorija su disk difuzijom dobili osjetljivost na kinolone (vrlo velika greška), ali su tri laboratorija korigirala rezultat prema MIK-u ciprofloksacina. Pet laboratorija nije upotrijebilo niti interpretiralo osjetljivost na kinolone. Svi europski laboratoriji koji su za *screening* koristili disk norfloksacina od 10 μg točno su interpretirali osjetljivost na kinolone.

Soj 0246: ***Enterococcus faecium**:* soj je rezistentan na vankomicin i teikoplanin, što odgovora VanA posredovanoj rezistenciji. Većina hrvatskih laboratorija je točno odredilo i prepoznalo VanA posredovanu rezistenciju. Prema CLSI interpretaciji disk difuzije 14 laboratorija je dobilo osjetljivost na teikoplanin (vrlo velika greška). Kad se primjeni EUCAST interpretacija samo 1 od tih laboratorija bi dobio krivi rezultat. Među europskim sudionicima EARS kontrole 1 % laboratorija pogrešno je odredilo graničnu vrijednost teikoplanina ako su za interpretaciju primjenili EUCAST preporuke odnosno 10 % europskih sudionika je pogrešno interpretiralo osjetljivost teikoplanina kad su koristili CLSI preporuke. Svi hrvatski laboratoriji su korektno odredili rezistenciju na vankomicin.

Soj 0247: ***Pseudomonas aeruginosa**:* soj je trebalo interpretirati kao rezistentan na piperacilin-tazobaktam (32 μg/mL) i granično osjetljiv na tobramicin. Samo devet laboratorija je točno odredilo osjetljivost soja na sve antibiotike, a petnaest laboratorija je imalo vrlo veliku grešku. Ponovo, soj su kao osjetljiv interpretirali laboratoriji koji su za interpretaciju dobivene vrijednosti upotrijebili CLSI, a ne EUCAST preporuke. I među europskim sudionicima EARS-a manje laboratorija je pogriješilo u interpretaciji ako su upotrijebili EUCAST preporuke (23 %) nego ako su koristili CLSI preporuke (47 %).

Soj 0248: ***Staphylococcus aureus****:* soj ST 239 je višestruko rezistentan MRSA, a osjetljiv je samo na vankomicin, teikoplanin i rifampicin. Hrvatski laboratoriji nisu imali problema u testiranju i interpretaciji osjetljivosti ovog soja.

Challenge strains: autumn 2010

For the autumn challenge NEQAS 2785 test strains obtained on July 2010 from EARS were used. Results were interpreted accordingl to the CLSI 2009 standards as these were the official standards for Croatia in 2010.

Strain 0243: ***Klebsiella pneumoniae****:* this strain is sensitive to cefepim and carbapenems. It does produce ESBL but produces CIT AmpC beta-lactamase. Two Croatian laboratories did not identify the isolate correctly. Out of 24 Croatian laboratories only seven correctly reported sensitivity to all tested antibiotics. Four laboratories reported this strain to be susceptible to ceftriaxon (a very major mistake) and one laboratory incorrectly reported ESBL production.

Strain 0244: ***Escherichia coli****:* this strain is sensitive to all tested antibiotics but it shows borderline sensitivity to amikacin (MIC 8-16 mg/L). All Croatian laboratories correctly identified the strain. Out of 24 laboratories 50 % laboratories (12/24) correctly reported sensitivity to all tested antibiotics. Two Croatian laboratories made a major mistake, and one laboratory incorrectly reported ESBL production. This strain demonstrates difference in disk diffusion interpretation depending on the standard used (EUCAST or CLSI) espetially evident at the borederline results.

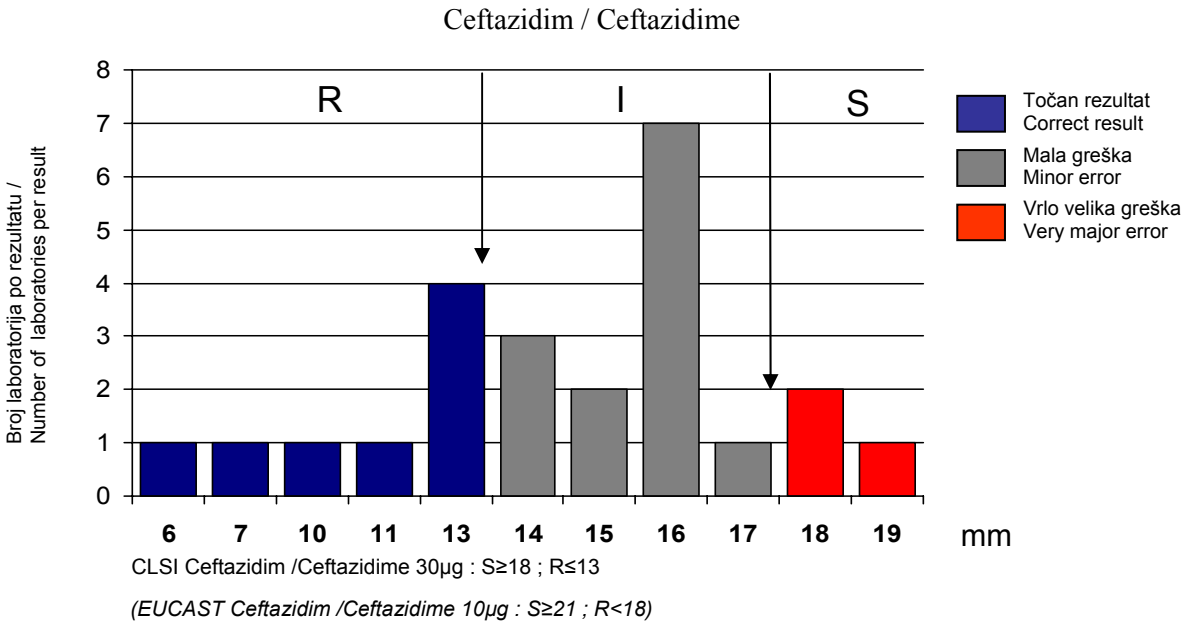
Strain 0245: ***Streptococcus pneumoniae****:* this strain is resistant to quinolones and erythromycin. The point of this challenge was on usage of 10 μg norfloxacin disc and 1 or 5 μg ciprofloxacin discs in screening for quinolone resistance. Most (75%) Eighteen Croatian laboratories correctly reported sensitivity of this strain. Four laboratories recorded sensitivity to quinolones but three of them eported correcated result according MIC to ciprofloxacin. Only one laboratory reported the isolate as sensitive to quinolones (a very major mistake), and five laboratories did not report susceptibility to quinolones at all. All European laboratories correctly reported quinolones as resistant when using 10 μg norfloxacin disc for screening.

Strain 0246: ***Enterococcus faecium****:* this strain is resistant to vancomycin and teicoplanin, which fits into Van A phenotype. Less than 50 % of Croatian laboratories (11/24) detected this resistance phenotype. According to CLSI 14 laboratories got sensitive result for teicoplanin. However when EUCAST standards are applied only one of these laboratories made a very major mistake. It was easier to detect Van A resistance by using EUCAST standards for interpretation of teicoplanin sensitivity. Less European laboratories incorrectly reported teicoplanin sensitivity when using EUCAST (1 %) than CLSI standards (10 *%).* All laboratories correctly reported result to vancomycine.

Strain 0247: ***Pseudomonas aeruginosa****:* this strain should be reported as resistant to piperacillin-tazobactam (32 μg/mL) and as borderline sensitive to tobramycin. Only nine Croatian laboratories correctly reported sensitivity of this strain. Fifteen laboratories reported incorrectly piperacillin-tazobactam as sensitive (very major mistake). Most of Croatian laboratories used CLSI interpretation and therefore these laboratories reported piperacillin-tazobactam as sensitive. Using EUCAST standards 23 % of European laboratories reported incorrectly piperacillin-tazobactam as sensitive but using CLSI standards as many as 47 % laboratories provided incorrect report.

Strain 0248: ***Staphylococcus aureus****:* this strain is an MRSA ST 239. It is only sensitive to vankomycin, teicoplanin and rifampicin. All Croatian laboratories had no problems in testing and interpretation of antibiotic susceptibility of this strain.

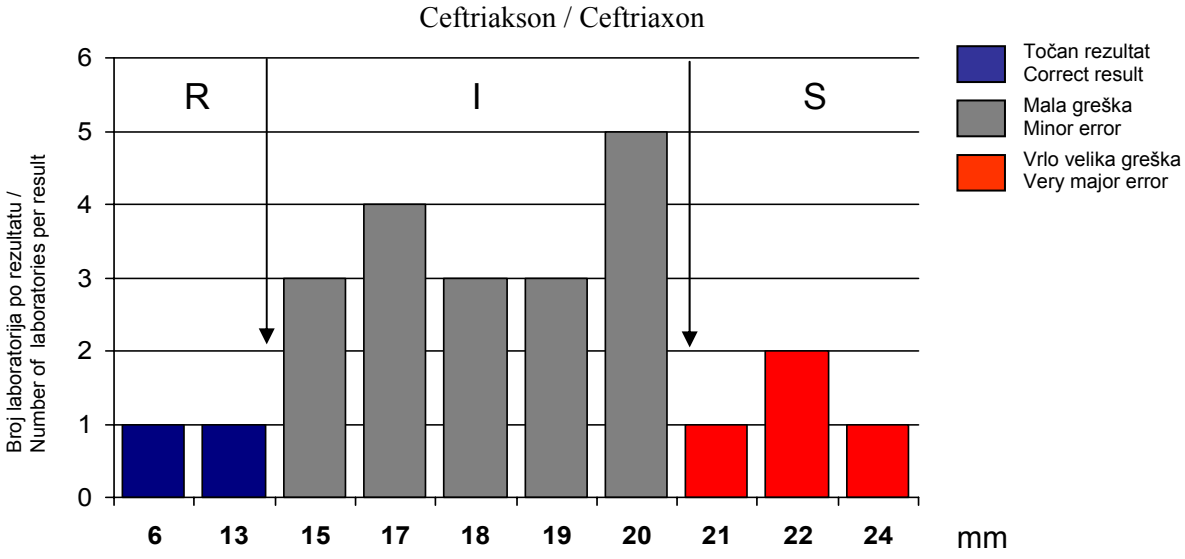
Slika-*Figure 1.*
NEQAS soj 0243: ***K.pneumoniae*** s AmpC beta-laktamazom - ceftazidim R
NEQAS strain 0243: ***K.pneumoniae*** + AmpC beta-lactamaze - Ceftazidime R
NEQAS: Ceftazidim/Ceftazidime MIK/MIC 32 mg/L



CLSI Ceftazidim /Ceftazidime 30µg : S≥18 ; R≤13

(EUCAST Ceftazidim /Ceftazidime 10µg : S≥21 ; R<18)

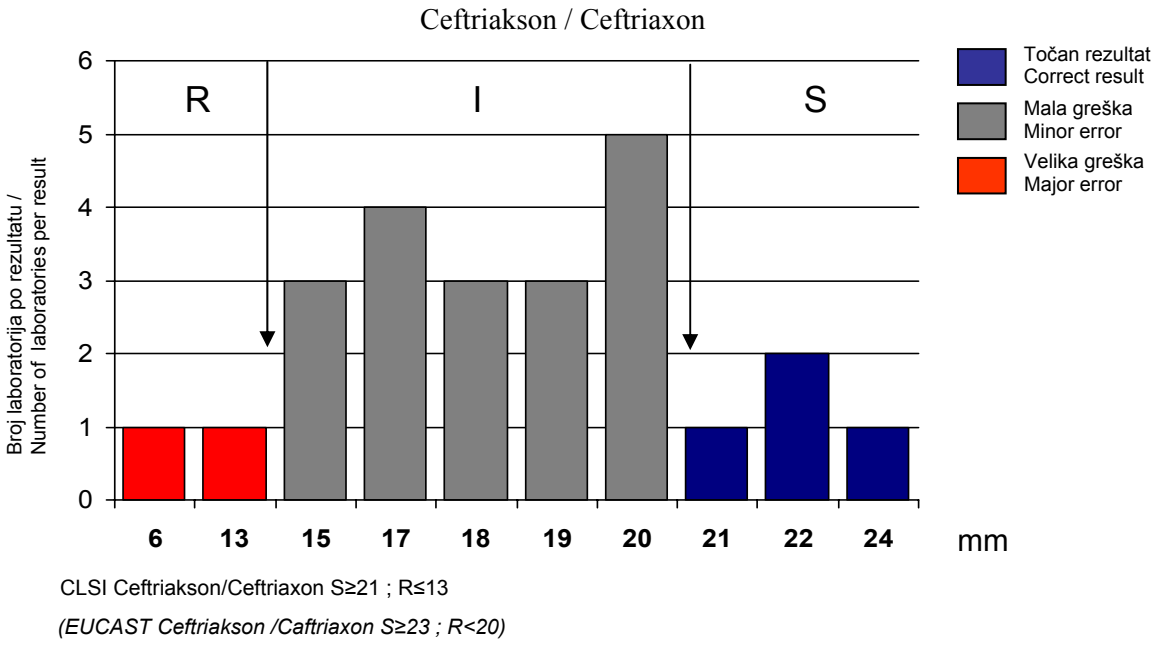
Slika-*Figure 2.*
NEQAS soj 0243: ***K.pneumoniae*** s AmpC beta-laktamazom - ceftriakson R
NEQAS strain 0243: ***K.pneumoniae*** + AmpC beta-lactamaze - Ceftriaxon R
NEQAS: Ceftriakson/Ceftriaxon MIK/MIC > 32 mg/L



CLSI Ceftriakson/Ceftriaxon S≥21 ; R≤13

(EUCAST Ceftriakson /Caftriaxon S≥23 ; R<20)

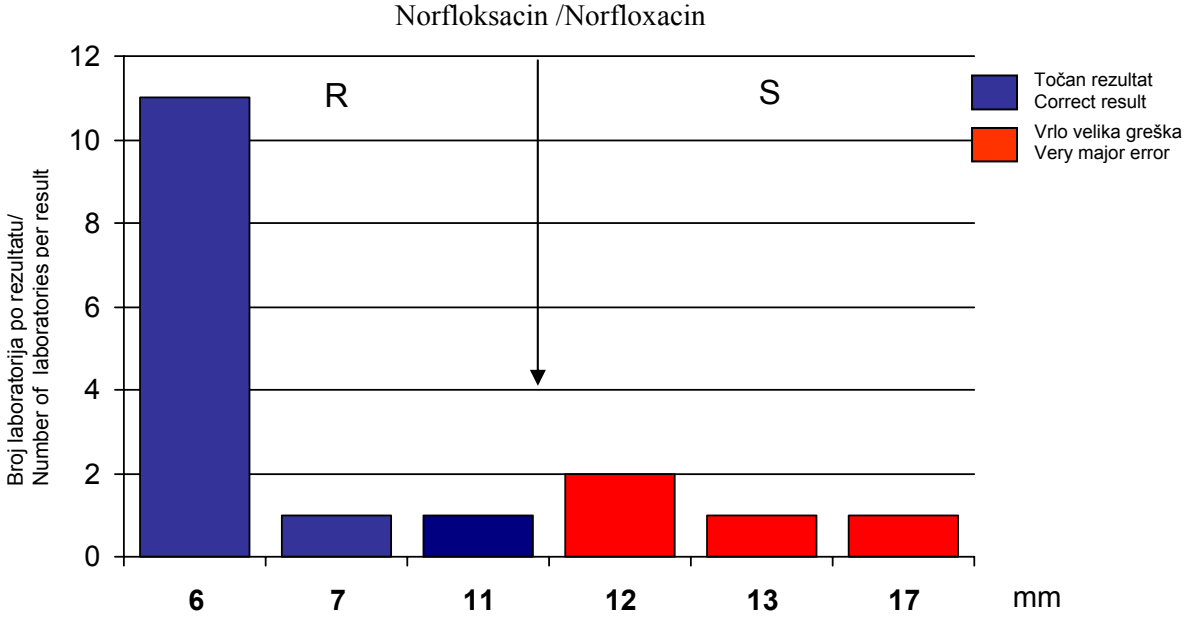
Slika-*Figure 3.*
NEQAS soj 0244: ***E.coli*** - granično osjetljiva na amikacin
NEQAS strain 0244: ***E.coli*** - Amikacin borderline sensitive
NEQAS: Amikacin MIK/MIC 8-16 mg/L



CLSI Ceftriakson/Ceftriaxon S≥21 ; R≤13

(EUCAST Ceftriakson /Caftriaxon S≥23 ; R<20)

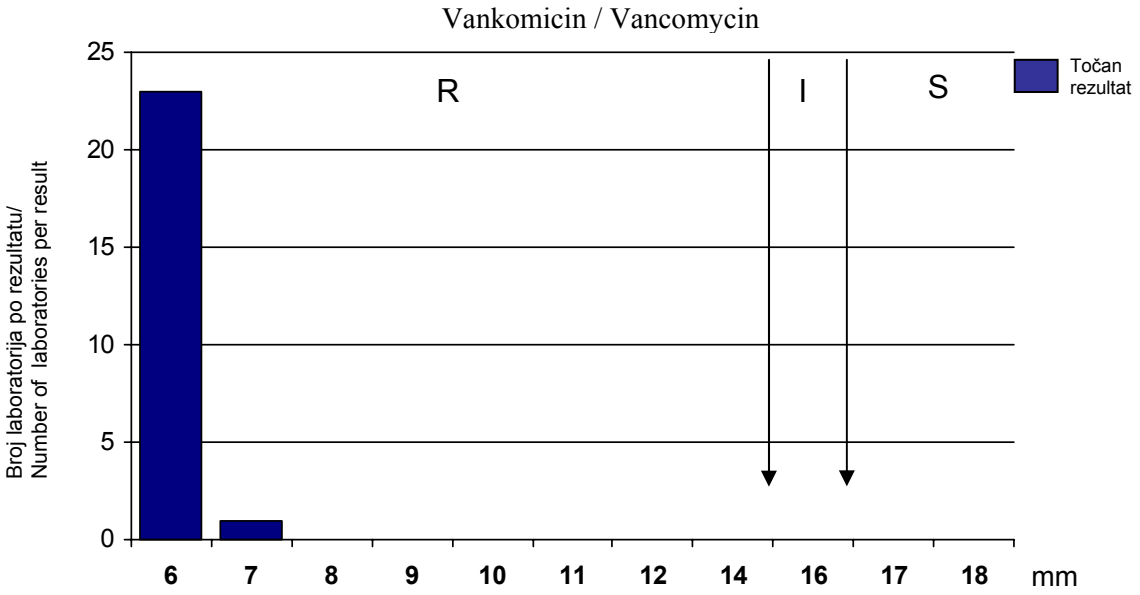
Slika-*Figure 4.*
NEQAS soj 0245: ***S.pneumoniae*** - kinoloni R
NEQAS strain 0243: ***S.pneumoniae*** - Quinolones R
NEQAS: Ciprolfokasin/Ciprofloxacin MIK/MIC > 32 mg/L



BSAC Norfloksacin /Norfloxacin S≥11 ; R≤11

(EUCAST Norfloksacin /NorfloxacinS≥12 ; R<12)

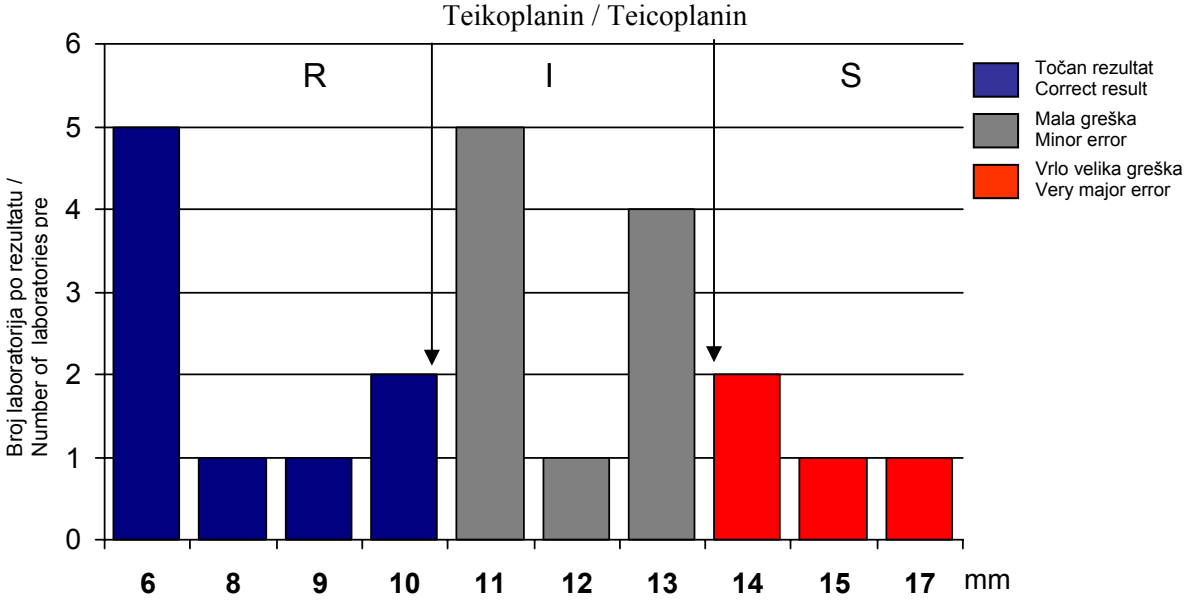
Slika-*Figure 5*.
NEQAS soj 0246: ***E.faecium*** - vankomicin R
NEQAS strain 0246: ***E.faecium*** **-** Vankomycin R
NEQAS: Vankomicin/Vankomycin MIK/MIC 64->128 mg/L



CLSI Vankomicin /Vancomycin S≥17 ; R≤14

(EUCAST Vankomicin /Vancomycin S≥16 ; R<16)

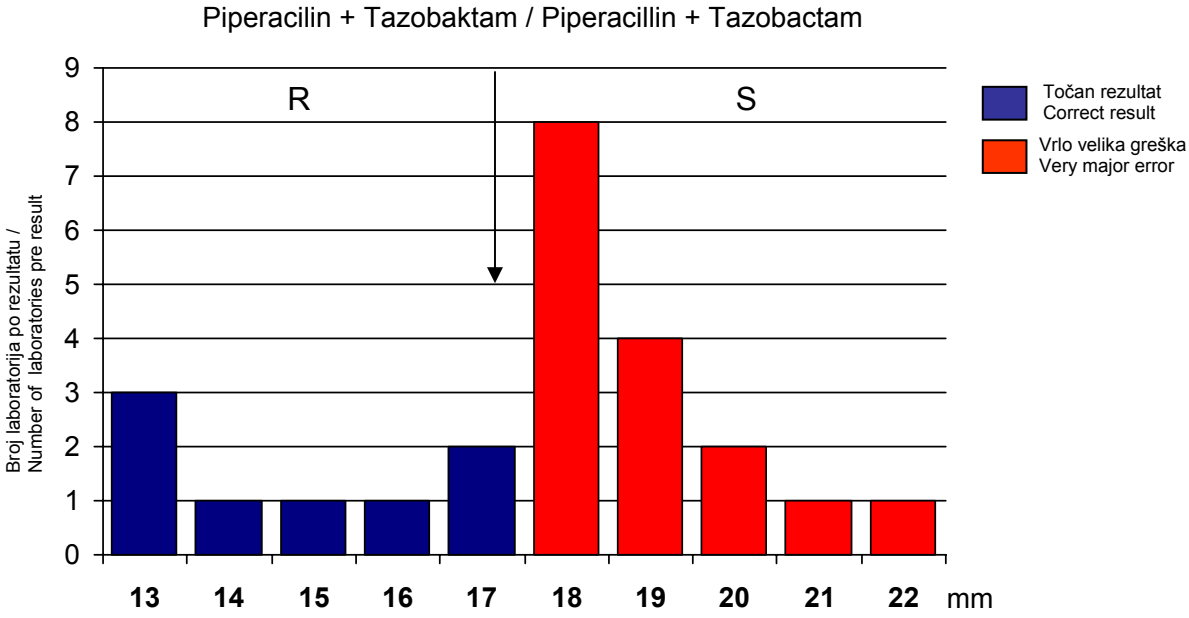
Slika-*Figure 6*.
NEQAS soj 0246: ***E.faecium*** -teikoplanin R
NEQAS strain 0246: ***E.faecium*** **-** Teicoplanin R
NEQAS: Teikoplanin/Teicoplanin MIK/MIC 8 mg/L



CLSI Teikoplanin/Teicoplanin S≥14 ; R≤10

(EUCAST Teikoplanin/Teicoplanin S≥16 ; R<16)

Slika-*Figure 7.*
NEQAS soj 0247: ***P.aeruginosa*** - piperacilin-tazobaktam R
NEQAS strain 0247: ***P.aeruginosa*** **-** Piperacillin-tazobactam R
NEQAS: Piperacilin-tazobaktam/ Piperacillin-tazobactam MIK/MIC 32 mg/L



CLSI Piperacilin + Tazobaktam S≥18 ; R≤17

(EUCAST Piperacilin + Tazobaktam S≥19 ; R<19)