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 ZDRAVLJA
UNIVERSITY HOSPITAL FOR INFECTIOUS DISEASES "DR. F. MIHALJEVIĆ"
REFERENCE CENTER FOR ANTIBIOTIC RESISTANCE SURVEILLANCE, CROATIAN MINISTRY OF HEALTH

Osjetljivost i rezistencija bakterija na antibiotike u Republici Hrvatskoj u 2011.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

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SADRŽAJ

PREDGOVOR:

Praćenje rezistencije bakterija na antibiotike ima u Hrvatskoj dugu tradiciju i zanimljiv razvoj. 1996.g. osnovan je pri Kolegiju za javno zdravstvo Akademije medicinskih znanosti Hrvatske (AMZH) Odbor za praćenje rezistencije bakterija na antibiotike u RH koji je tada prikupljao podatke iz 17 mikrobioloških laboratorija te okupljao istaknute stručnjake iz područja kliničke mikrobiologije, infektologije i kliničke farmakologije. Danas Odbor prikuplja podatke iz više od 30 mikrobioloških laboratorija tj. pokriva više od 90% populacije Hrvatske. Visoku pouzdanost rezultata jamči ne samo masovnost uzoraka već i stalni rad na standardizaciji metodologije testiranja te intenzivnoj komunikaciji članova Odbora koja se odvija kroz mnogobrojne sastanke, tečajeve, simpozije i kongrese. Okosnicu rada Odbora čine redoviti proljetni i jesenski sastanak na kojima se dogovaraju metodološke promjene u skladu s razvojem ovog područja mikrobiologije, komentiraju kretanja rezistentnih mikroorganizama u svijetu i Hrvatskoj. Praćenje rezistencije u Hrvatskoj dodatno je unaprijeđeno osnutkom Referentnog centra Ministarstva zdravlja (MZ) za praćenje rezistencije bakterija na antibiotike pri Klinici za infektivne bolesti "Dr. F. Mihaljević" 2003.g. Laboratorij Klinike za infektivne bolesti pružio je znatnu podršku nacionalnom praćenju preuzevši zadatke redovitog provođenja vanjske kontrole testiranja osjetljivosti na antibiotike te retestiranja izolata rijetkog i neuobičajenog fenotipa. Unutar Odbora osnovana je 2003.g. i hrvatska podružnica internacionalne organizacije The Alliance for the Prudent Use of Antibiotics (APUA) što je omogućilo još bolju komunikaciju sa stručnjacima iz drugih zemalja. Zahvaljujući dobro razvijenoj mreži mikrobioloških laboratorija koji su sudjelovali u praćenju rezistencije Odbor se spremno uključio u najvažnije internacionalne programe praćenja rezistencije (European Antimicrobial Resistance Surveillance System, EARSS) i potrošnje (European Surveillance of Antimicrobial Consumption, ESAC) antibiotika od njihovog osnutka pa do prelaska u program Europskog centra za kontrolu bolesti (engl. "European Center for Disease Control", ECDC). Sudjelovanje u ova dva europska projekta je bilo od velikog značaja za Hrvatsku jer smo mogli izravno pratiti najnoviji razvoj u metodologiji testiranja osjetljivosti, praćenja rezistentnih sojeva i interveniranja u cilju smanjenja potrošnje antibiotika i suzbijanja širenja rezistencije. Nakon deset godina rada Odbora i Referentnog centra praćenje rezistencije je bilo dobro uhodano, stručna javnost je bila senzibilizirana na problem rezistencije i navikla služiti se podacima o rezistenciji u vlastitoj sredini no veliki pomak naprijed u aktivnostima kontrole širenja rezistencije donio je MATRA projekt Ministarstva zdravlja Hrvatske kojeg je financirala vlada Nizozemske kao jedan od predpristupnih programa za zemlje koje pristupaju Europskoj uniji. U tijeku projekta osnovana je pri Ministarstvu zdravlja 2006.g. Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike (ISKRA), interdisciplinarno tijelo (engl. "intersectorial coordination mechanism", ICM) koje koordinira svim aktivnostima na području kontrole širenja rezistencije. Po prvi puta su se tako povezale aktivnosti na području humane medicine, veterine, farmacije i znanosti. Unutar medicinskih aktivnosti podaci o rezistenciji i potrošnji antibiotika postali su osnova za pisanje hrvatskih nacionalnih ISKRA smjernica za uporabu antibiotika koje su razvijane na principima AGREE metodologije i veliki napori su uloženi za njihovu implementaciju u praksi. ISKRA je također koordinator promidžbenih aktivnosti i javne kampanje čime se borba za racionalizacijom uporabe antibiotika proširila izvan granica stručnih društava i obuhvatila sve građane. Hrvatska je javnu kampanju započela 2008.g. slijedeći naputke ECDC-a koji je te godine proglasio 18. studenog Europskim danom svjesnosti

o antibioticima (engl. ”European Antibiotic Awareness Day”, EAAD). Tijekom 2011.g. nastavljane su ove mnogobrojne aktivnosti koje su rezultat kontinuiranog rada i stalnog prilagođavanja rastućem spektru mehanizama rezistencije bakterija na antibiotike. Ovu godinu je tako obilježio prelazak na europske standarde interpretacije testova osjetljivosti. Do 2011.g. svi laboratoriji koji su sudjelovali u radu Odbora dogovorno su koristili američke Clinical and Laboratory Standards Institute (CLSI) standarde, no nakon objavljivanja European Committee for Antimicrobial Sensitivity Testing (EUCAST) standarada 2010.g. mreža hrvatskih laboratorija u 2011.g. spremno je prešla na nove standarde koji su više klinički orjentirani i više uzimaju u obzir farmakokinetičke i farmakodinamske studije. Od samog osnutka Odbora, a pogotovo nakon osnutka Referentnog centra osiguranje standardizacije u radu laboratorija bilo je jedno od prioriteta među aktivnostima vezanim uz praćenje rezistencije. Kako je donošenje standarada dinamičan proces i unutar EUCAST-a na proljetnom sastanku Odbora 2011.g. odlučeno je brigu o standardizaciji rada i formalno ojačati osnutkom Povjerenstva za metodologiju testiranja osjetljivosti na antibiotike unutar Odbora za praćenje rezistencije na antibiotike. Spektar aktivnosti od osiguranja kvalitete podataka o rezistenciji i potrošnji antibiotika pa do konačnog cilja racionalizacije potrošnje antibiotika i očuvanja djelotvornosti ovih dragocjenih ljekova širok je i uključuje veliko zalaganje mnogih stručnjaka. Putokaz za optimaliziranje naših aktivnosti nalazimo u okrilju raznih matičnih europskih organizacija, prvenstveno Europskog društva kliničkih mikrobiologa i infektologa (engl. European Society for Clinical Microbiology and Infectious Diseases, ESCMID) i ECDC-a, no stvarna provedba ipak ovisi o svima nama koji antibiotike testiramo, propisujemo i konzumiramo.

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

PREFACE:

Antibiotic resistance surveillance in Croatia has a long and interesting history. In 1996 the Croatian Committee for Antibiotic Resistance Surveillance was founded at the Public Health Collegium of the Croatian Academy of Medical Sciences (CAMS). The Committee started with collecting data from 17 microbiology laboratories and it gathered distinguished experts in the field of clinical microbiology, infectious diseases and clinical pharmacology. Today the Committee collects data from more than 30 laboratories covering >90% of Croatian population. High reliability of published results is guaranteed not only by the large numbers of isolates but also by the high level of interlaboratory standardization that is achieved through regular communication at numerous meetings, courses, symposia and congresses. At the regular spring and autumn Committee meetings methodology standards are updated and recent data on the spread of resistant organisms in Croatia and internationally are discussed. Antibiotic resistance surveillance was further strengthened by the establishment of the Croatian Ministry of Health Reference Centre for Antibiotic Resistance in 2003 at the University Hospital for Infectious Diseases "Dr. F. Mihaljević". The microbiology laboratory at the University Hospital for Infectious Diseases provides important support to the national surveillance network by conducting regular external quality control and by retesting isolates of rare and unusual phenotypes. In 2003 the Committee founded the Croatian Chapter of the Alliance for the Prudent Use of Antibiotics (APUA) which enhanced international communication with experts from other countries. Thanks to the well established antibiotic resistance surveillance network of microbiology laboratories Croatia readily joined the European Antimicrobial Resistance Surveillance System (EARSS) and the European Surveillance of Antimicrobial Consumption (ESAC) and remained their member until their transition to the European Center for Disease Control (ECDC) networks. Participation in these two projects was of great significance for Croatia as we were directly involved in the development of sensitivity testing methodology, resistance surveillance and interventions aiming to reduce antibiotic resistance rates. After ten years of Committee's and Reference Center's activities antibiotic resistance surveillance network was well established, professional society was well informed about the problem of resistance and it became customary to make use of local resistance data. The next big step forward was through the MATRA pre-accession project of the Croatian Ministry of Health that was financed by the Dutch government. As one of the outcomes of the project a Croatian intersectorial coordination mechanism (ICM), the so called „Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike" (ISKRA) was founded at the Croatian Ministry of Health. ISKRA coordinates all the activities in the field of antibiotic resistance control and for the first time activities in the field of human medicine, veterinary medicine, pharmacy and science are linked. In the field of human medicine antibiotic resistance and antibiotic consumption data became the basis for the development of ISKRA national guidelines on the prudent use of antibiotics. These guidelines are developed using the AGREE methodology and lots of effort was used in the implementation of these guidelines. ISKRA also coordinates national public campaign activities that started in 2008 following the ECDC recommendations and proclamation of the European Antibiotic Awareness Day (EAAD) on 18 November. During 2011 all these activities were continued as a result of continuous work and our constant efforts to adapt to the growing spectrum of antibiotic resistance mechanisms. The year 2011 was marked as a year when we switched to the European Committee for Antimicrobial Sensitivity Testing (EUCAST) antibiotic sensitivity testing standards. Until 2011 all the laboratories that took part in the surveillance were obliged to use American Clinical and Laboratory Standards Institute (CLSI) standards but after EUCAST published standards for disk diffusion in 2010 the Croatian antibiotic resistance surveillance

network readily adopted European standards as official methodology in sensitivity testing as of January 2011. Ever since the Croatian Committee was founded and especially after Reference Center was established interlaboratory standardization was one of the priorities among the activities related to antibiotic resistance control. As setting up methodology for sensitivity testing is a dynamic process within EUCAST as well, the Committee decided at the 2011 spring meeting to found a Subcommittee for Antibiotic Sensitivity Testing and thus to formally strengthen care about accurate and standardized sensitivity testing methodology. A spectrum of activities, which range from warranting the quality of data on resistance and antibiotic consumption to achieving a final goal of rationalization in antibiotic use and preservation of these valuable drugs, is broad and involves high input from many experts. In optimizing our activities we follow the guidelines of our European mother institutions, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and ECDC in the first place, but implementation of improvements is mostly dependant on us alone, all of us who test, prescribe and consume antibiotics.

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

POGLAVLJE/CHAPTER 1.

REZISTENCIJA BAKTERIJSKIH IZOLATA U 2011. GODINI
ANTIBIOTIC RESISTANCE IN 2011

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UVOD:

Podaci Odbora za praćenje rezistencije bakterija na antibiotike Akademije medicinskih znanosti Hrvatske (AMZH) i Referentnog centra za praćenje rezistencije bakterija na antibiotike Ministarstva zdravlja (MZ) pri Klinici za infektivne bolesti "Dr. Fran Mihaljević" osnova su za empirijsku terapiju infektivnih bolesti u Hrvatskoj. Dok se za mnoge izvanbolničke infekcije mogu primjenjivati zajedničke nacionalne smjernice, za većinu bolničkih infekcija potrebna je lokalna modifikacija prema lokalnim stopama rezistencije. U okviru nacionalnog praćenja rezistencije veliku ulogu ima slanje izolata rijetkog i neuobičajenog fenotipa u referentni centar na retestiranje i daljnju karakterizaciju. Na taj način može se uočiti prva pojava rezistentnih sojeva s novim mehanizmima rezistencije od kojih neki mogu posjedovati i izraziti epidemijski potencijal ili visoku virulenciju. Jedan od velikih izazova svake mreže za praćenje podataka je osiguranje kvalitete podataka, a kad se radi o praćenju stopa rezistencije na antibiotike iznimno je važna interlaboratorijska standardizacija u izvođenju testova osjetljivosti na antibiotike. European Committee for Antimicrobial Sensitivity Testing (EUCAST) je uspio objediniti stavove različitih stručnih društava diljem Europe, što je rezultiralo donošenjem zajedničkih standarada prvo za određivanje minimalnih inhibitornih koncentracija antibiotika, a potom 2010.g. i za disk difuzijsku metodu određivanja osjetljivosti. Kako se većina testiranja osjetljivosti na antibiotike u Hrvatskoj zasniva na disk difuzijskoj metodi Hrvatska je u izradi i interpretaciji antibiograma 2011.g. službeno prešla na EUCAST standarde. U dosadašnjim publikacijama Odbora i Referentnog centra izneseni podaci su se zasnivali na američkim Clinical and Laboratory Standards Institute (CLSI) standardima, što je dogovoreno davne 1996.g. pri osnutku Odbora kao jedna od prvih mjera standardizacije rada među laboratorijima u mreži praćenja rezistencije. Iako su promjene graničnih vrijednosti u 2011. godini za neke antibiotike i mikroorganizme značajne u odnosu na prije primjenjivane vrijednosti, u suštini su manjkavosti prijašnjih graničnih vrijednosti i prije bile korigirane kroz pravila interpretativnog čitanja antibiograma. Prelaskom na EUCAST standarde u 2011.g. ne očekuju se, stoga, velike razlike u stopama rezistencije nastale ne zbog prirodnog kretanja rezistencije već zbog administrativnog mijenjanja graničnih vrijednosti. Prelazak na EUCAST standarde imat će bitan učinak samo na mali broj antibiotika i bakterija što će biti naglašeno u raspravi.

INTRODUCTION:

Data provided by 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 (MH) at the University Hospital for Infectious Diseases "Dr Fran Mihaljević" are the basis for empirical treatment of infectious diseases in Croatia. Treatment of many community acquired infections can be guided by the common national guidelines but in case of nosocomial infections therapy should be modified according to the local resistance rates. Very important part of the national resistance surveillance is recognition of isolates with unusual and rare phenotype and their sending to reference laboratory for retesting and further characterization. That way the first isolates of strains with novel resistant mechanisms can be picked up through the national resistance surveillance network which is very important as some of them may also express high epidemic potential, high virulence or both. One of the major challenges of every surveillance network is warranting data quality and in case of antibiotic resistance surveillance interlaboratory standardization in sensitivity testing is crucial. The European Committee for Antimicrobial Sensitivity Testing (EUCAST) has consolidated opinions of many national Antibiotic Sensitivity Testing Committees which resulted in unique European standards first for minimal inhibitory concentration testing and later on, in 2010 for disk diffusion testing. As the majority of sensitivity testing in Croatia is being done by disk diffusion Croatia officially switched to EUCAST standards in 2011. In the publications of the Croatian Committee for Antibiotic Resistance Surveillance and the Reference Center for Antibiotic Resistance Surveillance so far, the American Clinical and Laboratory Standards Institute (CLSI) standards were used. This was agreed upon in 1996 when the Committee was founded as the first initiative towards interlaboratory standardization. Changes in break-point concentrations for some antibiotics and some organisms are substantial when 2011 and earlier years are compared but the earlier break-points were corrected through interpretative reading of the antibiogram. Therefore, we do not expect that the administrative change of break-point concentrations will substantially influence resistance rates in 2011. The switch to EUCAST standards has a significant impact only on a small number of drug bug combinations and this will be stressed in the discussion part.

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 31.12.2011.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 31.12.2011. Podatke za 2011.g. podnjelo je 39 centara (popis u legendi za tablice), što obuhvaća >90% populacije u Hrvatskoj.

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

a. u ispitivanom razdoblju svi izolati određene bakterijske vrste testiraju se na sve antibiotike predviđene za tu vrstu. Od 2010.g. na snazi je dogovor da iznimka za ovo pravilo bude testiranje osjetljivosti *P. aeruginosa* i *A. baumannii* na kolistin. Zbog skupoće testiranja 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 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. enterobakterije rezistentne na karbapeneme

Tijekom 2011.g. po prvi puta primjenjeno je testiranje i interpretacija nalaza u skladu s EUCAST standardima (verzija 1.3). U testiranju većina laboratorija koristi disk difuzijsku metodu, a određivanje minimalnih inhibitornih koncentracija (MIK) se koristi za određivanje osjetljivosti na penicilin kod pneumokoka smanjene osjetljivosti na penicilin, za određivanje osjetljivosti stafilokoka na glikopeptide te pseudomonasa i acinetobaktera na kolistin.

Preporuka Odbora je da se izolati *A. baumanii* i *P. aeruginosa* rezistentni na jedan, ali ne i oba karbapenema retestiraju određujući MIK za imipenem i meropenem. Minimalne inhibitorne koncentracije su određivane E-test metodom.

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

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

Hrvatska je 2001.g. započela prikupljanje i analizu invazivnih izolata (izolati iz krvi i likvora) u sklopu European Antimicrobial Resistance Surveillance System (EARSS) projekta. Kad je 2010.g. EARSS 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 međunarodnu suradnju s mrežom ECDC-a, koja, međutim, nije uključivala objavljivanje rezultata za zemlje izvan Europske unije. Hrvatska je nastavila prikupljati podatke o invazivnim izolatima vrsta *S. pneumoniae*, *S. aureus, E. faecalis, E. faecium, E. coli*, *K. pneumoniae* i *P. aeruginosa*. U svrhu detaljnije analize invazivni izolati enterokoka, stafilokoka i *P. aeruginosa* šalju se 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.

Hrvatska je 2001.g. počela pratiti potrošnju antibiotika izraženu u definiranim dnevnim dozama na 1000 stanovnika dnevno (DDD/TID) u sklopu European Surveillance of Antimicrobial Consumption (ESAC) projekta. Podaci o potrošnji dobivaju se preko veledrogerija i prikazuju odvojeno za bolničku i izvanbolničku potrošnju. Od 2006.g. u sklopu APUA Croatia inicijative i u skladu s naputcima ISKRA-e Odbor prati bolničku potrošnju antibiotika i preko podataka dobivenih iz bolničkih ljekarni. Prelaskom ESAC-a u ESAC-Net ECDC-a sredinom 2011.g. Hrvatska, kao zemlja izvan Europske unije, nije više sudjelovala u prikupljanju europskih podataka, ali je nastavila prikupljati podatke potrošnje antibiotika u Hrvatskoj po načelima ESAC metodologije. Izvješće o potrošnji antibiotika nalazi se u posebnom poglavlju ove publikacije.

Tijekom 2009.g. u okviru Odbora prikupljani su izolati *Acinetobacter baumannii* radi detaljnije analize mehanizama rezistencije i klonalne rasprostranjenosti. Rezultati ove studije sažeto su prikazani u posebnom poglavlju ove publikacije.

MATERIALS AND METHODS:

Global surveillance

Global antibiotic resistance surveillance includes all clinical isolates of designated bacterial species isolated from 1 October till 31 December, 2011. Exceptionally, data on group A streptococci, salmonellae, shigellae and anaerobic bacteria are collected throughout the year due to the small number of isolates. In 2011 a total of 39 centers took part in antibiotic resistance surveillance (names of the centers are listed in the legend to the tables) which makes a catchment population of >90%.

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

a. during the study period all isolates of a given species are to be tested against all the designated antibiotics. Since 2010 the exception from this rule is applied for *P. aeruginosa* 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 and acinetobacter.

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 and / 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

In 2011 EUCAST standards (version 1.3) was introduced as official methodology for sensitivity testing. Disk diffusion method is the most widely used sensitivity testing method in Croatia and minimal inhibitory concentration (MIC) testing is used for detection of penicillin resistance in penicillin non-susceptible pneumococci, glycopeptide resistance in staphylococci and colistin resistance in pseudomonas and acinetobacter.

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. MIC testing was done by E-test.

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

Resistance in *Mycobacterium tuberculosis* is described in separate chapter of this publication. The same as every year sensitivity data on *M. tuberculosis* were processed in the National Laboratory for Tuberculosis at the Croatian Public Health Institute.

In 2001 Croatia started to collect and analyze invasive isolates (from blood and cerebrospinal fluid) in the framework of the European Antimicrobial Resistance Surveillance System (EARSS) project. When EARSS was transferred to EARS-Net, a part of The European Surveillance System (Tessy), a global European Center for Disease Control (ECDC) surveillance network, Croatia continued collaboration with ECDC Tessy program but this did not include reporting of resistance rates outside the European Union region. Nevertheless, Croatia continued collecting data on invasive isolates of *S .pneumoniae*, *S. aureus, E. faecalis, E .faecium, E. coli*, *K. pneumoniae* and *P. aeruginosa*. For the purpose of more detailed analysis 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.

Croatia started to analyze antibiotic consumption data expressed as defined daily doses per thousand inhabitants daily (DDD/TID) in 2001 in the framework of the European Surveillance of Antimicrobial Consumption (ESAC) project. Antibiotic consumption data are based on wholesales data and hospital and ambulatory care data are reported separately. Since 2006, as a part of the APUA Croatia initiative and in line with ISKRA requirements, the Committee also analyses consumption data obtained from hospital pharmacies. After ESAC transition to the ECDC ESAC-Net in 2011 only the Member States of the European Union were invited to participate in European data collection but, nevertheless Croatia continued data collection and analysis based on ESAC methodology. Antibiotic consumption data are reported in a separate chapter of this publication.

In 2009 collection of *Acinetobacter baumannii* isolates was one of the Committee's activities aiming at more detailed analysis of resistance mechanisms and clonal spread of these isolates. Concise report on this study is a separate part of this publication.

REZULTATI

U praćenju rezistencije u 2011.g. sudjelovalo je 39 centara u Hrvatskoj. Prosječni rezultati za Hrvatsku i rezultati za pojedinačne centre prikazani su u tablicama i grafovima u daljnjem tekstu. Rezultati laboratorija koji su prijavili manje od 30 izolata pojedine bakterijske vrste smatraju se nepouzdanim podacima za taj centar, ali su uvršteni u tablice i uključeni su u zbirne rezultate za RH. Podaci o izolatima malo vjerojatnog fenotipa koji nisu potvrđeni u jednom od centralnih laboratorija označeni su zvjezdicom kao nepotvrđeni i ne smatraju se važećima.

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

- GS ZZJZ je za *A. baumannii* prikazao rezultate za cijelu godinu
- KA OB i KT KZKB su za sve vrste prikazali rezultate za cijelu godinu
- PU ZZJZ je za *H. influenzae* i *A. baumannii* prikazao rezultate za cijelu godinu
- PŽ ZZJZ je za streptokok grupe A prikazao rezultate za razdoblje 1.10. do 31.12.2011.
- SB ZZJZ, ZG KBM i ZG KBSD su za *S. pneumoniae* i *H. infulenzae* prikazali rezultate za cijelu godinu

Šest laboratorija je prijavilo izolaciju šigela u 2011.g.: ČK ZZJZ *Sh. sonnei* (2), *Sh. flexneri* (1); IG ZZJZZŽ *Sh. sonnei* (1); RI NZZJZ *Sh. sonnei* (1); ZD ZZJZ *Sh. sonnei* (1); ST ZZJZ *Sh. sonnei* (1); ZG KIB *Sh. sonnei* (5), *Sh. flexneri* (3). Ukupno je tijekom 2011.g. izolirano 15 šigela.

U 2011.g. ukupno je obrađeno 361 anaerobnih bakterija, 164 gram-pozitivnih i 197 gram-negativnih anaeroba iz 13 centara: ČK ZZJZ gram-pozitivni anaerobi (11), gram-negativni anaerobi (18); KL BPB gram-negativni anaerobi (5); OS ZZJZ gram-pozitivni anaerobi (4), gram-negativni anaerobi (11); SB ZZJZ gram-pozitivni anaerobi (2), gram-negativni anaerobi (3); ŠI ZZJZ gram-pozitivni anaerobi (5), gram-negativni anaerobi (13); VK ZZJZ gram-pozitivni anaerobi (1), gram-negativni anaerobi (4); VT ZZJZ gram-negativni anaerobi (23); VŽ ZZJZ gram-pozitivni anaerobi (34), gram-negativni anaerobi (24); ZD ZZJZ gram-pozitivni anaerobi (14), gram-negativni anaerobi (36); ZG KBC gram-pozitivni anaerobi (11), gram-negativni anaerobi (31); ZG KBM gram-pozitivni anaerobi (7), gram-negativni anaerobi (7); ZG KIB gram-pozitivni anaerobi (12), gram-negativni anaerobi (10); ZG KDB gram-pozitivni anaerobi (40), gram-negativni anaerobi (35).

RESULTS

Thirty-nine centers took part in antibiotic resistance surveillance in Croatia in 2011. Average data for Croatia and results for individual laboratories are presented in tables and figures further in the text. Results of the laboratories that reported less than 30 isolates of a single bacterial species were included in tables as to add to the total number for Croatia, but were flagged as not reliable resistance rate data for that individual centre. Where isolates of less probable phenotype were reported without being sent to a central laboratory for retesting, data were flagged as not retested centrally and these data are not considered to be 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:

- GS ZZJZ reported *A. baumannii* data for the whole year
- KA OB and KT KZKB reported data for the whole year for all species
- PU ZZJZ reported *H. influenzae* and *A. baumannii* data for the whole year
- PŽ ZZJZ reported data for group A streptococcus for the period 1.10. till 31.12.2011.
- SB ZZJZ, ZG KBM and ZG KBSD reported *S. pneumoniae* and *H. infulenzae* data for the whole year

Six laboratories reported isolation of shigella in 2011: ČK ZZJZ *Sh. sonnei* (2), *Sh. flexneri* (1); IG ZZJZZŽ *Sh. sonnei* (1); RI NZZJZ *Sh. sonnei* (1); ZD ZZJZ *Sh. sonnei* (1); ST ZZJZ *Sh. sonnei* (1); ZG KIB *Sh. sonnei* (5), *Sh. flexneri* (3). Altogether 15 shigella isolates were reported in 2011.

Altogether 361 anaerobic bacteria were reported in 2011. Out of these 164 were gram-positive and 197 were gram-negative. They were reported from 13 centers: ČK ZZJZ gram-positive anaerobs (11), gram-negative anaerobs (18); KL BPB gram-negative anaerobs (5); OS ZZJZ gram-pozitive anaerobs (4), gram-negative anaerobs (11); SB ZZJZ gram-positive anaerobs (2), gram-negative anaerobs (3); ŠI ZZJZ gram-positive anaerobs (5), gram-negative anaerobs (13); VK ZZJZ gram-positive anaerobs (1), gram-negative anaerobs (4); VT ZZJZ gram-negative anaerobs (23); VŽ ZZJZ gram-positive anaerobs (34), gram-negative anaerobs (24); ZD ZZJZ gram-positive anaerobs (14), gram-negative anaerobs (36); ZG KBC gram-positive anaerobs (11), gram-negative anaerobs (31); ZG KBM gram-positive anaerobs (7), gram-negative anaerobs (7); ZG KIB gram-positive anaerobs (12), gram-negative anaerobs (10); ZG KDB gram-positive anaerobs (40), gram-negative anaerobs (35).

DISKUSIJA

Penicilin je prvi lijek izbora u liječenju infekcija uzrokovanih beta-hemolitičkim streptokokom grupe A (BHS-A) i rezistencija ovog uzročnika na penicillin još nije opisana. Makrolidi se primjenjuju u pacijenata preosjetljivih na penicillin, a klindamicin se preporuča pri rekurirajućim streptokoknim grloboljama i kožnim infekcijama. Otpornost BHS-A na makrolide u 2011.g. (7%) i klindamicin (4%) je neznatno niža negoli prethodne godine (8% i 5%) no ukazuje na trend smanjenja rezistencije od 2008.g. kad je rezistencija na ove antibiotike iznosila 13% i 7%. Otpornost na klindamicin je i u 2011.g. bila pretežno konstitutivna (3%), a rjeđe inducibilna (1%).

S obzirom na veliku učestalost kolonizacije sluznice nazofarinksa pneumokokima, hemofilusima i morakselama, naročito u dječjoj dobi, nalaz ovih bakterija u brisu nazofarinksa ne upućuje nužno na njihovu etiološku ulogu u infekciji gornjih dišnih puteva. Bakteriološka obrada brisa nazofarinksa je, stoga, pretraga niske specifičnosti i osjetljivosti i ne preporučuje se u rutinskoj dijagnostici. U Hrvatskoj je, međutim, još uvijek uobičajeno uzimati briseve nazofarinksa te najveći broj izolata pneumokoka i hemofilusa prijavljenih kroz masovno praćenje ima upitno kliničko značenje, ali zbog velikog broja izolata pruža dobar epidemiološki podatak o kretanju rezistencije među bakterijama koje koloniziraju gornji dišni sustav. Rezistencija na antibiotike u invazivnih izolata pneumokoka je obrađena u drugom poglavlju ove publikacije. Zbog povoljnije farmakokinetike i farmakodinamike od penicilina te dobre učinkovitosti na pneumokoke i *Haemophilus influenzae* u većini međunarodnih smjernica amoksicilin predstavlja prvi lijek izbora u liječenju bakterijske upale srednjeg uha. S obzirom da se testiranje osjetljivosti pneumokoka na bilo koji beta-laktamski antibiotik moralo provoditi određivanjem minimalnih inhibitornih koncentracija (MIK) testiranje beta-laktamskih antibiotika se do 2011.g. ograničavalo na penicilin uz sugeriranje da amoksicilin dobro djeluje na sve penicillin osjetljive i umjereno rezistentne izolate. Prema EUCAST standardima moguće je disk difuzijom testirati osjetljivost pneumokoka na ampicilin te od 2011.g. po prvi puta u izvješće uključujemo podatke i za ampicilin. Zadnji podaci o osjetljivosti pneumokoka na ampicilin na razini Hrvatske dostupni su iz studije koja je obuhvatila 585 izolata pneumokoka iz 22 centra u Hrvatskoj (AAC, 2002;46:2671). U toj studiji svi izolati osjetljivi i umjereno rezistentni na penicillin ($MIK_{penicilina} \leq 0.008 - 1.0$ mg/L) bili su osjetljivi na ampicilin ($MIK_{ampicilina} \leq 2.0$ mg/L) prema CLSI standardima uključujući i verziju CLSI standarda iz 2009.g. (M100 – S19) koja je bila zadnja službeno korištena verzija CLSI standarada prije prelaska na EUCAST. U skladu s tim te činjenicom da se MIK-ovi penicilina i ampicilina rijetko razlikuju više od jednog razrjeđenja očekivali smo da rezistencija na ampicilin neće prelaziti stope visoke rezistencije na penicillin (3%), no prema prvim rezultatima testiranja otpornosti na ampicilin disk difuzijskom metodom ona iznosi 16%, što je puno više od očekivane. S obzirom na ovakve rezultate trebat će s EUCAST-om detaljnije raspraviti na koje doziranje amoksicilina u djece se ova interpretacija odnosi. Za razliku od ampicilina, stopa neosjetljivosti na penicillin se nije značajnije promijenila prelaskom na EUCAST. To nismo niti očekivali s obzirom da se CLSI granične koncentracije korištene u 2010.g. (≤ 0.06 osjetljivo, ≥ 2.0 rezistentno) samo neznatno razlikuju od EUCAST graničnih koncentracija korištenih u 2011.g. (≤ 0.06 osjetljivo, > 2.0 rezistentno). Prema podacima za

2011.g. smanjena osjetljivost pneumokoka na penicillin iznosi 29% (26% umjerena rezistencija i 3% visoka rezistencija), što je u skladu s podacima prethodnih godina (20% umjerena i 4% visoka rezistencija u 2010.g., 24% umjerena i 5% visoka rezistencija u 2009.g.). I raspon MIK-ova ukazuje da ni u jednom centru MIK 90 ne prelazi 2.0 mg/L te da je ≥ 90% pneumokoka dostupno terapiji penicilinom u slučaju da se radi o pneumoniji. Točno doziranje penicilina u terapiji pneumonije ovisi o MIK penicilina i detaljno je opisano u EUCAST standardima. Rezistencija pneumokoka na druge antibiotike se ne razlikuje značajnije u odnosu na prethodnu godinu, osim što se rezistencija na ko-trimoksazol sa 43% spustila na 35%. Malo je vjerojatno da je na taj pad rezistencije utjecao prelazak na EUCAST standard s obzirom da se CLSI i EUCAST granična zona ralikuju u samo jednom milimetru.

Otpornost *H. influenzae* na ampicilin se zadnjih godina kretala oko 10% (9% u 2006.g., 11% u 2007.g., 8% u 2008.g., 10% u 2009.g., 11% u 2010.g). Prema EUCAST istraživanjima disk ampicilina od 10µg ne detektira dovoljno dobro rezistentne sojeve, pogotovo ne one koji u podlozi rezistencije na ampicilin imaju mutaciju PBP molekula (tzv. "beta-lactamase negative ampicillin resistant", BLNAR sojevi). EUCAST je, stoga, uveo disk od 2µg koji pouzdanije detektira rezistentne sojeve, smanjuje mogućnost neprepoznavanja rezistentnih izolata, ali istovremeno dozvoljava mogućnost precjenjivanja rezistencije kad se rezultati disk difuzije uspoređuju s minimalnim inhibitornim koncentracijama. U tijeku u 2011.g. rezistencija hemofilusa na ampicilin (13%) je neznatno povećana u odnosu na prethodnu godinu (11%) što se može pripisati i primjeni osjetljivijeg diska. Do puno veće promjene nakon prelaska na EUCAST došlo je kod interpretacije osjetljivosti *H. influenzae* na cefuroksim i azitromicin. Do ove godine *in vitro* nalazi su upućivali na osjetljivost od 100% i 99% na ove antibiotike dok se po EUCAST standardima divlji tipovi *H. influenzae* smatraju intermedijarno osjetljivima na azitromicin i oralni cefuroksim. Zbog niske stečene rezistencije, ali prirodno prisutne umjerene rezistencije *H. influenzae* na azitromicin, ovaj antibiotik je u 2011.g. isključen iz palete antibiotika za *H. influenzae*. Također, po prvi puta je razdvojena interpretacija osjetljivosti na oralni i parenteralni cefuroksim, pri čemu izolati mogu biti potpuno osjetljivi samo na parenteralni cefuroksim. Osjetljivost na parenteralni cefuroksim u 2011.g. iznosi 93%, umjerena rezistencija 5%, a rezistencija 2%.

Trend smanjenja stope meticilin rezistentnih *S. aureus* (MRSA) (25% u 2007.g., 26% u 2008.g., 21% u 2009.g., 16% u 2010.g.) nastavlja se i u 2011.g. u kojoj udio ovih sojeva iznosi 14%. Među MRSA sojevima uočen je manji pad rezistencije na makrolide, klindamicin i gentamicin što bi moglo ukazivati na češću pojavu izvanbolničkih MRSA sojeva. Rezistencija na glikopeptide (teikoplanin) se do ove godine testirala disk difuzijskom metodom, no od 2011.g. usvojeno je da se osjetljivost na glikopeptide u stafilokoka može testirati jedino određivanjem MIK-ova. Po prvi puta tako na razini Hrvatske imamo podatke o rasponu MIK-ova vankomicina kod MRSA sojeva. Vankomicin rezistentni sojevi nisu još uočeni, ali je uočen visok udio sojeva s MIK vrijednostima 2.0 mg/L (19%). Mnogi stručnjaci savjetuju primjenu alternativnih antibiotika (linezolida, daptomicina) kod teških infekcija izazvanih sojevima MRSA koji imaju MIK vankomicina >1.0 mg/L. Od 2011.g. usvojeno je jedinstveno testiranje osjetljivosti stafilokoka na mupirocin diskom od 200 µg, što omogučuje procjenjivanje učestalosti i visoko i umjereno rezistentnih sojeva. Podaci o rezistenciji na mupirocin ne razlikuju se bitno od prošlogodišnjih osim što je uvedena kategorija umjereno rezistentnih izolata, a

izostavljena klinički upitna interpretacija niske rezistencije detektirane preko diska od 5 µg. Po prvi puta u testiranje osjetljivosti stafilokoka uveden je tigeciklin, novi antibiotik širokog spektra koji osim učinka na gram-negativne bakterije pokazuje i djelotvornost na stafilokoke, uključujući i MRSA sojeve.

Osjetljivost enterokoka je podjednaka kao prethodne godine, a vankomicin rezistentni *E. faecium* (VRE) sojevi su i nadalje rijetki.

U 1.3 verziji EUCAST standard divlji tipovi enterobakterija se smatraju ili osjetljivima ili intermedijarnim na ampicilin i njegove kombinacije s inhibitorima. Na sastanku Odbora za praćenje rezistencije odlučeno je da će se divlji tipovi smatrati osjetljivima. U ni jednom slučaju EUCAST ne pruža kategoriju između ove dvije kategorije jer se smatra da takva kategorija ne korelira s kliničkim ishodom. Intermedijarna kategorija, međutim, ima i značenje pufer zone za izolate s MIK-ovima blizu graničnih koncentracija, što će nam u novim standardima nedostajati, posebno za ko-amoksiklav. Očekivano stope rezistencije enterobakterija na ove antibiotike u 2011.g. odgovaraju prijašnjim stopama neosjetljivih sojeva (intermedijarnih i rezistentnih sojeva zajedno). Usprkos promjeni diska za testiranje piperacilin/tazobaktama nije došlo do značajnijih promjena u stopama osjetljivosti enterobakterija na ovaj antibiotik.

U europskoj stručnoj javnosti često je najavljivano da će uvođenje strožih graničnih koncentracija (engl. „break-point concentrations") za cefalosporine dovesti do povećanja izdavanja nalaza *Escherichia coli* i *Klebsiella pneumoniae* izolata rezistentnih na te antibiotike, no u Hrvatskoj to nismo očekivali. Tijekom zadnjeg desetljeća mehanizam rezistencije na cefalosporine III. generacije u *E. coli* i *K. pneumoniae* je dominantno bio posredovan proizvodnjom beta-laktamaza proširenog spektra (engl. „extended spectrum beta-lactamases", ESBL), a od 1998.g. svi su hrvatski laboratoriji usvojili rutinsko testiranje na prisutnost ESBL metodom dvostrukog diska. Sukladno CLSI preporukama, kojih smo se do 2011.g. pridržavali, svim ESBL izolatima možebitna *in vitro* osjetljivost na bilo koji od penicilina i cefalosporina (osim kombinacije s inhibitorima) prepravljala se u rezistenciju i kao takva izdavala. Redovita vanjska kontrola tijekom prošlog desetljeća pokazivala je da su takvo testiranje i interpretaciju nalaza usvojili svi hrvatski laboratoriji. Oštrije EUCAST granične koncentracije više koreliraju s kliničkim učinkom beta-laktamskih antibiotika, a ujedno i prepoznaju većinu ESBL sojeva (one s klinički značajnom razinom proizvodnje ESBL) kao rezistentne te ispravljanje *in vitro* nalaza više nije potrebno. Prema prvim podacima dobivenim uporabom EUCAST standarada očito je da su obje metode dovodile do sličnih rezultata. U malom broju izolata proizvodnja ESBL, ipak, ne dovodi do klinički značajne rezistencije na sve cefalosporine te se od 2011.g. počinju uočavati manje razlike u stopama rezistencije na cefalosporine. U *E.coli* rezistencija na cefiksim i ceftriakson je identična prošlogodišnjim stopama (5%), a rezistencija na ceftazidim (4%), cefepim i ceftibuten (3%) je nešto niža. Kod *K. pneumoniae*, stope rezistencije na ceftazidim i ceftriakson su u porastu što je vjerojatno manje posljedica novih graničnih koncentracija već više posljedica stvarnog povećanja sojeva koji proizvode ESBL.

Iako je dominantan mehanizam rezistencije na cefalosporine III. generacije u *E.coli* i *K. pneumoniae* proizvodnja ESBL, u zadnje vrijeme uočava se i porast plazmidnih ampC beta-laktamaza. Sojevi *E. coli* i *K. pneumoniae* koji proizvode plazmidne

ampC beta-laktamaze su u Hrvatskoj predmet ciljanog praćenja i slanja suspektnih izolata Referentnom centru za praćenje rezistencije već više od 10 godina. Prvi put su takvi sojevi opisani 2003.g. i od tada su se godinama javljali sporadično s incidencijom 0 – 8 izolata godišnje. Od 2009.g. počeli su se, međutim, javljati s većom učestalošću (20 *E. coli* i 5 *K. pneumoniae* izolata), a u 2011.g. detektirano je 8 *K. pneumoniae* i čak 50 *E.coli* izolata koji proizvode ampC beta-laktamaze.

U *E. coli* rezistencija na kinolone i ko-trimoksazol je identična prošlogodišnjim vrijednostima, a ni rezistencija na aminoglikozide i nitrofurantoin se, usprkos promjeni koncentracije diskova, nije značajnije promijenila. Rezistencija klebsijela na kinolone je u blagom porastu, a čini se da je promjena koncentracije diska netilmicina imala kod klebsijela veće značenje jer je u 2011.g. registrirana rezistencija od 21% što je znatno više od prošlogodišnje vrijednosti (8%) i približava se vrijednostima gentamicina.

Otpornost *P. mirabilis* na antibiotike se nije značajnije promijenila u odnosu na prethodnu godinu, a u grupi *Enterobacter* spp*., Serratia* spp*., Citrobacter* spp. rezistencija na III. generaciju cefalosporina je u porastu i više izražena kod ceftriaksona i ceftazidima, negoli ostalih cefalosporina III. generacije.

Enterobakterije neosjetljive na karbapeneme su, također, predmet istraživanja u Hrvatskoj već više od 10 godina. Prema rezultatima retestiranja ovih izolata u Referentnom centru za praćenje rezistencije, smanjena osjetljivost na karbapeneme je još uvijek dominantno posljedica kombinacije smanjene propusnosti stjenke i hiperprodukcije ESBL ili ampC beta-laktamaza i najčešće je ograničena na smanjenu osjetljivost na ertapenem. U 2011.g. potvrđena je proizvodnja karbapenemaza u 13 enterobakterija; VIM u sedam izolata (4 *K. pneumoniae* i 3 *Enterobacter* spp.), NDM-1 u četiri izolata (1 Citrobacter diversus i 3 *K. pneumoniae*) te po prvi puta KPC-2 u dva izolata *K. pneumoniae*. Već više godina s posebnom strepnjom iščekujemo pojavu prvih KPC *K. pneumoniae* izolata s obzirom da je poznat veliki epidemijski potencijal ovakvih sojeva, poglavito ST258 klona. Za sada prva dva izolata nisu bila epidemijski povezana.

Kod *P. aeruginosa* uočena je veća otpornosti na piperacilin/tazobaktam (12%) negoli prethodne godine (7%) što je vjerojatno dijelom posljedica i oštrijih graničnih koncentracija postavljenih od strane EUCAST-a. Granične koncentracije za ceftazidim i karbapeneme se nisu bitnije mijenjale te je lagano povećanje rezistencije u 2011.g. vjerojatno posljedica širenja rezistentnih sojeva. Na podatke o osjetljivosti na kolistin utječe činjenica da je dozvoljeno testirati osjetljivost na kolistin samo u izolata otpornih na karbapeneme što odstupa od pravila da se svi izolati u razdoblju praćenja testiraju na sve antibiotike. Podaci nam, ipak, govore da su izolati rezistentni na kolistin u Hrvatskoj još uvijek vrlo rijetki.

Promjenom graničnih vrijednosti za karbapeneme većina intermedijarno osjetljivih izolata *Acinetobacter baumanii* prešla je u kategoriju rezistentnih, a za očekivati je da će dio osjetljivih izolata preći u kategoriju intermedijarnih. U 2011.g. evidentiran je mali postotak intermedijarnih izolata, a mogućnost da je do porasta rezistencije na karbapeneme u 2011.g. došlo zbog prelaska intermedijarnih izolata u rezistentne ne objašnjava porast rezistencije na 64% (u 2010.g. registrirano je 34% rezistentnih i 11% intermedijarnih izolata). Prema tome zaključujemo da je širenje

multiplorezistentnog *Acinetobacter baumanii* u daljnjem porastu i još uvijek predstavlja vodeći problem rezistencije u Hrvatskoj. Izolati rezistentni na kolistin nisu registrirani.

Salmonele pokazuju visoke stope osjetljivosti na sve antibiotike osim ampicilina, na koji rezistencija iznosi 10%, slično prošlogodišnjim rezultatima (11%). Iako su registrirani pojedinačni izolati salmonela rezistentni na ciprofloksacin, stopa osjetljivosti na ciprofloksacin u Hrvatskoj iznosi 100%. Prema EUCAST standardima, nalidiksična kiselina je nepouzdan predskazatelj niske rezistencije na kinolone, jer ne registrira nisku plazmidsku rezistenciju. Imajući to u vidu, Odbor za praćenje rezistencije je donio odluku da se ipak nastavi s testiranjem osjetljivosti na nalidiksičnu kiselinu jer time dobivamo uvid u početne kromosomske mutacije. Odbor je također izdao naputak da se kod invazivnih izolata svakako odrede minimalne inhibitorne koncentracije ciprofloksacina kako bi se kod sistemnih infekcija prepoznala i eventualna niska, plazmidski posredovana rezistencija (MIK>0.016mg/L) koja može utjecati na klinički neuspjeh terapije, naročito kod *Salmonella typhi* infekcija.

Tijekom 2011.g. prikupljeno je 15 izolata šigela. Uobičajeno rezistencija je bila visoka na ampicilin i ko-trimoksazol. Rezistencija nije zabilježena na cefalosporine III. generacije, niti na kinolone.

Među gram-negativnim anaerobima zabilježena je visoka rezistencija na penicilin (86%) i klindamicin (33%). Rezistencija na metronidazol je iznosila 11%. Među gram-pozitivnim anaerobima izražena je rezistencija na metronidazol (40%). Rezistencija na klindamicin je iznosila 12%, a na penicilin 11%.

DISCUSSION

Penicillin is a first choice therapy for infections caused by group A streptococcus (GAS) and penicillin resistance in streptococci has not yet emerged. Macrolides are drugs of choice in patients with penicillin allergy and clindamycin is recommended in skin and recurrent streptococcal sorethroat infections. In 2011 resistance to macrolides (7%) and clindamycin (4%) is slightly lower than in the previous year (8% and 5%) and shows a decreasing trend since 2008 when resistance rates were 13% and 7%. Clindamycin resistance was predominantly constitutive (3%) and occasionally inducible (1%).

Pneumococci, haemophilus and moraxella often colonize nasopharyngeal mucosa, especially in children. Therefore, isolation of these bacteria in nasopharyngeal swabs does not necessarily indicate bacterial infection of upper respiratory tract. Due to the low sensitivity and specificity nasopharyngeal swabs are not recommended for routine bacteriological testing. In Croatia, however, this is still a very popular diagnostic method and therefore the majority of pneumococcal and haemophilus isolates reported through global surveillance have uncertain clinical significance but due to the large number of isolates these data provide good epidemiological insight in resistance among bacteria colonizing upper respiratory tract. Antibiotic resistance in invasive pneumococci is analyzed in a separate chapter of this publication. Ampicillin has better pharmacokinetic and pharmacodynamic parameters than penicillin and shows good activity against pneumococci and *Haemophilus influenzae* and is therefore recommended as a first choice therapy for bacterial middle ear infection in majority of international guidelines. Sensitivity testing to beta-lactam antibiotics in pneumococci was possible only by determining minimal inhibitory concentration (MICs) and therefore, until 2011 it was restricted to penicillin only. Pneumococci that showed sensitivity and low level resistance to penicillin were considered to be sensitive to ampicillin. According to the EUCAST standards it is possible to use disk diffusion for ampicillin sensitivity testing so in 2011 ampicillin data are for the first time included in the national report. Last national data for ampicillin resistance in pneumococci in Croatia are available from the study on 585 pneumoccocal isolates from 22 Croatian centers (AAC, 2002;46:2671). In this study all the penicillin sensitive and low level resistant isolates ($MIC_{penicillin} \leq 0.008 - 1.0$ mg/L) were sensitive to ampicillin ($MIC_{ampicillin} \leq 2.0$ mg/L) according to the CLSI standards including the CLSI 2009 version (M100 – S19), the last version used by the Croatian surveillance network before switching to EUCAST. In line with these findings and the fact that penicillin and ampicillin MICs are rarely more than one dilution apart we expected that ampicillin resistance will not exceed high level resistance rates for penicillin (3%) but according to the first results of ampicillin disk diffusion testing it is 16% which is much higher than expected. It should be further discussed with EUCAST to what dosing regimen in children this ampicillin disk diffusion interpretation correlates best. Unlike ampicillin the penicillin non-susceptibility rates did not change substantially after switching to EUCAST. This was not to be expected as the CLSI breakpoints used in 2010 (≤ 0.06 sensitive, ≥ 2.0 resistant) only slightly differ from the EUCAST break-points used in 2011 (≤ 0.06 sensitive, > 2.0 resistant). In 2011 penicillin non-susceptibility rate was 29% (26% low level and 3% high level resistance), which is not that much different from the previous findings (20% low level and 4% high level resistance in 2010, 24% low

level and 5% high level resistance in 2009). Penicillin MIC range also indicates that MIC 90 does not exceed 2.0 mg/L in any of the centers and that ≥ 90% of pneumococci can be treated by penicillin in case of pneumonia. Penicillin dosing according to the penicillin MIC value is well described by EUCAST. Resistance of pneumococci to other antibiotics does not differ much from the rates described in the previous year, except for co-trimoxazole. Co-trimoxazole resistance decreased from 43% to 35%. It is not very likely that this change is influenced by the switch in methodology because interpretation of the co-trimoxazole inhibition zone by EUCAST and CLSI standards differ in one millimetre only.

Ampicillin resistance in *H. influenzae* over the past few years was approx. 10% (9% in 2006, 11% in 2007, 8% in 2008, 10% in 2009, 11% in 2010). According to the EUCAST studies a 10μg ampicillin disk does not detect resistant isolates very well and most of the isolates with PBP mutations (beta-lactamase negative ampicillin resistant, BLNAR) will be missed when this disk is used. Therefore EUCAST introduced a 2μg ampicillin disk that more reliably detects resistant strains but sometimes overcalls resistance when compared to MICs. In 2011 ampicillin resistance in *H. influenzae* (13%) slightly increased compared to the previous year (11%) which may be attributed to the use of a more sensitive disk. A more dramatic change after switching to EUCAST is recorded for cefuroxime and azithromycin resistance rates in *H. influenzae*. Until this year *in vitro* testing indicated 100% and 99% sensitivity to these antibiotics. According to the EUCAST standards wild type *H. influenzae* strains are considered to be intermediately resistant to azithromycin and oral cefuroxime. Because of the very low acquired resistance rates and innate low level resistance azithromycin was excluded from surveillance for *H. influenzae* in 2011. For the first time reporting for cefuroxime sensitivity was split into oral and parenteral category with full sensitivity possible for parenteral cefuroxime only. In 2011 93% of isolates were fully sensitive to parenteral cefuroxime, 5% were intermediate and 2% were resistant.

A decreasing trend in methicillin resistant *Staphylococcus aureus* (MRSA) rates (25% in 2007, 26% in 2008, 21% in 2009, 16% in 2010) was continued in 2011 with an MRSA rate of 14%. Among MRSA isolates a slight decrease in resistance to macrolides, clindamycin and gentamicin was recorded which may reflect the increasing incidence of community acquired MRSA. Until this year glycopeptides (teicoplanin) resistance was tested by disk diffusion method but in 2011 it was adopted that for staphylococci sensitivity to glycopeptides can only be determined by MIC testing. For the first time we have national data for Croatia on vancomycin MIC range in MRSA isolates. Vancomycin resistant strains are not detected yet but a high rate of isolates with MIC of 2.0 mg/L (19%) was recorded. Many experts recommend a switch to alternative antibiotics (linezolid, daptomycin) in case of severe infections caused by MRSA strains with vancomycin MICs of >1.0 mg/L. In 2011 mupirocin 200 μg disk was introduced as the single disk that distinguishes between high and low level resistance. Mupirocin resistance rate does not differ much from the last year rate, the only change is that intermediate category was introduced and low level resistance as detected by 5μg disk was left out because of the questionable clinical significance. For the first time sensitivity testing for tigecycline, a novel broad spectrum antibiotic with MRSA coverage, was introduced.

Sensitivity of enterococci is similar as reported previously and vancomycin resistant *E.faecium* (VRE) strains continue to be rarely reported.

In 1.3 EUCAST version wild type enterobacteriaceae are considered either sensitive or intermediate to ampicillin and its combinations with inhibitors. At the Croatian Committee meeting we decided to consider wild type enterobacteriaceae as sensitive. In any case EUCAST does not provide a category in between because it does not correlate well with clinical outcome. However, intermediate zone is also defined as a a technical bufer that minimizes confusion for organisms with MICs close to the breakpoint and this is what we miss with the new standards, especially for co-amoxiclav. As expected, co-amoxiclav resistance rates in 2011 seem to correlate well with the non-susceptibility rates (intermediate and resistant strains) recorded previously. In spite of the change in disk of piperacillin/tazobactam no major changes in the resistance to this antibiotic was seen.

The European scientific community often speculated that the introduction of the lower break-point concentrations for cephalosporins will result in reporting of higher resistance rates for these antibiotics in *Escherichia coli* and *Klebsiella pneumoniae* isolates. In Croatia we did not expect that to happen. During the last decade a predominant mechanism of resistance to 3rd generation cephalosporins in *E.coli* and *K. pneumoniae* was production of extended spectrum beta-lactamases (ESBL), and since 1998 all the Croatian microbiology laboratories adopted routine screening for ESBL production by double disk method. In line with the CLSI guidelines that were mandatory for the Croatian network until 2011, all the ESBL isolates were reported as resistant to all penicillins and cephalosporins (except the combinations with inhibitors) regardless of the possible *in vitro* sensitivity. This interpretative reading covered for the loose break-points. Over the last decade regular external quality control proved that all the laboratories in the network adopted such testing and interpretation. Lower EUCAST break-point concentrations correlate better with the clinical efficacy of beta-lactam antibiotics and at the same time detect better ESBL production (if it reaches clinically relevant levels) and correction of *in vitro* findings is no longer necessary. According to our first results after switching to EUCAST it seems that both methods led to similar results. In small number of isolates, however, ESBL production does not lead to the same level of clinical resistance for all cephalosporins so in 2011 we started to report slightly different rates of resistance for different cephalosporins. In *E.coli* resistance rates for cefixime and ceftriaxone are identical to the previous year rates (5%), and resistance to ceftazidime (4%), cefepime and ceftibuten (3%) is somewhat lower. In *K. pneumoniae*, ceftazidime and ceftriaxone resistance rates are increasing which is probably not due to the change in break-points but rather reflects true spread of ESBL isolates.

Although ESBL production is the major resistance mechanism to 3rd generation cephalosporins in *E. coli* and *K. pneumoniae*, we have noted lately an increase in isolates with plasmid ampC beta-lactamases. *E.coli* and *K. pneumoniae* isolates that produce plasmid ampC beta-lactamases are subject of investigation in Croatia for more than ten years. All 3rd generation cephalosporin resistant isolates that were not ESBL positive were to be sent to the Reference Center for Antibiotic Resistance Surveillance for retesting. First ampC producing isolates were described in 2003 and ever since these isolates were reported infrequently with incidence of 0 – 8 isolates per year. Since 2009 these isolates became more common (20 *E. coli* and 5 *K.*

pneumoniae isolates in 2009), and in 2011 8 *K. pneumoniae* and 50 *E.coli* isolates that produce ampC beta-lactamases were detected.

Quinolone and co-trimoxazole resistance in *E. coli* is identical to the last year values and no substantial change in resistance to aminoglycozides and nitrofurantoin was recorded either in spite of the change in disk contents. Quinolone resistance in *K. pneumoniae* has slightly increased, and it seems that the change in netilmicin disk had significant influence in klebsiella as resistance rate of 21% is much higher than the last year rate (8%) and approaches resistance rates to gentamicin.

Antibiotic resistance in *P. mirabilis* did not change much. In the *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp. group 3rd generation cephalosporin resistance has increased and is higher for ceftriaxone and ceftazidime than for other 3rd generation cephalosporins.

Carbapenem non-susceptible enterobacteriaceae are also subject of continuous surveillance in Croatia for more than ten years. Retesting of these isolates in the Reference Center for Antibiotic Resistance Surveillance showed that non-susceptibility to carbapenems in Croatia is still predominatly caused by the combination of ESBL or ampC hyperproduction and decreased permeability and is mostly expressed as ertapenem non-susceptibility only. In 2011 carbapenemaze production was confirmed in 13 isolates: VIM in seven isolates (4 *K. pneumoniae* and 3 *Enterobacter* spp.), NDM-1 in four isolates (1 *Citrobacter diversus* and 3 *K. pneumoniae*) and for the first time KPC-2 production was recorded in two *K. pneumoniae* isolates. For years we feared the advent of KPC *K. pneumoniae* in Croatia considering the huge potential for epidemic spread of the ST258 clone. So far these first two isolates were not epidemiologically related.

For *P. aeruginosa* piperacillin/tazobactam resistance (12%) increased as compared to the previous year (7%) which is probably partly due to the lower break-points set by EUCAST. Break-point concentrations for ceftazidim and carbapenems did not change much and slight increase of resistance to these antibiotics is probably due to the spread of resistance. Colistin data are biased as it is allowed for colistin to be tested on carbapenem resistant isolates only. However, colistin resistant isolates are still very rare in Croatia.

With the change in break-point concentrations for carbapenems a majority of *Acinetobacter baumannii* isolates that were considered intermediate before entered the resistant category according to EUCAST. It was also expected that a part of sensitive isolates will enter an intermediate category. In 2011 only a small number of isolates were categorized as intermediate and the fact that resistance to carbapenems further increased to 64% (in 2010 there were 34% resistant and 11% intermediate) can not be atributed to the change in break-points only. We conclude, therefore, that multiply resistant *A. baumannii* is still on the rise and this is still the leading antibiotic resistance problem in Croatia. Colistin resistant isolates were not reported.

Salmonellae are highly sensitive to all antibiotics but ampicillin. Ampicillin resistance is 10% which is close to the previous year results (11%). Although sporadic quinolone resistant isolates were reported sensitivity rate for ciprofloksacin

in Croatia is still 100%. According to EUCAST standards, nalidixic acid is not a reliable indicator of low level quinolone resistance because it does not detect plasmid mediated resistance. Bearing this in mind the Croatian Committee for Antibiotic Resistance Surveillance, nevertheless, decided to continue using nalidixic acid as an indicator of first step chromosomal mutations. At the same time the Committee recommended ciprofloxacin MIC testing in all invasive salmonella isolates, so that in systemic infections low level plasmid mediated quinolone resistance (MIK>0.016mg/L) may not be missed. Low level resistance can have an impact on clinical outcome especially in *Salmonella typhi* infections.

In 2011 only 15 shigella isolates were reported. As recorded previously, resistance rates were high for ampicillin and co-trimoxazole. Resistance to 3rd generation cephalosporins and quinolones was not detected.

Among gram-negative anaerobic bacteria high resistance rates for penicillin (86%) and clindamycin (33%) were recorded. Resistance to metronidazole was 11%. Among gram-positive anaerobic bacteria resistance to metronidazole was high (40%), and resistance to clindamycin was 12% and to penicillin 11%.

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*
KT KZKB	*Klinika za kardiovaskularne bolesti «Magdalena», Krapinske Toplice*
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*
PŽ ZZJZ	*ZZJZ Požeško-slavonske županije, Požega*
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 KZT	*Klinika za traumatologiju, 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»*

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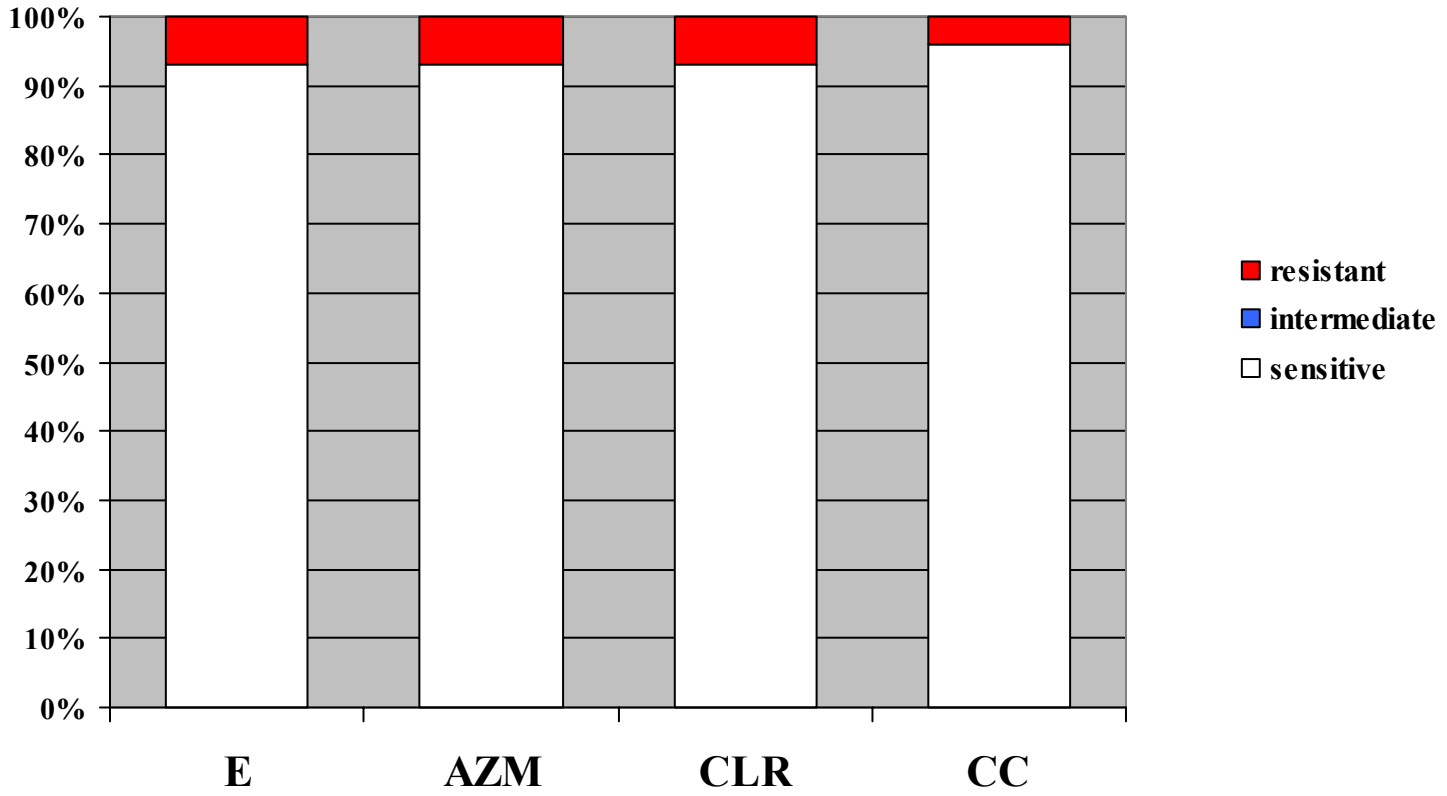
** uključuje podatke i za: Kliniku za plućne bolesti "Jordanovac", Zagreb
*** uključuje podatke i za: Sveučilišnu Kliniku za dijabetes, endokrinologiju i bolesti metabolizma "Vuk Vrhovac", Zagreb
**** uključuje podatke i za: Institut za tumore, Zagreb

ANTIBIOTICI / ANTIBIOTICS:

P	penicillin
AMP	ampicillin
AMC	amoxicillin + clavulanic acid
SAM	ampicillin + sulbactam
FOX	cefoxitin
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)
CFEP	cefepime (IV. gen. cephalosporins)
PTZ	piperacillin/tazobactam
ERT	ertapenem
IMP	imipenem
MER	meropenem
E	erythromycin
AZM	azithromycin
CLR	clarythromycin
CC	clindamycin
TE	tetracycline
SXT	co-trimoxazole
NF	nitrofurantoin
VA	vancomycin
RIF	rifampicin
CIP	ciprofloxacin
NOR	norfloxacin
GM	gentamicin
NT	netilmicin
AN	amikacin
MUP	mupirocin
MTZ	metronidazole
MOX	moxifloxacin
LZD	linezolid
NA	nalidixic acid
COL	colistin
TGC	tigecycline

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

Beta-hemolitički streptokok grupe A
Group A beta-hemolytic streptococcus
(1.01. - 31.12. 2011.) - osjetljivost na antibiotike u RH
- sensitivity to antibiotics in Croatia



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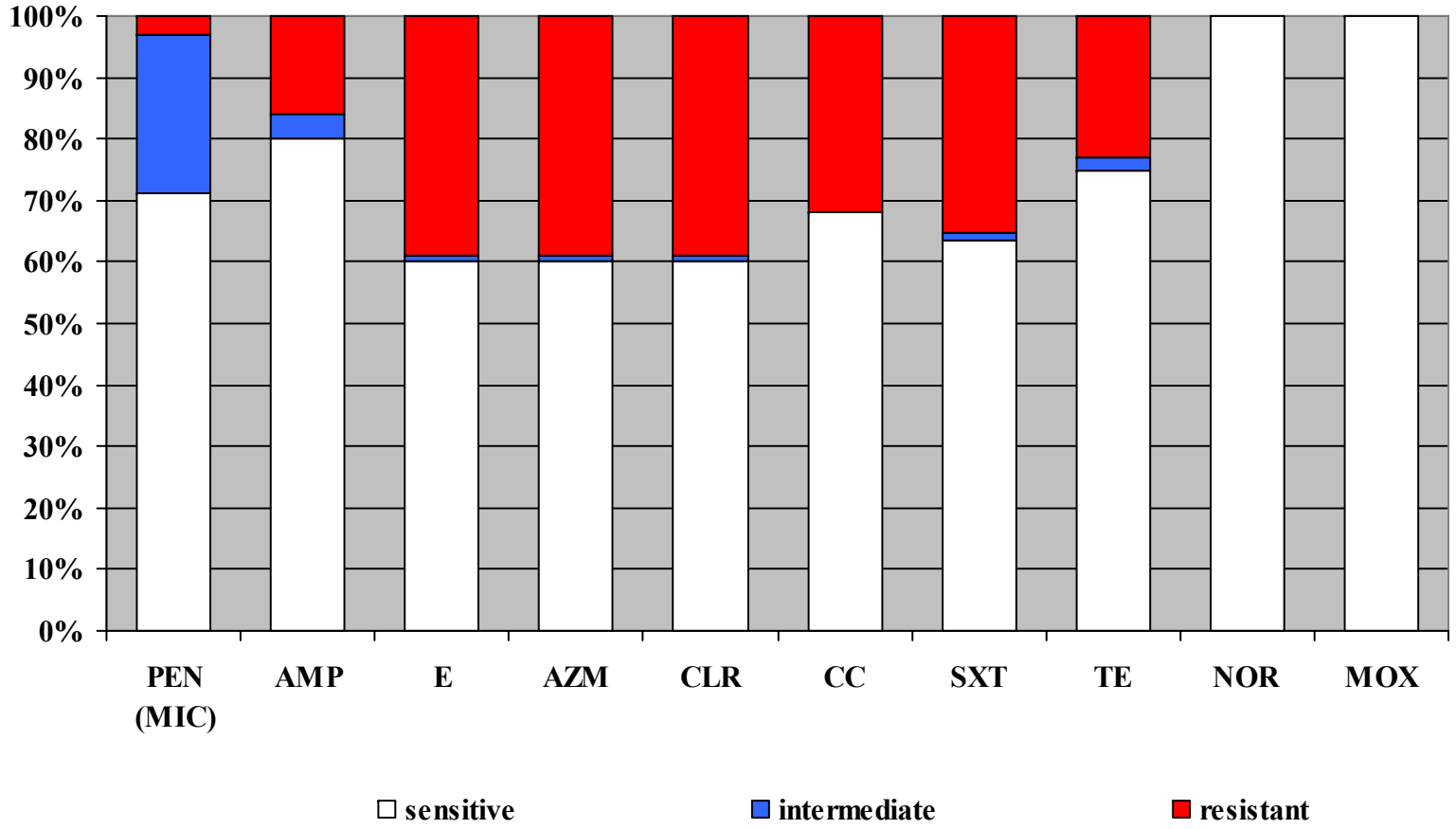
Beta-hemolitički streptokok grupe A
Group A streptococcus

- rezistencija na antibiotike u razdoblju od 1.01.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.01. - 31.12. 2011.
summary results for the isolates from 39 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	14 422	7 (0)	2 (0) - 21 (6)
Azithromycin	14 422	7 (0)	2 (0) - 21 (6)
Clarythromycin	14 422	7 (0)	2 (0) -21 (6)
Clindamycin	14 255	4 (0)	
constitutive		3	0 -14
inducible		1	0 - 3

* 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. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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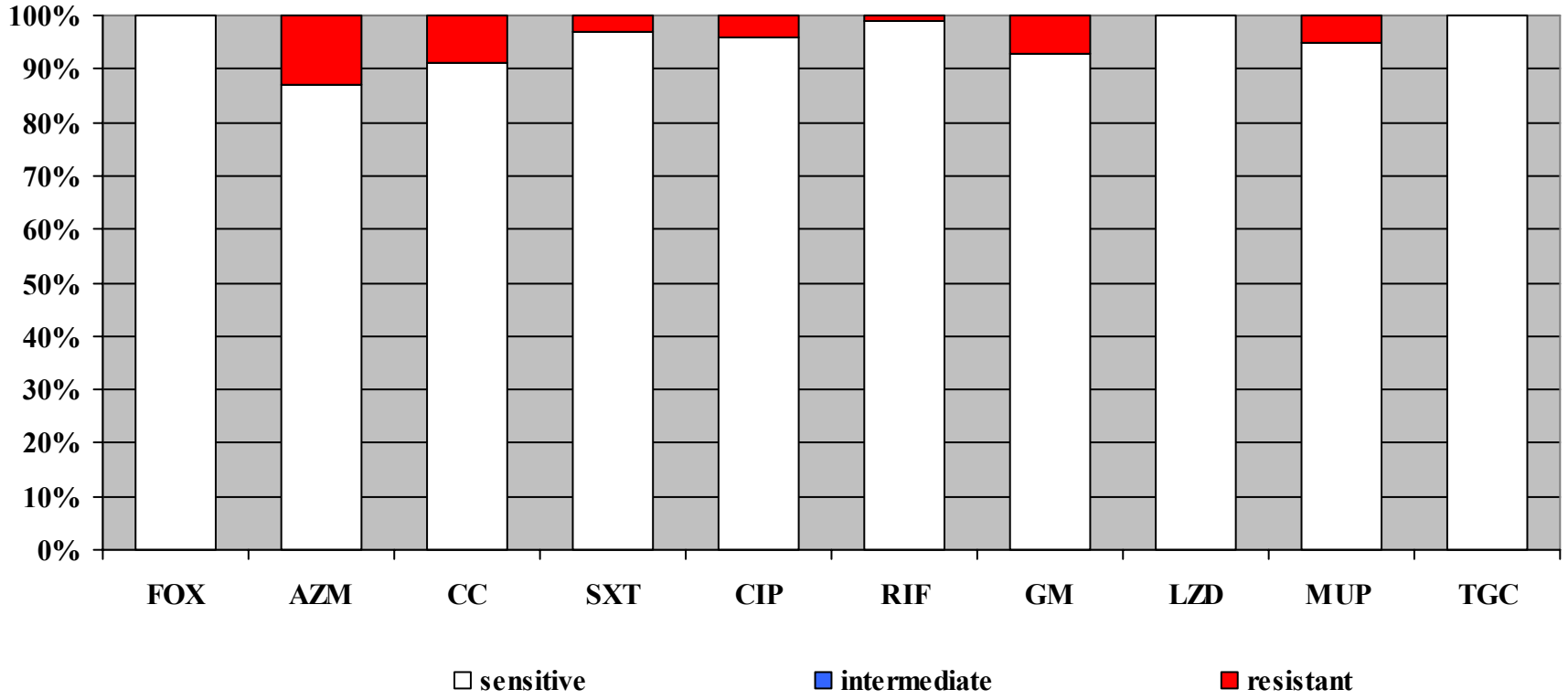
Streptococcus pneumoniae

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 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	3 904		
visoko rez. / high		3	0 -27
umjereno rez. / low		26	0 - 48
Ampicilin	3 339	16 (4)	0 (0) - 39 (4)
Erythromycin	3 684	39 (1)	18 (0) - 60 (6)
Azithromycin	3 684	39 (1)	18 (0) - 60 (6)
Clarythromycin	3 684	39 (1)	18 (0) - 60 (6)
Clindamycin	3 892	32 (0)	14 (0) - 46 (0)
Co-trimoxazole	3 911	35 (1)	18 (0) - 59 (0)
Tetracycline	3 461	23 (2)	9 (0) - 46 (3)
Norfloxacin	3 697	0 (0)	0 (0) - 5 (0)
Moxifloxacin	3 508	0 (0)	0 (0) - 4 (0)

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

Staphylococcus aureus MSSA (1.10. - 31.12. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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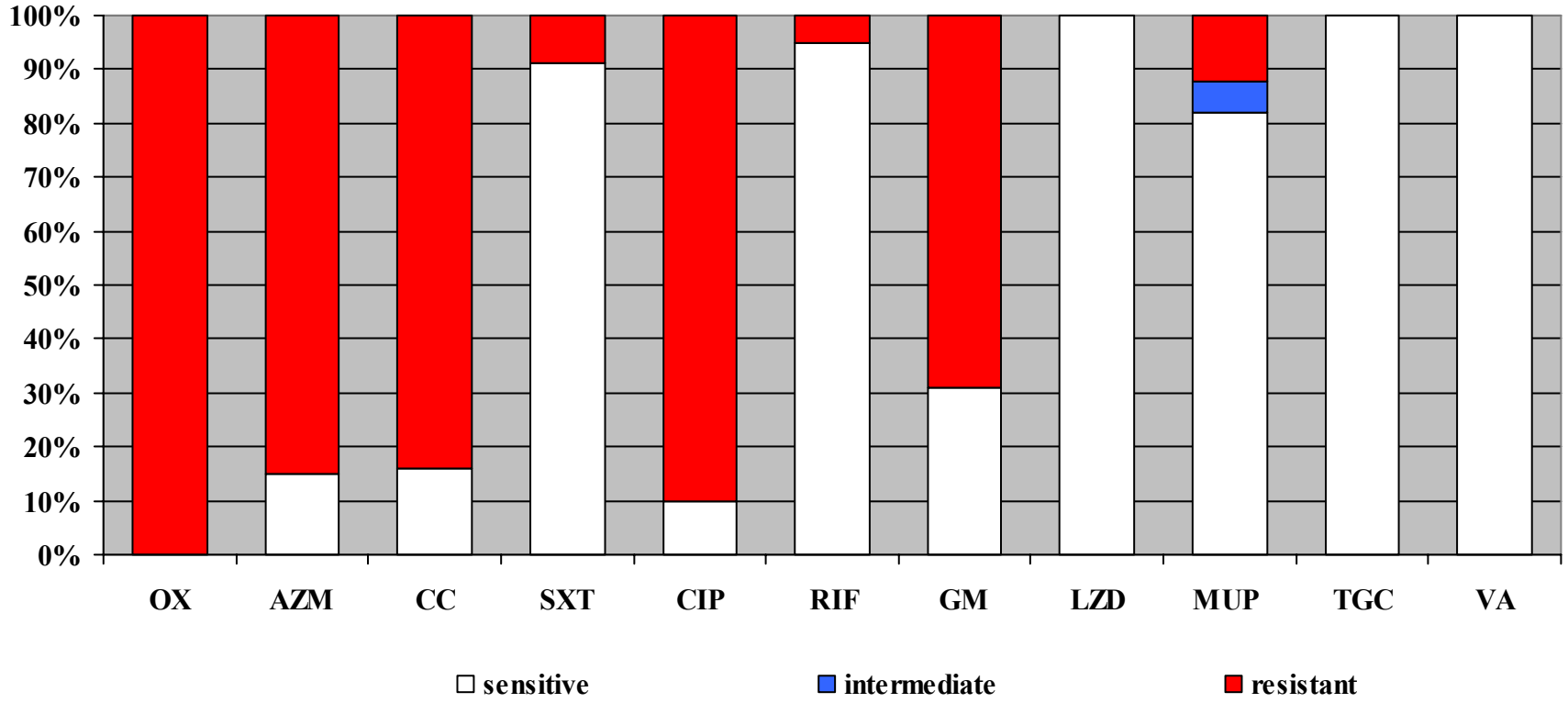
Staphylococcus aureus / MSSA

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 centers in Croatia

ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Cefoxitin	4 365	0	0
Azithromycin	4 309	13 (0)	1 (0) - 29 (0)
Clindamycin	4 309	9 (0)	1 (0) - 17 (0)
Co-trimoxazole	4 267	3 (0)	0 (0) - 15 (0)
Ciprofloxacin	4 231	4 (0)	0 (0) - 17 (0)
Rifampicin	3 918	1 (0)	0 (0) - 4 (0)
Gentamicin	4 260	7 (0)	0 (0) - 13 (0)
Linezolid	3 840	0 (0)	0 (0) - 0 (0)
Mupirocin	3 796	5 (0)	0 (0) - 18 (0)
Tigecycline	2 889	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. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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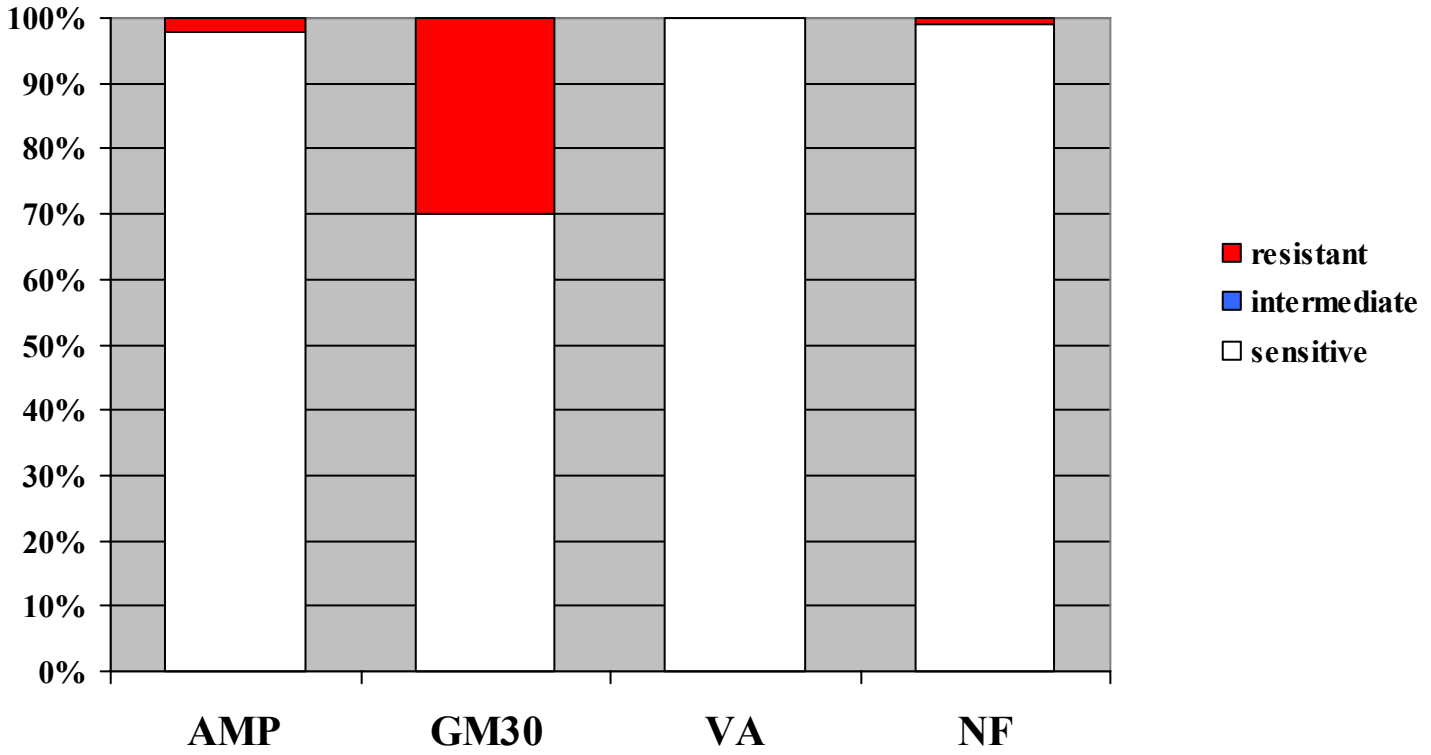
Staphylococcus aureus / MRSA

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 centers in Croatia

ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Cefoxitin	741	100 (0)	100 (0) - 100 (0)
Azithromycin	736	85 (0)	56 (0) - 98 (0)
Clindamycin	735	84 (0)	56 (0) - 98 (0)
Co-trimoxazole	738	9 (0)	7 (0) - 22 (0)
Ciprofloxacin	724	90 (0)	78 (0) - 100 (0)
Rifampicin	695	5 (0)	0 (0) - 16 (0)
Gentamicin	742	69 (0)	42 (0) - 93 (0)
Linezolid	674	0 (0)	0 (0) - 0 (0)
Mupirocin	621	12 (6)	0 (8) - 27 (3)
Tigecycline	502	0 (0)	0 (0) - 2 (0)
Vankomycin	685	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. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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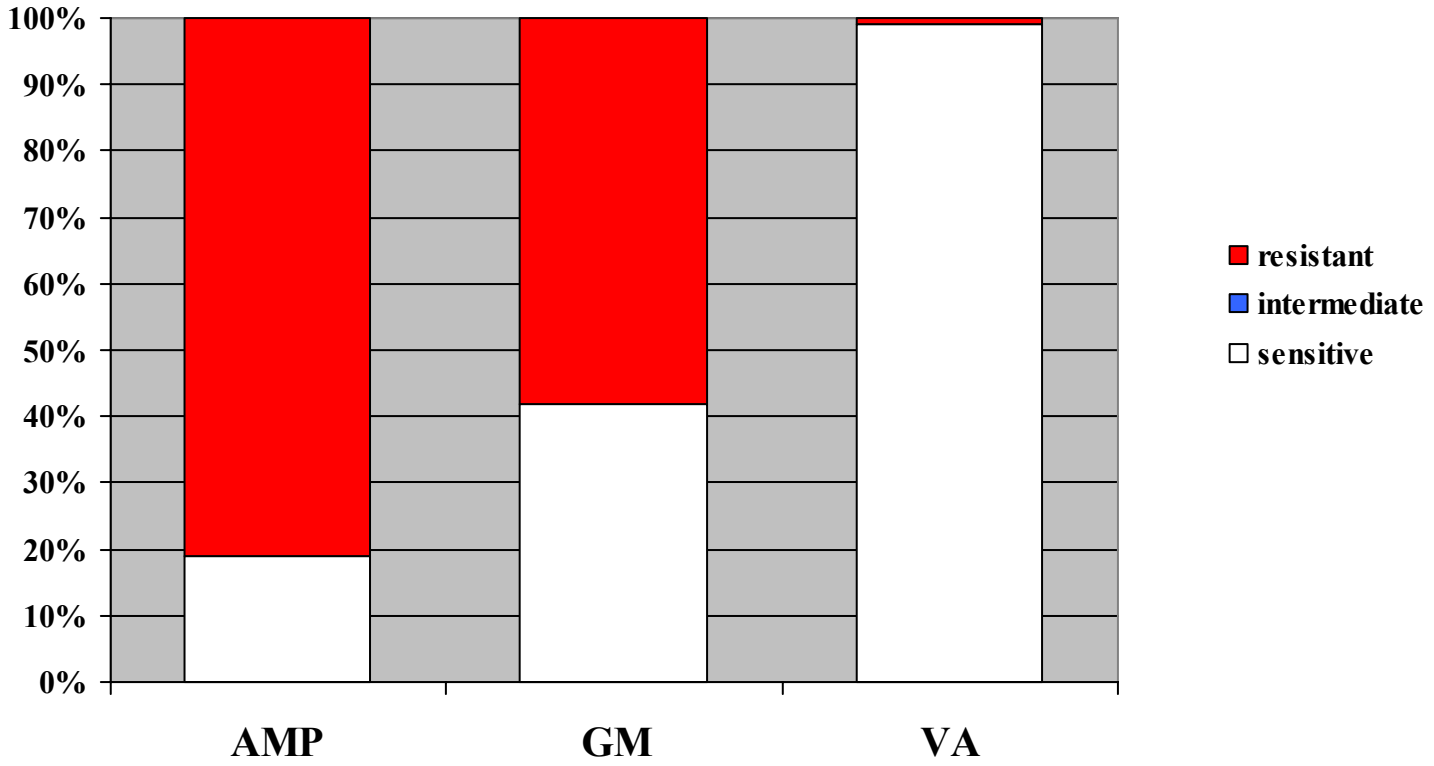
Enterococcus faecalis

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 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	6 193	2 (0)	0 (0) - 15 (0)
Gentamicin	5 699	30 (0)	0 (0) - 53 (0)
Vancomycin	5 835	0 (0)	0 (0) - 0 (0)
Nitrofurantoin	5 920	1 (0)	0(0) - 7 (0)

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

Enterococcus faecium (1.10. - 31.12. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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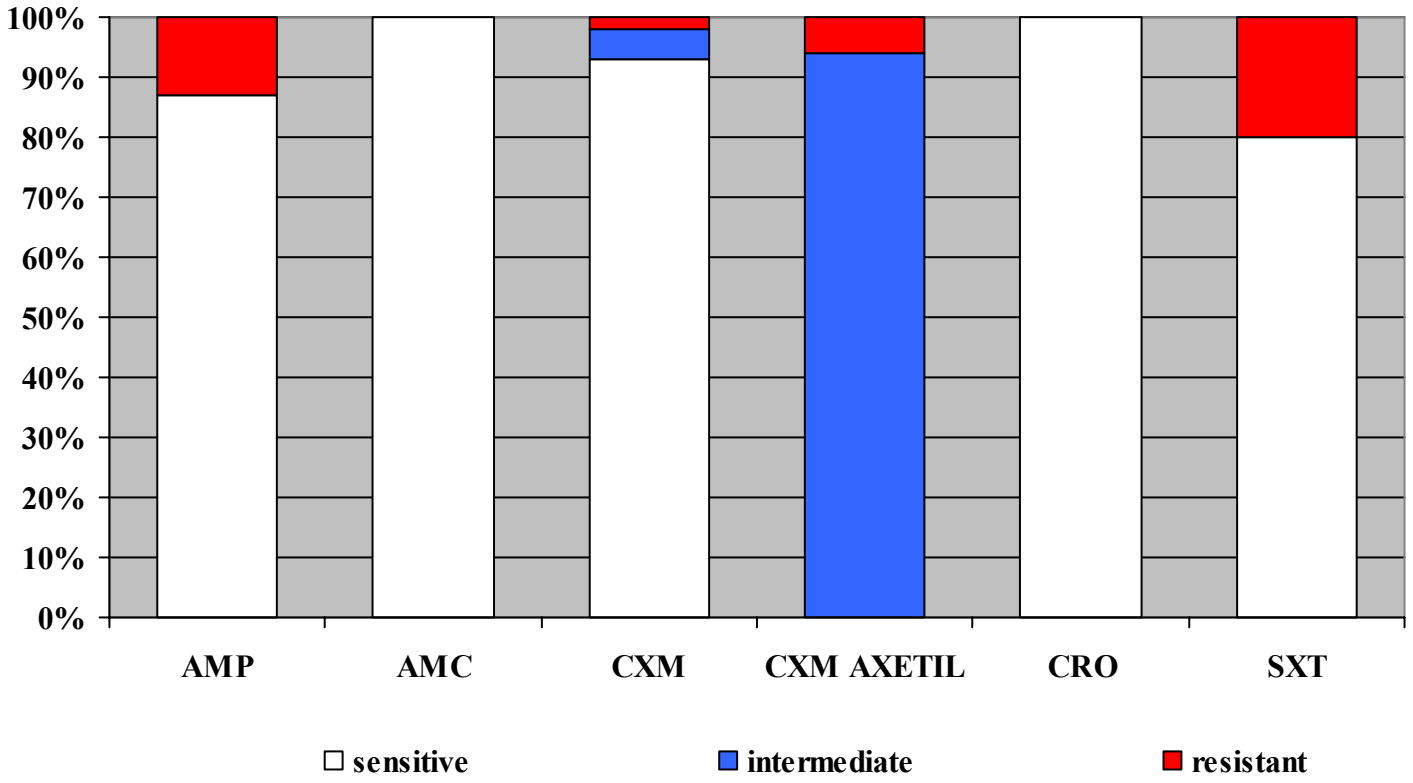
Enterococcus faecium

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 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	469	81 (0)	43 (0) - 100 (0)
Gentamicin	413	58 (0)	33 (0) - 72 (0)
Vancomycin	481	1 (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

Haemophilus influenzae (1.10. - 31.12. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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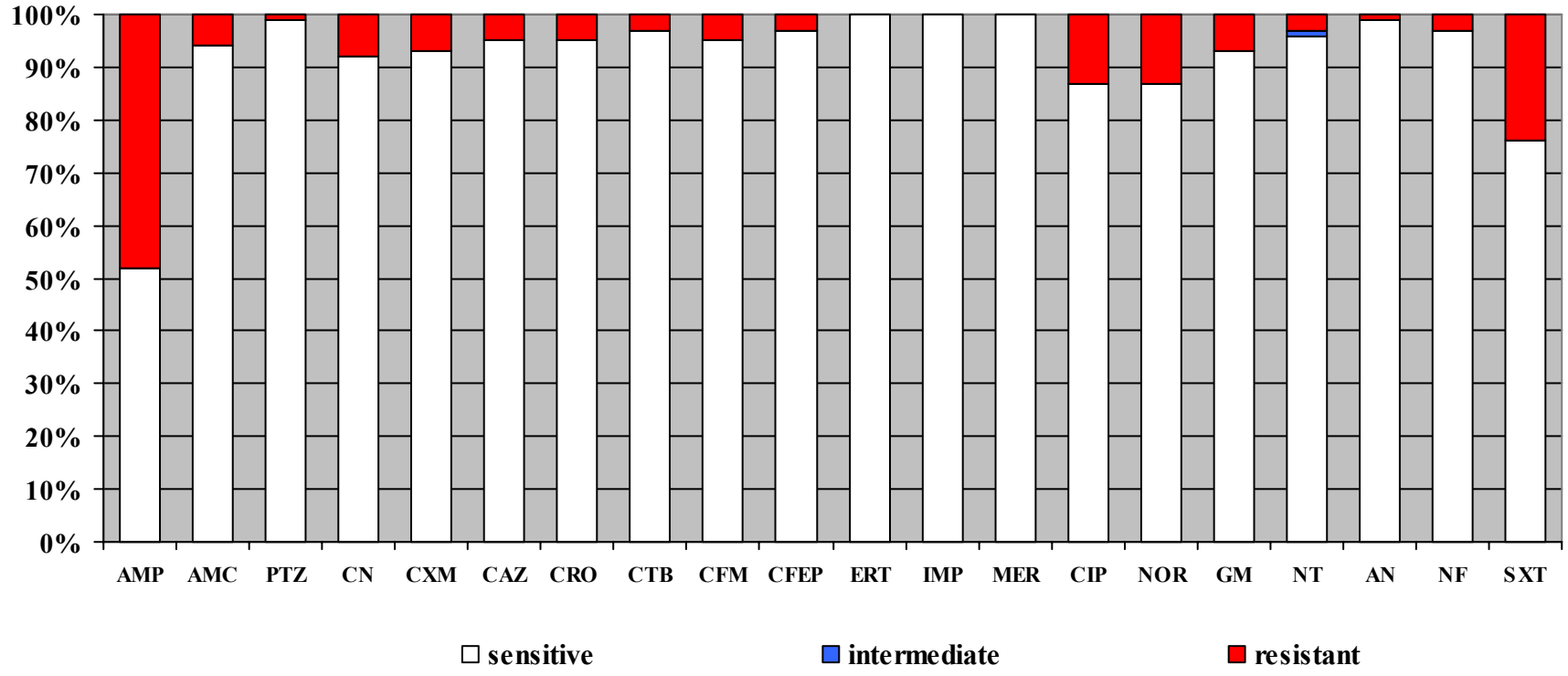
Haemophilus influenzae

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 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*
Co-trimoxazole	2 417	20 (0)	6 (5) - 39 (0)
Ampicillin	2 451	13 (0)	1 (0) - 81(0)
Amoxicillin + clav. acid	2 432	0 (0)	0 (0) - 7 (0)
Cefuroxime	2 433	2 (5)	0 (0) - 17 (83)
Cefuroxime axetil	2 054	6 (94)	0 (100) - 31 (69)
Ceftriaxone	2 355	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

Escherichia coli (1.10. - 31.12. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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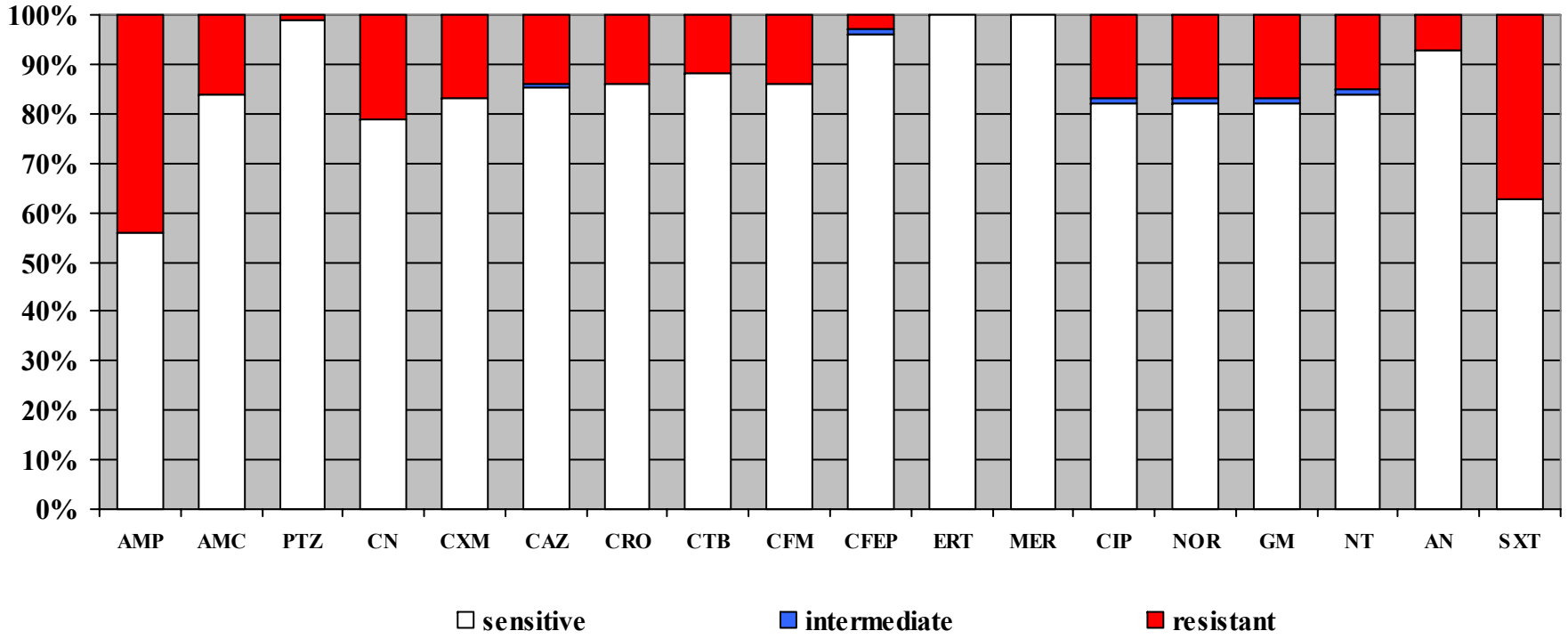
Escherichia coli

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 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	20 909	48 (0)	36 (0) - 59 (0)
Amoxicillin + clav. acid	19 983	6 (0)	1 (0) - 12 (0)
Piperacillin + tazobactam	19 027	1 (0)	0 (0) - 4 (1)
Cephalexin	18 660	8 (0)	1 (0) - 24 (0)
Cefuroxime	20 359	7 (0)	1 (0) - 13 (0)
Ceftazidime	19 437	4 (0)	1 (0) - 8 (0)
Ceftriaxone	19 431	5 (0)	1 (0) - 11 (0)
Cefepime	18 846	3 (0)	0 (0) - 9 (3)
Ceftibuten	18 196	3 (0)	0 (0) - 11 (0)
Cefiksime	17 877	5 (0)	1 (0) - 64 (0)
Ertapenem	18 984	0 (0)	0 (0) - 4 (0)
Imipenem	19 611	0 (0)	0 (0) - 0 (0)
Meropenem	19 610	0 (0)	0 (0) - 0 (0)
Ciprofloxacin	20 525	13 (0)	3 (0) - 24 (0)
Norfloxacin	18 670	13 (0)	3 (0) - 21 (0)
Gentamicin	20 869	7 (0)	2 (0) - 14 (2)
Netilmicin	19 064	3 (1)	0 (0) - 8 (3)
Amikacin	18 638	1 (0)	0 (0) - 4 (0)
Nitrofurantoin	20 145	3 (0)	0 (0) - 10 (0)
Co-trimoxazole	20 620	24 (0)	12 (0) - 35 (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. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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Proteus mirabilis

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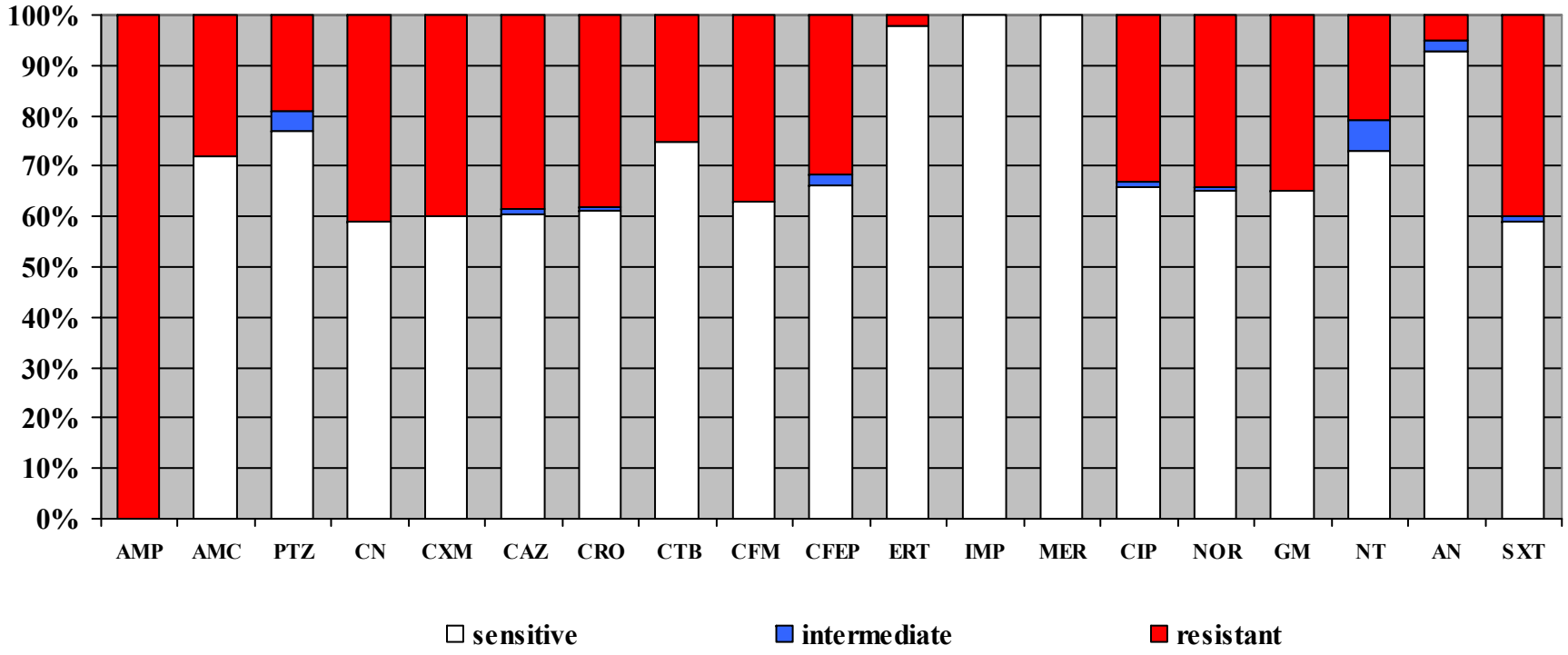
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 centers in Croatia

ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Ampicillin	3 953	44 (0)	26 (0) - 65 (0)
Amoxicillin + clav. acid	3 461	16 (0)	4 (0) - 49 (0)
Piperacillin + tazobactam	3 701	1 (0)	0 (0) - 14 (0)
Cephalexin	3 446	21 (0)	0 (0) - 59 (0)
Cefuroxime	3 859	17 (0)	4 (0) - 45 (0)
Ceftazidime	3 751	14 (1)	0 (0) - 36 (8)
Ceftriaxone	3 738	14 (0)	0 (0) - 44 (1)
Cefepime	3 675	3 (1)	0 (0) - 12 (0)
Ceftibuten	3 582	12 (0)	0 (0) - 32 (0)
Cefixime	3 273	14 (0)	0 (0) - 63 (0)
Ertapenem	3 561	0 (0)	0 (0) - 2 (0)
Meropenem	3 721	0 (0)	0 (0) - 2 (0)
Ciprofloxacin	3 906	17 (1)	3 (2) - 55 (3)
Norfloxacin	3 634	17 (1)	3 (2) - 56 (0)
Gentamicin	3 942	17 (1)	4 (0) - 37 (1)
Netilmicin	3 510	14 (1)	0 (0) - 42 (0)
Amikacin	3 557	7 (0)	0 (0) - 21 (0)
Co-trimoxazole	3 856	36 (0)	14 (0) - 59 (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. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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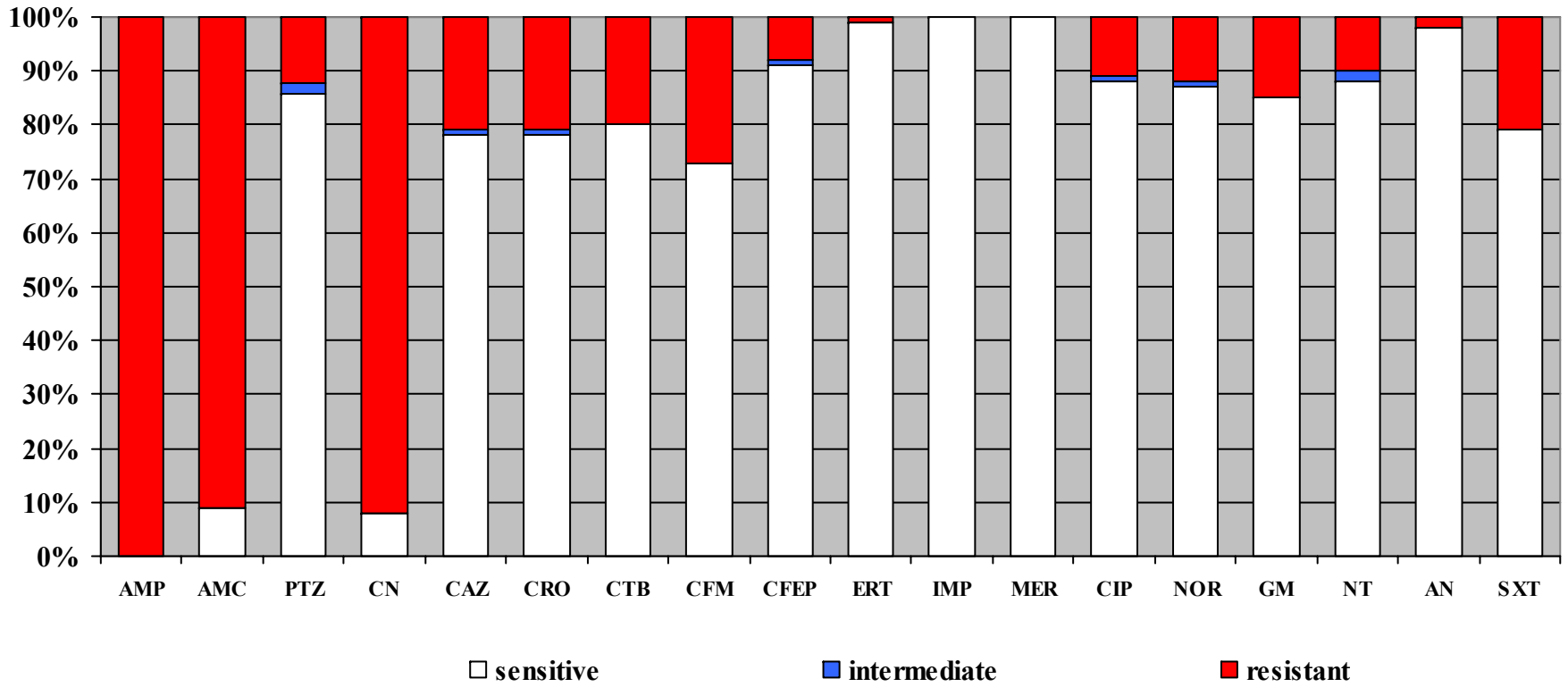
Klebsiella pneumoniae

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 centers in Croatia

ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Ampicillin	4 530	100 (0)	100 (0) - 100 (0)
Amoxicillin + clav. acid	4 317	28 (0)	2 (0) - 52 (0)
Piperacillin + tazobactam	4 261	19 (4)	0 (0) - 46 (3)
Cephalexin	3 625	41 (0)	11 (0) - 78 (0)
Cefuroxime	4 453	40 (0)	11 (0) - 78 (0)
Ceftazidime	4 424	39 (1)	0 (0) - 75 (0)
Ceftriaxone	4 408	38 (1)	0 (0) - 75 (0)
Cefepime	4 284	32 (2)	0 (0) - 59 (6)
Ceftibuten	3 667	25 (0)	0 (0) - 49 (0)
Cefixime	3 563	37 (0)	2 (0) - 87 (0)
Ertapenem	4 018	2 (0)	0 (0) - 15 (0)
Imipenem	4 309	0 (0)	0 (0) - 2 (0)
Meropenem	4 316	0 (0)	0 (0) - 2 (0)
Ciprofloxacin	4 417	33 (1)	11 (0) - 63 (0)
Norfloxacin	4 020	34 (1)	8 (0) - 66 (1)
Gentamicin	4 518	35 (0)	6 (0) - 63 (2)
Netilmicin	4 260	21 (6)	0 (0) - 58 (3)
Amikacin	4 311	5 (2)	0 (0) - 45 (0)
Co-trimoxazole	4 179	40 (1)	19 (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. 2011.) - osjetljivost na antibiotike u RH
- sensitivity to antibiotics in Croatia



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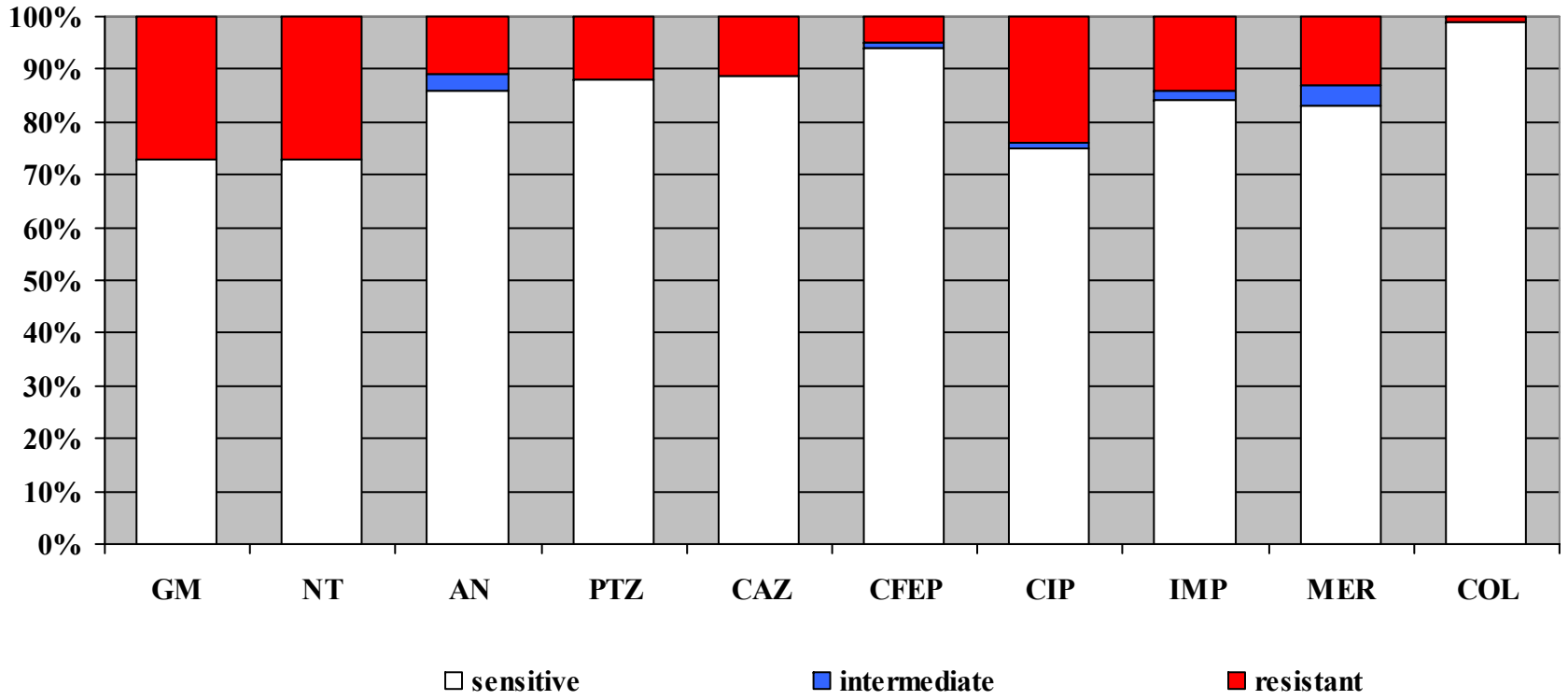
Enterobacter spp., *Serratia* spp., *Citrobacter* spp.

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 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	2 848	100 (0)	95 (0) - 100 (0)
Amoxicillin + clav. acid	2 503	91 (0)	64 (0) - 100 (0)
Piperacillin + tazobactam	2 777	12 (2)	0 (0) - 66 (0)
Cephalexin	2 359	92 (0)	0 (0) - 100 (0)
Ceftazidime	2 832	21 (1)	0 (0) - 53 (0)
Ceftriaxone	2 771	21 (1)	0 (0) - 53 (0)
Cefepime	2 770	8 (1)	0 (0) - 44 (0)
Ceftibuten	2 518	20 (0)	0 (0) - 51 (0)
Cefixime	2 260	27 (0)	0 (0) - 71 (0)
Ertapenem	2 711	1 (0)	0 (0) - 8 (6)
Imipenem	2 813	0 (0)	0 (0) - 3 (0)
Meropenem	2 817	0 (0)	0 (0) - 2 (0)
Ciprofloxacin	2 822	11 (1)	0 (0) - 25 (0)
Norfloxacin	2 343	12 (1)	0 (0) - 31 (0)
Gentamicin	2 841	15 (0)	0 (0) - 40 (0)
Netilmicin	2 779	10 (2)	0 (0) - 25 (1)
Amikacin	2 795	2 (0)	0 (0) -15 (0)
Co-trimoxazole	2 634	21 (0)	0 (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

Pseudomonas aeruginosa (1.10. - 31.12. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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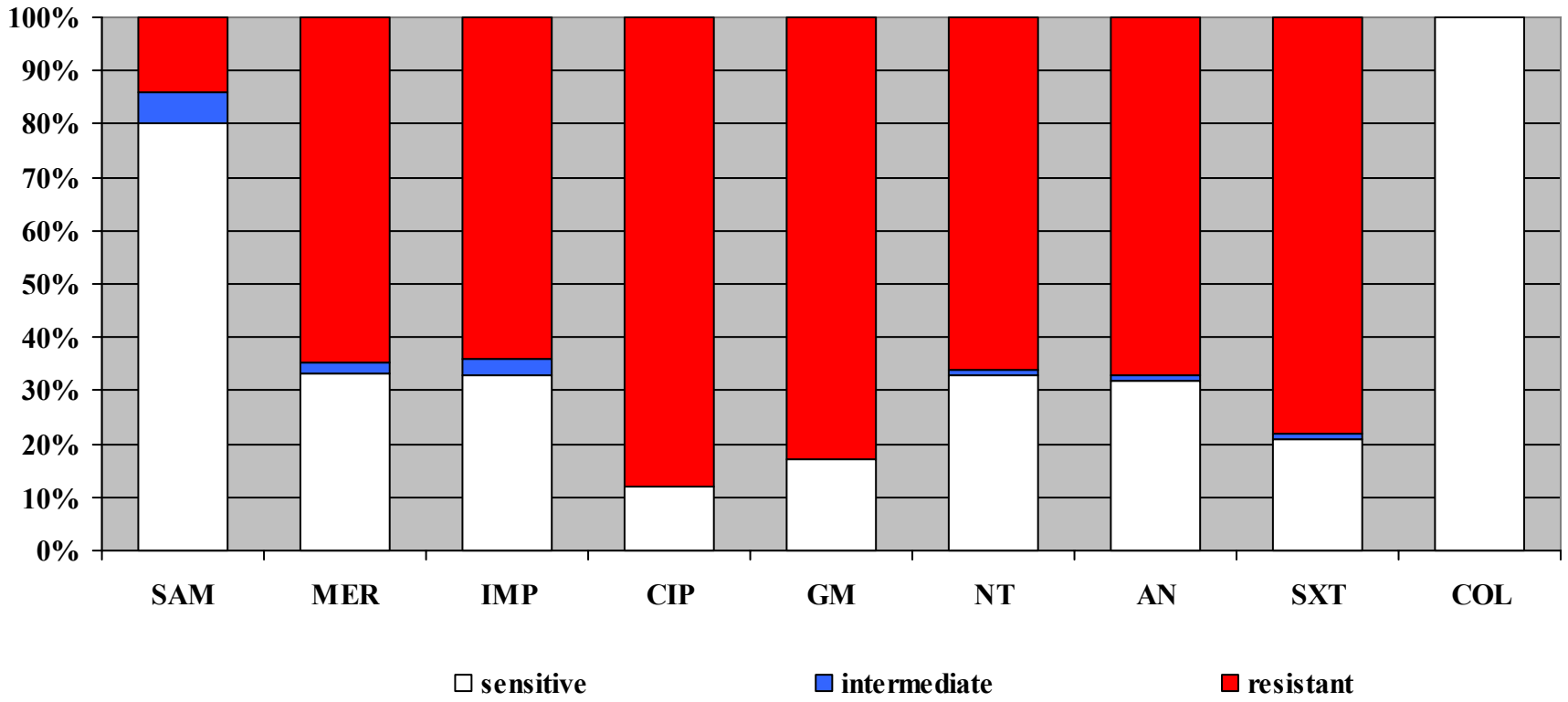
Pseudomonas aeruginosa

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 centers in Croatia

ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Piperacilin + tazobaktam	3 715	12 (0)	0 (0) - 47 (0)
Ceftazidim	3 607	11 (0)	2 (0) - 50 (0)
Cefepim	3 893	5 (1)	0 (0) - 53 (0)
Imipenem	3 908	14 (2)	0(0) - 41 (3)
Meropenem	3 921	13 (4)	0 (0) - 56 (0)
Ciprofloxacin	3 916	24 (1)	10 (0) - 49 (0)
Gentamicin	3 922	27 (0)	10 (0) - 56 (0)
Netilmicin	3 798	27 (0)	7 (0) - 65 (0)
Amikacin	3 920	11 (3)	0 (1) - 40 (0)
Colistin	959	1 (0)	0 (0) - 2 (0)

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

Acinetobacter baumannii (1.10. - 31.12. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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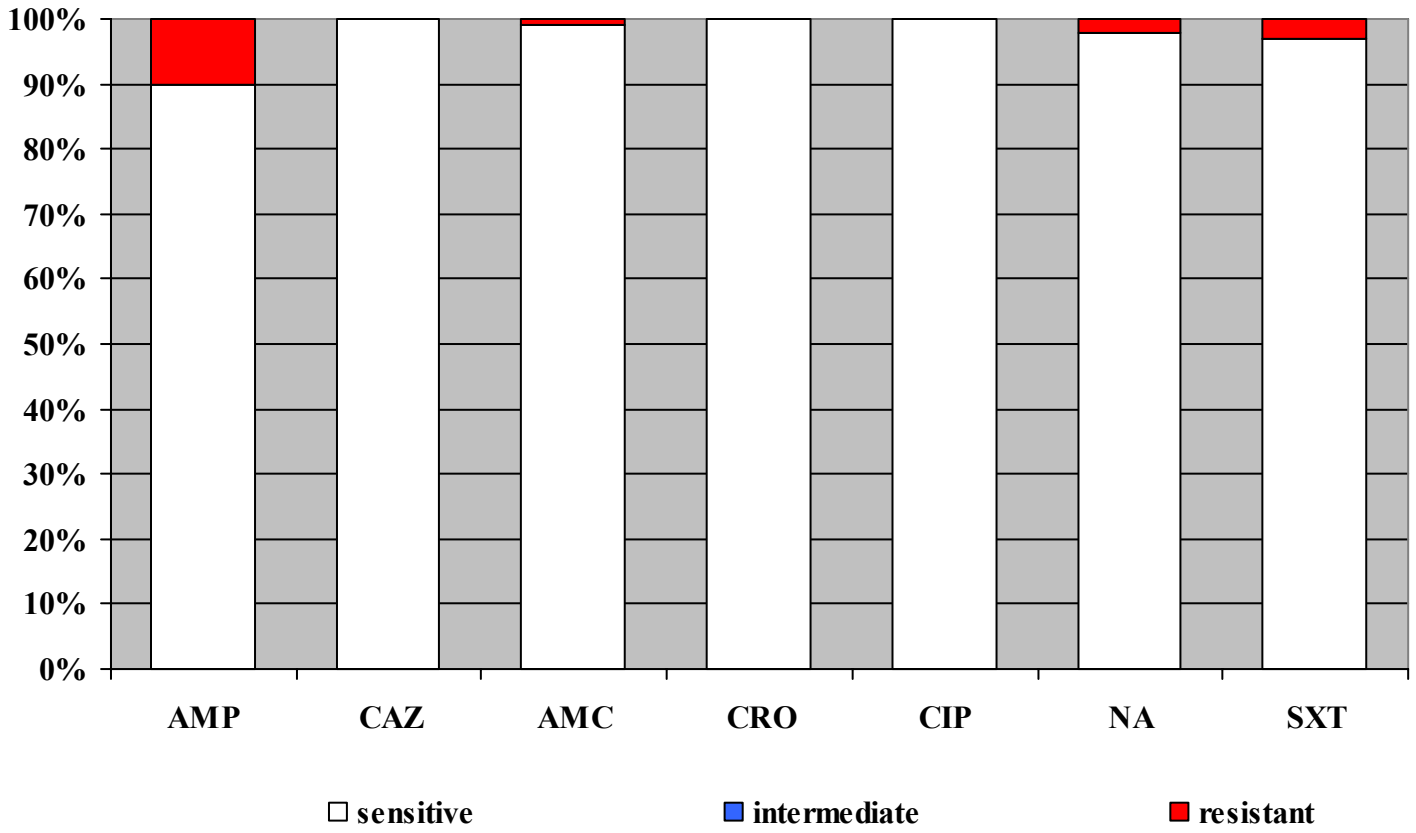
Acinetobacter baumannii

- rezistencija na antibiotike u razdoblju od 1.10.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 1.10. - 31.12. 2011.
summary results for the isolates from 39 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	949	14 (6)	0 (0) - 29 (0)
Meropenem	1 009	64 (2)	34 (7) - 94 (0)
Imipenem	1 016	64 (3)	34 (7) - 94 (0)
Ciprofloxacin	1 021	88 (0)	78 (0) - 100 (0)
Gentamicin	1 025	83 (0)	71 (0) - 98 (0)
Netilmicin	971	66 (1)	25 (0) - 96 (0)
Amikacin	1 018	67 (1)	40 (0) - 94 (0)
Co-trimaxazole	806	78 (1)	52 (0) - 97 (0)
Colistin	749	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

Salmonella spp. (1.01. - 31.12. 2011.) - osjetljivost na antibiotike u RH - sensitivity to antibiotics in Croatia



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Salmonella spp.

- rezistencija na antibiotike u razdoblju od 01.01.- 31.12. 2011.
zbirni prikaz izolata iz 39 centra u RH
- antibiotic resistance for the period 01.01. - 31.12. 2011.
summary results for the isolates from 39 centers in Croatia

ANTIBIOTIK ANTIBIOTIC	Broj izolata No. of isolates	% rezistentnih (% intermedijarnih) izolata % of resistant (% of intermediate) isolates	Raspon lokalnih rezultata* Range of local results*
Ampicillin	3 755	10 (0)	0 (0) - 53 (0)
Amoxicillin + clav. acid	3 670	1 (0)	0 (0) - 8 (0)
Ceftazidim	3 743	0 (0)	0 (0) - 3 (0)
Ceftriaxone	3 745	0 (0)	0 (0) - 3 (0)
Ciprofloxacin	3 748	0 (0)	0 (0) - 2 (0)
Nalidixic acid	3 617	2 (0)	0 (0) - 9 (0)
Co-trimoxazole	3 752	3 (0)	0 (0) - 9 (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

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***Shigella* spp.** - rezistencija na antibiotike u RH / antibiotic resistance in Croatia, 01.01 - 31.12.2011.

	AMP			AMC			CAZ			CRO			CIP			SXT		
***Shigella* spp.**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**
Shigella* sonnei	11	0	**73**	11	0	**9**	11	0	**0**	11	0	**0**	11	0	**0**	11	0	**82**
Shigella* flexneri	4	0	**75**	4	0	**0**	4	0	**0**	4	0	**0**	4	0	**0**	4	0	**25**
UKUPNO* ***TOTAL***	15	0	**73**	15	0	**7**	15	0	**0**	15	0	**0**	15	0	**0**	15	0	**67**

***** 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 - 31.12.2011.

Anaerobes

	P			AMC			PTZ			ERT			MTZ			CC		
	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**
Gram pozitivni anaerobi osim C.difficile	141	1	**11**	139	0	**0**	138	1	**1**	73	0	**0**	140	0	**40**	139	0	**12**
Gram negativni anaerobi	220	0	**86**	229	1	**6**	226	3	**2**	126	0	**2**	228	0	**11**	225	0	**33**
UKUPNO ***TOTAL***	361	1	**57**	368	1	**4**	364	2	**2**	199	0	**2**	368	0	**22**	364	0	**25**

POGLAVLJE/CHAPTER 2.

OSJETLJIVOST *M. TUBERCULOSIS* U HRVATSKOJ U 2011. GODINI
SENSITIVITY OF M. TUBERCULOSIS IN CROATIA, 2011

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Mikobakterije izolirane u Hrvatskoj u 2011. godini

Trend pada incidencije tuberkuloze u Hrvatskoj nastavljen je i u 2011. godini i iznosila je 15/100 000 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 2011. godini".

Ukupno je pregledano 46.807 kliničkih uzoraka na tuberkulozu. U 4,3% uzoraka kultivacijom su otkrivene mikobakterije. Ukupno je izolirano 2.351 sojeva mikobakterija, što je u odnosu na 2010. godinu 7,7% manje izolata.

M. tuberculosis je i dalje dominantna mikobakterija s 2000 (85,0%) izolata i taj postotak je na razini prethodnih godina. Udio NTM među izoliranim mikobaktrijama se smanjio s 15,8% na 14,8%. I tijekom 2011. godine iz humanih kliničkih materijala nije bilo izolata *M. bovis* i *M. caprae*, a *M. bovis* – BCG soj je izoliran iz 4 klinička uzorka (Tablica 1.).

Laboratorijski podaci o osobama s višekratno izoliranim NTM se sustavno bilježe od 1982. godine. Broj bolesnika s mikobakteriozom je 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), u 2010. 30 (0,68/100 000), a u 2011. su zabilježena 22 bolesnika s zadovoljenim mikrobiološkim kriterijima za dijagnozu mikobakterioze.

Saprofitna mikobakterija *M. gordonae* bila je i u 2011. najzastupljenija. Identificirana je u 37,5% NTM izolata. Najčešće se radilo o kontaminaciji uzoraka, slučajnim nalazima i pseudoinfekcijama u više zdravstvenih ustanova. Među uvjetno patogenim NTM u Hrvatskoj i dalje prevladavaju *M. xenopi* s 13,8% izolata, *M. fortuitum* s 16,2% te *M. avium* i *M. intracellulare* s 7,2% izolata. *M. kansasii* je rijedak i otkriven je u 2,0% izolata. Rijedak je i *M. marinum*, iako bi se očekivalo više izolata obzirom na broj izolata u zemljama koje nemaju more. (Tablica 2.).

Broj rezistentnih sojeva *M. tuberculosis*, a time i bolesnika s rezistentnom tuberkulozom, nije pokazao porast. Od 2000 izoliranih sojeva *M. tuberculosis*, 1879 (93,9%) ih je bilo osjetljivo, a 121 (6,1%) rezistentno na prvu liniju antituberkulotika (Tablica 3.). Među rezistentnim sojevima 24,8% je bilo monorezistentno, dok je više od 60% izolata *M. tuberculosis* bilo rezistentno na 3 i više antituberkulotika iz prve linije. Kod 18,2% izoliranih sojeva utvrđena je monorezistencija na izoniazid (H), kod 6,6% monorezistencija na streptomicin (S). Ni tijekom 2011. godine nije zabilježena monorezistencija na rifampicin (R) i 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 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 kod 62,5% sojeva izoliranih u bolesnika s multirezistentnom tuberkulozom u 2011. godini, a na H u 59,0% sojeva. U 2011. godini su izolirani i polirezistentni sojevi čiji je profil rezistencije uključivao rezistenciju na H. Mutacija u genu *katG*, čest prekursor multirezistencije, pronađena je u 37,5% multirezistentnih sojeva, a otkrivanje te mutacije u monorezistentnih sojeva predstavlja upozorenje o mogućem razvoju daljnje rezistencije kao i multirezistencije (Tablica 5.). Kako za 9 (40,9%) 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 2011

TB incidence hit an all time low in Croatia in 2011 with a rate of 15/100 000 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 2011 was used.

A total of 46,807 clinical samples were analyzed for tuberculosis. In 4.3% of samples, cultivation detected mycobacteria. A total of 2,351 mycobacterial strains were isolated, which was 7% less than in 2010.

M. tuberculosis remained the predominant mycobacterium with 2,000 (85.0%) isolates, though on a lower scale than the previous year. The number of nontuberculous mycobacteria (NTM) decreased from 15.8% in 2010 to 14.8% in 2011. In 2011 there were no *M. bovis* or *M. caprae* isolates, while four *M. bovis* BCG strain were 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 or stabile. To illustrate, in 1995 only 3 (0.07/100 000) cases were registered; in 2009, 22 (0.48/100 000), in 2010, 30 (0.68/100 000); in 2011, 22 (0.48/100 000) cases fulfilling the microbiological criteria for mycobacteriosis were documented.

Saprophytic mycobacterium *M. gordonae* was most common in 2011. It was identified in 37.5% 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 13.8% isolates, *M. fortuitum* with a share of 16.2%, and *M. avium* and *M. intracellulare* with 7.2%. *M. kansasii* remains rare in Croatia with mere 2.0% of isolates. Unexpectedly, Croatia has rare detection of *M. marinum* (only one case in 2011) comparing with the isolation rate of other European countries (Table 2).

The number of resistant *M. tuberculosis* strains and, by extension, cases of resistant TB has not demonstrated any significant increase. Of the 2,000 isolated *M. tuberculosis* strains, 1,879 (93.9%) were sensitive to first-line antituberculotic drugs, while 121 6.1%) were resistant (Table 3). Twenty-five percent of the resistant strains were monoresistant, while over 60% of *M. tuberculosis* isolates were resistant to 3 or more first-line antituberculotics. Monoresistance to isoniazid (H) was established in 18.2% of isolated cases,

monoresistance to streptomycin (S) in 6.6% isolated cases. In 2011, no monoresistance to rifampicin (R) and ethambutol (E) were 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 5 (62.5%) isolated patients with multiresistant TB in 2011, while the resistance to H could be determined in 59.0% strains. In 2011 were poly-resistant strains isolated with a profile of resistance to H. Mutation in the gene *katG*, a common precursor of multiresistance, was detected in 37.5% 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. Still, as for 9 (40.9%) 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, 2001. –2011.
Mycobacteria strains isolated in Croatia, 2001-2011

Godina **Year**	**Ukupno mikobakterija** **Total**	**M. tuberculosis**		***M. bovis***		**Netuberkulozne mikobakterije** *Nontuberculous mycobacteria*	
		Broj ***No***	**%**	***M. bovis***	**BCG - soj**	**Broj** ***No***	**%**
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
2011	2351	2000	85,0	-	4	347	14,8

Tablica -*Table* 2.
Netuberkulozne mikobakterije (NTM) izolirane u Hrvatskoj u 2011. godini
Nontuberculous mycobacteria (NTM) isolated in Croatia in 2011

	Vrsta	**Broj**	**%**
UVJETNO PATOGENE MIKOBAKTERIJE			
sporog rasta	*M. avium*	17	4,9
	M. intracellulare	8	2,4
	M. kansasii	7	2,0
	M. xenopi	48	13,8
	M. lentiflavum	1	0,3
	M. marinum	1	0,3
brzog rasta	*M. fortuitum*	56	16,2
	M. chelonae	12	3,5
	M. peregrinum	2	0,5
	M. abscessus	5	1,5
	M. mucogenicum	2	0,5
	M. celatum	1	0,3
SAPROFITNE MIKOBAKTERIJE			
sporog rasta	*M. gordonae*	130	37,5
	M. terrae	29	8,4
	M. nonchromogenicum	4	1,1
	M. triviale	4	1,1
brzog rasta	*M. flavescens*	4	1,1
	M. vaccae	4	1,1
	M. thermoresistibile	5	1,5
	Mycobacterium sp.	7	2,0
Ukupno		**347**	**100**

Tablica –*Table* 3.
Osjetljivost sojeva *M. tuberculosis* na antituberkulotike u Hrvatskoj, 2011. g.
Drug Susceptibility Testing of M. tuberculosis strains in Croatia, 2011

Ustanova *Institution*	**M. tuberculosis** *strains*	**Osjetljivi** Sensitive	***Rezistentni*** Resistant
ZJZ Čakovec	33	29	4
SB Klenovnik	749	675	74
OB Nova Gradiška	43	43	-
ZJZ Osijek	106	106	-
ZJZ Pula	82	82	-
ZJZ Rijeka	112	109	3
ZJZ Sl.Brod	43	41	2
KB Split	89	87	2
ZJZ Split	21	21	-
ZJZ Šibenik	35	31	4
ZJZ Virovitica	43	43	-
ZJZ Zadar	105	105	-
KBC Zagreb	219	203	10
HZJZ	320	298	22
Ukupno	**2000**	**1879**	**121**

Tablica -*Table* 4.
Rezistentni sojevi *M. tuberculosis* u Hrvatskoj, 2011. godina
Drug resistant M. tuberculosis strains isolated in Croatia in 2011

1 ATL	**Broj sojeva (No.)**
S (streptomicin)	8 (6,6%)
H (izoniazid)	22 (18,2%)
R (rifampicin)	-
Z (pirazinamid)	-
	30 (24,8%)
2 ATL	
S,H	15 (12,4%)
H,R	-
	15 (12,4%)
3 ATL	
H,R,S	10 (8,3%)
H,R,E	4 (3,3%)
H,R,Z	1 (0,8%)
S,R,Z	-
S,H,Z	-
	15 (12,4%)
4 i 5 ATL	
S,H,R,Z	9 (7,4%)
H,R,E,Z	4 (3,3%)
S,H,R,E,Z	48 (39,7%)
	61 (50,4%)
Ukupno - *Total*	**121** (100,0%)

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

Tablica -*Table* 5.
Mutacije odgovorne za rezistenciju na rifampicin i izoniazid u 2011. godini
Mutations responsible for rifampicin and isoniazid resistance in 2011

	No of strains	***kat*G (%)**	***inh*A(%)**	**DT**	***rpo*B**
MDR	8	3 (37.5 %)	0	5 (62.5%)	5 (62.5%)
Polyresistant	4	3 (75.0%)	1 (25.0%)	0	-
Monoresistant	10	4 (40.0%)	2 (20.0%)	4 (40.0%)	-
Total	22	10 (45.5%)	3 (13.6%)	9 (40.9%)	

POGLAVLJE/CHAPTER 3.

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

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Reference Centre for Antibiotic Resistance Surveillance of the Croatian Ministry of Health

Važnost praćenja rezistencije u invazivnih izolata

Praćenje rezistencije na antibiotike u svih kliničkih izolata pojedinih bakterijskih vrsta, na način kako je to opisano u 1. poglavlju ove publikacije pruža vrijedne podatke na nacionalnoj i lokalnoj razini, jer obuhvaća velik broj izolata i ukazuje na širenje rezistentnih klonova u pojedinim sredinama te omogućuje pravovremeno otkrivanje sojeva s novim ili rijetkim mehanizmima rezistencije. Takav način praćenja ima povoljan omjer korisnosti podataka i obima vremena utrošenog na prikupljanje podataka. Međutim, takvo praćenje ne uzima u obzir podatke o pacijentu i ne pruža uvid u kliničku značajnost prikazanih izolata. Izolati iz krvi i likvora imaju neupitnu kliničku značajnost i praćenje osjetljivosti ovakvih izolata pruža klinički izuzetno značajne podatke. Zbog manjeg broja takvih izolata podatke u postotcima je teže proučavati na razini pojedinih centara, no podaci su izuzetno korisni na nacionalnoj razini i omogućuju Hrvatskoj komparaciju s drugim europskim zemljama, s obzirom da je takvo praćenje u Europi uvedeno 1999.g. u okviru European Antimicrobial Resistance Surveillance System (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. U okviru EARSS projekta prikupljali su se podaci za invazivne izolate 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*. Kada je 2010.g. EARSS prešao u EARS-Net koji je dio The European Surveillance System (Tessy), mreže Europskog centra za prevenciju i kontrolu bolesti (engl. "European Center for Disease Prevention and Control", ECDC) Hrvatska je nastavila suradnju s ECDC Tessy programom. S obzirom da ECDC objavljuje rezultate samo zemalja članica Europske unije, ova suradnja trenutno ne uključuje publiciranje hrvatskih podataka u sklopu Tessy rezultata, no hrvatski podaci o rezistenciji invazivnih izolata nastavljaju se publicirati u ovoj publikaciji.

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. Kombinacija kontinuiranog masovnog praćenja rezistencije u svim kliničkim uzorcima i praćenja fokusiranog na invazivne izolate godinama predstavlja optimalan način praćenja rezistencije u Hrvatskoj.

Rezultati praćenja rezistencije u invazivnih izolata

U 2011.g. prikupljen je veći broj izolata negoli prošle godine. Broj laboratorija i broj prikupljenih invazivnih izolata pojedinih vrsta prikazani su u Tablici 1.

Podaci o izolatima šalju se na formularu i obrađuju u Referentnom centru za praćenje rezistencije na antibiotike u Klinici za infektivne bolesti. Sa svrhom retestiranja izolata s rijetkim fenotipom i eventualne daljnje obrade invazivni izolati *S. pneumoniae, E. coli* i *K. pneumoniae* se šalju u Referentni centar za praćenje rezistencije, a izolati *S. aureus, E. faecalis, E. faecium* i *P. aeruginosa* u Referentni Centar za bolničke infekcije. Tijekom 2011.g. prikupljeno je 127 izolata *S. pneumoniae,* 1007 izolata *E. coli*, 314 izolata *K. pneumoniae*, 451 izolata *S. aureus,* 244 izolata enterokoka (180 *E. faecalis* i 64 *E. faecium* izolata) te 265 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). Nešto niže stope pneumokoka rezistentnih na penicilin dijelom su i posljedica drugačijih graničnih koncentracija prema European Committee for Antimicrobial Sensitivity Testing (EUCAST) standardima koji su se u Hrvatskoj počeli primjenjivati u 2011.g. Sojevi s minimalnom inhibitornom koncentracijom (MIK) penicilina od 2.0 mg/L smatrani su prijašnjih godina prema Clinical and Laboratory Standards Institute (CLSI) visoko rezistentnima, dok se od 2011.g. smatraju intermedijarno rezistentnima na penicilin. Rezistencija je u invazivnih pneumokoka uobičajeno niža negoli u izolata koji koloniziraju nazofarinks.

Vrlo je bitno da je udio MRSA izolata (27%) ostao na razini prošlogodišnje stope i potvrdio trend pada MRSA stopa u odnosu na prijašnje godine. To odgovara uočenom padu stope MRSA u sklopu praćenja rezistencije uzročnika iz svih uzoraka (14% u 2011.g.). Udio enterokoka rezistentnih na glikopeptide je nizak, ali je stopa visoke rezistencije na aminoglikozide visoka.

Rezistencija *E. coli* na fluorokinolone je u blagom, ali stalnom porastu. Prema standardima važećim do ove godine, sojevi *E. coli* i *K. pneumoniae* koji su proizvodili beta-laktamaze proširenog spektra (engl. „extended spectrum beta-lactamases“, ESBL) su smatrani rezistentnim na sve cefalosporine. Kako je proizvodnja ESBL daleko najčešći mehanizam rezistencije na cefalosporine 3. generacije u ovih bakterija, podaci za sve cefalosporine 3. generacije bili su identični i poklapali su se s podacima o stopama ESBL sojeva. Od 2011.g., prema EUCAST standardima, *in vitro* osjetljivost ESBL sojeva na beta-laktamske antibiotike se ne korigira te se podaci o rezistenciji na različite cefalosporine više nužno ne podudaraju, a ne podudaraju se nužno niti s ESBL stopama. U 2011.g. rezistencija na 3. generaciju cefalosporina izražena je kao rezistencija na ceftazidim. Po prvi puta je udio ESBL izolata prikazan izdvojeno i odgovara prije referiranim stopama rezistencije na cefalosporine 3. generacije.

Porast rezistencije *P. aeruginosa* na piperacilin/tazobaktam se može dijelom pripisati oštrijim graničnim vrijednostima po EUCAST standardu, ali rezistencija je u laganom porastu i na ostale beta-laktamske antibiotike, uključujući karbapeneme.

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

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

Impact of antibiotic resistance surveillance in invasive isolates

Antibiotic resistance surveillance that includes all clinical isolates, as described in chapter 1 of this publication, provides valuable data on national and local level because it is based on a large number of isolates which gives good insight into the local spread of resistant clones and enables timely detection of novel or rare resistance mechanisms. Such a surveillance system has a good ratio between the usefulness of information provided and time consumed for reporting. However, such a system does not provide any information on patient and clinical significance of the laboratory finding. Blood and cerebrospinal fluid (CSF) isolates have unquestionable clinical significance and antibiotic resistance surveillance in these isolates provides data of high clinical importance. Due to the smaller number of these isolates percentage data do not provide sufficiently informative results at local levels but these data are highly reliable national data that can be compared with data of other European countries. The system of antibiotic resistance surveillance in invasive isolates was introduced in European countries in 1999 when the European Antimicrobial Resistance Surveillance System (EARSS) was started. The Croatian network of microbiological laboratories formed at the Croatian Committee for Antibiotic Resistance Surveillance readily joined the EARSS project in 2001, and provided national data until 2010, when the project ended. Within the EARSS project, only invasive isolates limited to specific bacterial species were collected: at first this included *S.aureus, E. faecalis, E. faecium, S. pneumoniae* and *E. coli*, and then from 2005 *K. pneumoniae* and *P. aeruginosa* were added. When EARSS was transformed in 2010 into EARS-Net which is a subunit of the European Surveillance System (Tessy), a network of the European Center for Disease Prevention and Control (ECDC), Croatia continued collaboration with ECDC Tessy program. As ECDC reports data from European Union Member States this collaboration does not include reporting of Croatian data at the moment but Croatian data continue to be reported in these yearly publications.

A disadvantage of limiting surveillance to blood and CSF isolates only is a limited coverage of clinical isolates which becomes an obstacle especially when looking for novel resistance mechanisms. Such strains can often first be observed in other more frequently taken samples, such as urin and wound swabs. For many years a combination of continuous mass surveillance of antimicrobial resistance in all clinical specimens and focused surveillance in invasive isolates represents an optimal approach to surveillance of antimicrobial resistance in Croatia.

Results of the antibiotic resistance surveillance in invasive isolates

In 2011 a larger number of isolates was collected than the previous year. Number of laboratories reporting and number of invasive isolates collected are shown in Table 1.

Forms with data for each isolate are sent to and analysed at the Reference Centre for Antimicrobial Resistance Surveillance at the University Hospital for Infectious Diseases. With a purpose of retesting and further analysis of isolates with unusual phenotype isolates of *S. pneumoniae*, *E. coli* and *K. pneumoniae* are sent to the Reference Centre for Antimicrobial Resistance Surveillance while isolates of *S. aureus, E. faecalis, E. faecium* and *P. aeruginosa* are sent to the Reference Centre for Hospital Infections. During 2011 we have collected 127 isolates of *S. pneumoniae,* 1007 isolates of *E. coli*, 314 isolates of *K. pneumoniae*, 451 isolates of *S.aureus,* 244 enterococcal isolates (180 *E. faecalis* and 64 *E. faecium* isolates) and 265 isolates of *P.aeruginosa* (Table 1).

For the majority of pathogens the percentage of antibiotic non-susceptible isolates has not changed significantly (Table 2). Somewhat lower penicillin resistance rates are partially a consequence of switching to the European Committee for Antimicrobial Sensitivity Testing (EUCAST) break-point concentrations in 2011. Strains with a penicillin minimum inhibitory concentration (MIC) of 2.0 mg/L were previously considered as resistant according to the Clinical and Laboratory Standards Institute (CLSI) while in 2011 these strains are reported as intermediate. Resistance in invasive pneumococcal isolates is expectedly lower than resistance in isolates that colonize nasopharinx.

It is very important that the proportion of MRSA isolates (27%) remained at the last year rate which confirms a decreasing trend in MRSA rates. This correlates well with the decrease of MRSA observed in mass surveillance (14% in 2011). The proportion of glycopeptide resistant enterococci is low but the rate of high level aminoglycoside resistance is high.

Quinolone resistance in *E. coli* is slightly but steadily increasing. According to the previously applied standards *E. coli* and *K. pneumoniae* isolates producing extended spectrum beta-lactamases (ESBL) were considered to be resistant to all cephalosporins. As ESBL production is by far the most frequent resistance mechanism in 3rd generation cephalosporin resistant isolates of these species, data for all 3rd generation cephalosporins were identical and they equalled the ESBL rates. Since 2011, according to the EUCAST standards, *in vitro* sensitivity of ESBL isolates should not be corrected into resistance and therefore data for different cephalosporins are no longer identical and they do not necessarily match the ESBL rates. For 2011, 3rd generation cephalosporin resistance is expressed as resistance to ceftazidime. For the first time ESBL rates are reported separately and this rate matches the previously reported 3rd generation cephalosporin resistance rates.

The increase in piperacillin/tazobactam resistance in *P. aeruginosa* can be partially explained by the lower break-point concentrations set up by EUCAST but resistance to other beta-lactams, including carbapenems, is also slightly increasing.

Demographic patient data and sample origin data are 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.-2011.
Number of laboratories and number of isolates reported for the period 2001-2011

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
2011	16	127	14	451	16	1007	15	244	14	314	15	265

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

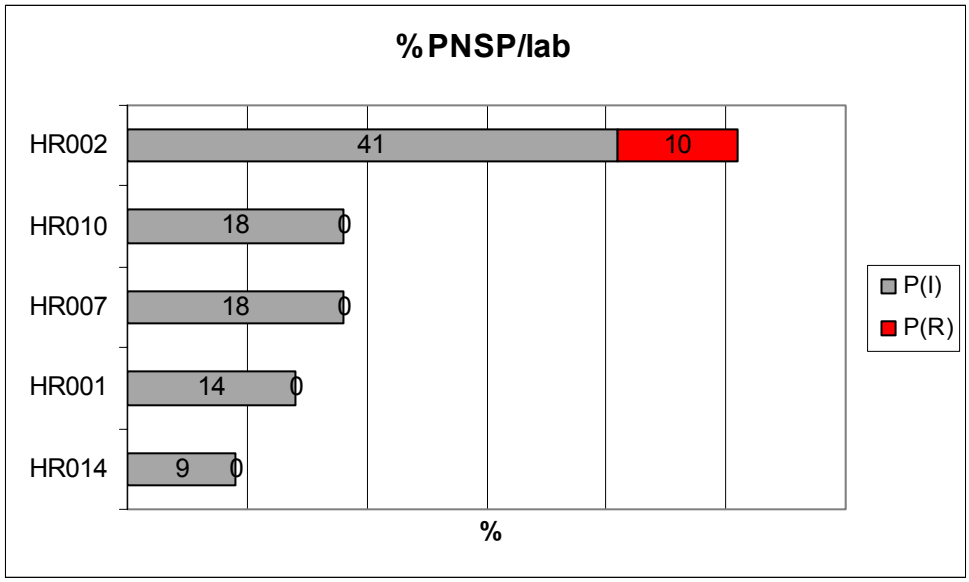
PATOGEN / PATHOGEN	ANTIBIOTICI/ Antimicrobial classes	2001 %	2002 %	2003 %	2004 %	2005 %	2006 %	2007 %	2008 %	2010 %	2011 %
S. pneumoniae	Penicillin R	1	1	1	3	1	1	1	4	7	1
	Penicillin I+R	15	19	20	17	17	18	18	17	21	18
	Macrolides I+R	15	23	18	19	17	16	8	14	29	24
S. aureus	Oxacillin/Met R	32	37	37	38	37	36	38	35	27	27
E. coli	Aminopenicillins R	51	47	46	45	46	51	51	53	55	55
	Aminoglycosides R	6	7	7	6	5	6	6	6	6	7
	Fluoroquinolones R	5	5	7	8	9	15	13	15	17	20
	3. gen Cef R	2	3	4	3	1	1	3	4	8	7
	ESBL										9
E. faecalis	Aminopenicillins I+R	13	5	4	5	6	3	2	5	5	1
	HL Aminoglycosides R	50	40	28	35	31	37	37	46	37	33
	Glycopeptides R	3	<1	<1	<1	<1	<1	<1	<1	<1	1
E. faecium	Aminopenicillins I+R	100	56	47	69	82	69	78	79	82	98
	HL Aminoglycosides R	100	67	41	63	62	59	59	65	60	66
	Glycopeptides R	<1	22	6	3	6	3	2	6	12	2
K. pneumoniae	Aminoglycosides R					38	33	38	51	49	43
	Fluoroquinolones R					18	23	34	44	48	43
	3. gen Cef R					46	34	40	54	56	50
	ESBL										51
P. aeruginosa	Piperacillin R					25	38	30	34	23	
	Piperacllin/Tazobactam R									16	23
	Ceftazidime R					6	11	14	13	12	17
	Carbapenems R					24	25	26	30	26	30
	Aminoglycosides R					35	47	40	39	26	34
	Fluoroquinolones R					34	35	30	33	27	34

Tablica-*Table 3.*
Prikaz invazivnih izolata u 2011.g. prema demografskim podacima pacijenata
Selected details on invasive isolates from the reporting period 2011

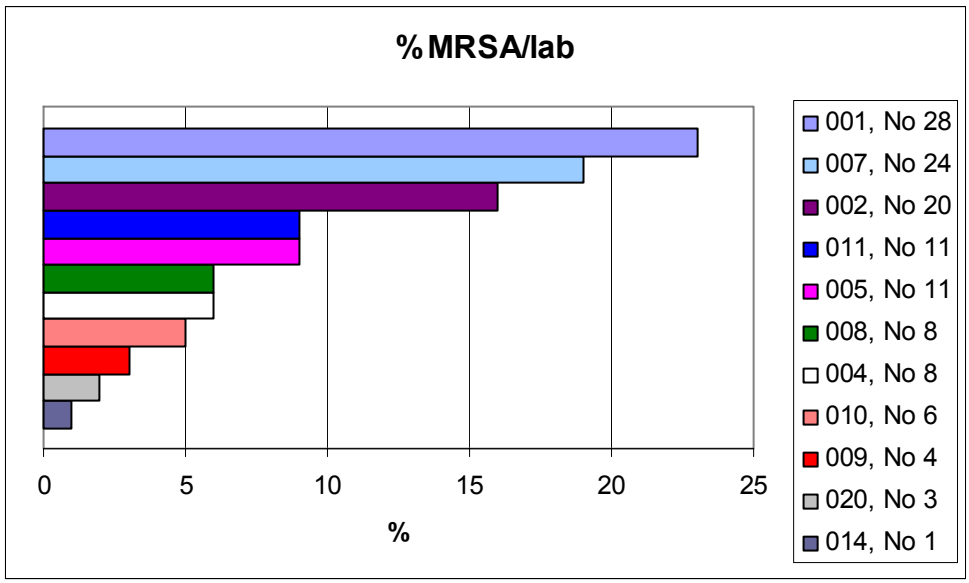
	S.pneumoniae		*S.aureus*		*E.coli*			*Enterococcus* spp.		*K.pneumoniae*		*P.aeuroginosa*	
	n=103		n=363		n=897			n=176		n=286		n=217	
	% tot	% PNPS	% tot	% MRSA	% tot	% FREC	% CREC	% tot	% VRE	% tot	% CRKP	% tot	% CRPA
UZORAK ***SAMPLE***													
Krv / Blood	85	22	99	26	99	16	7	99	3	100	50	99	26
Likvor / CSF	15	19	<1	100	<1	50	0	1	0	0	0	1	0
SPOL ***GENDER***													
M	56	22	68	28	43	21	10	58	3	61	58	67	25
Ž / F	43	21	32	21	56	13	5	40	4	37	41	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	68	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	7	36	4	42	53	41	32
>65	24	8	46	25	59	19	7	45	4	40	43	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	70	29	23
Interna / Medical	84	21	71	15	81	15	7	70	5	63	9	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*
CREC=3rd gen. Cepfalosporine Resistant *E.*coli VRE=Vancomycin Resistant Enterococcus CRKP=3rd gen. Cepfalosporine Resistant *K. pneumoniae*
CRPA=Carbapenem Resistant *P. aeruginosa*

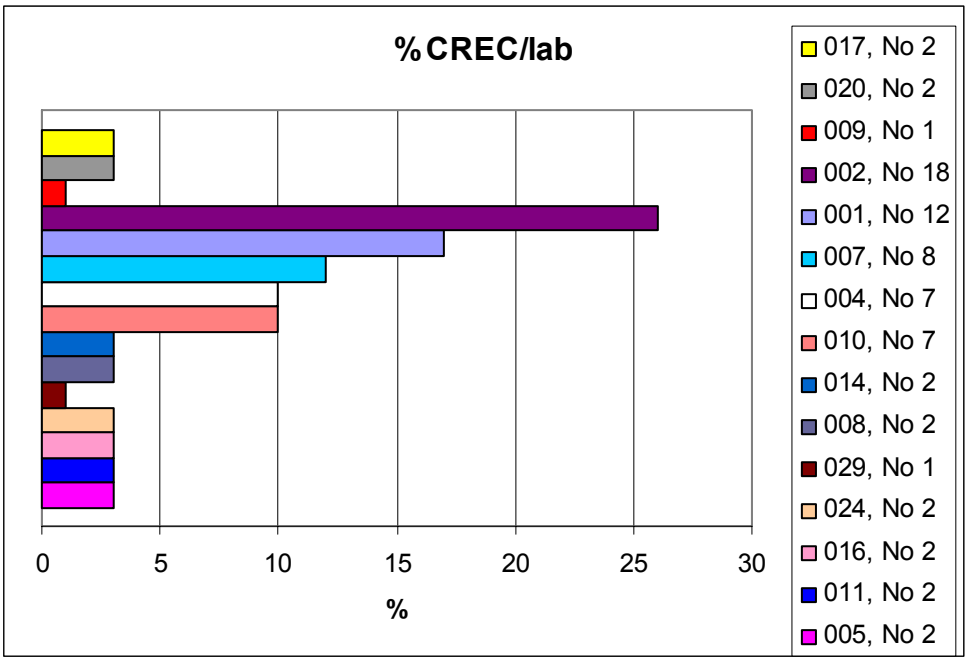
Slika-*Figure 1.*
Udio (%) izolata *S. pneumoniae* smanjene osjetljivosti na penicilin (PNSP) po laboratorijima
Proportion (%) of penicillin non-susceptible S. pneumoniae (PNSP) by laboratory



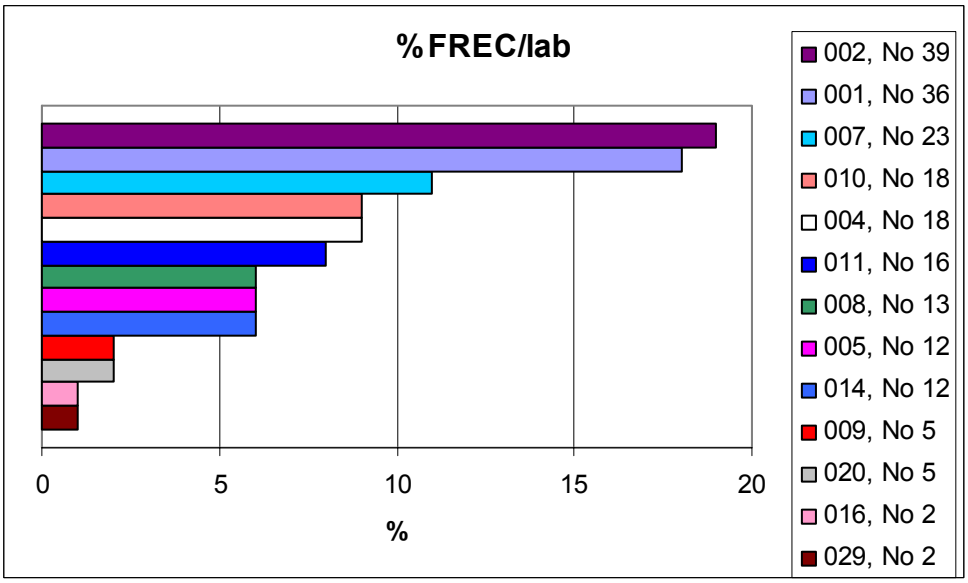
Slika-*Figure 2.*
Udio (%) MRSA izolata po laboratorijima
Proportion (%) of MRSA isolates by laboratory



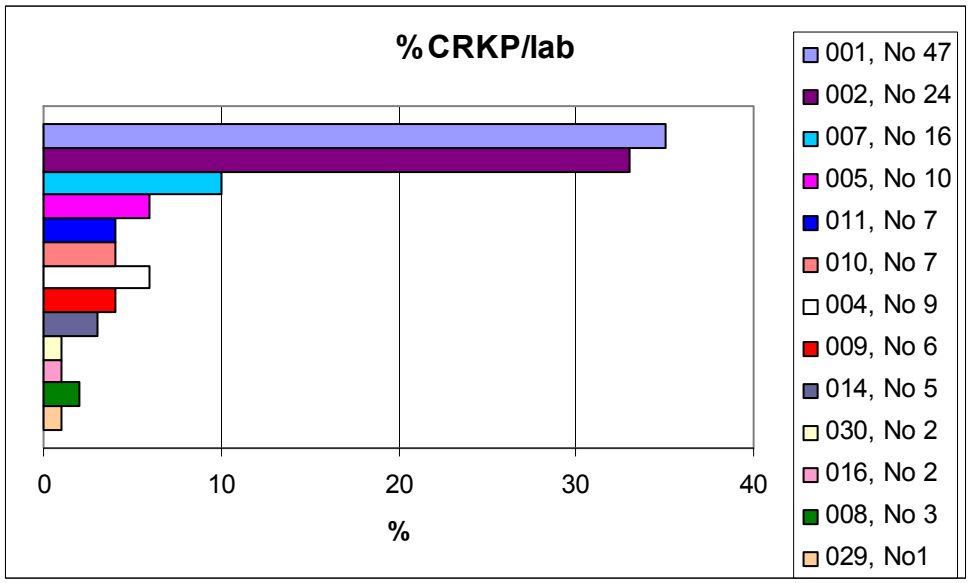
Slika-*Figure 3.*
Udio (%) ceftazidim rezistentnih izolata *E. coli* (CREC) po laboratorijima
Proportion (%) of ceftazidime resistant E. coli isolates (CREC) by laboratory



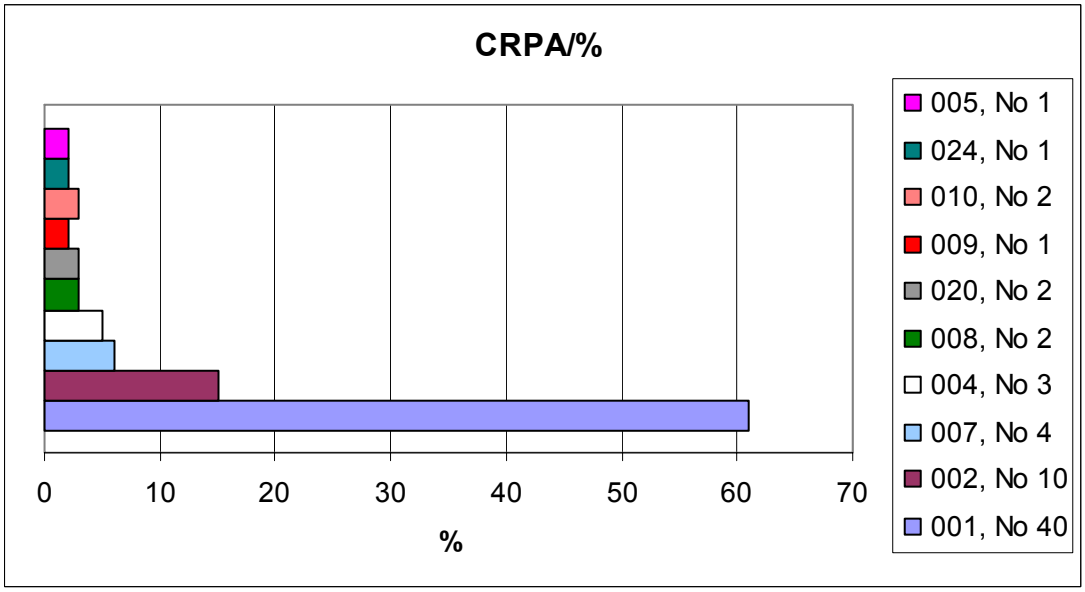
Slika-*Figure 4.*
Udio (%) fluorokinolon rezistentnih izolata *E. coli* (FREC) po laboratorijima
Proportion (%) of fluoroquinolone resistant E.coli isolates (FREC) by laboratory



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

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Potrošnja antibiotika u Hrvatskoj
Antibiotic consumption in Croatia

Izvanbolniočka potrošnja antibiotika u Hrvatskoj

Hrvatska se 2001.g. uključila u projekt European Surveillance of Antibiotic Consumption (ESAC) te počela pratiti potrošnju antibiotika izraženu kao broj definiranih dnevnih doza na tisuću stanovnika dnevno (DDD/TID). Uključivanje u ESAC omogućilo je Hrvatskoj uspoređivanje s drugim europskim državama te potaklo diskusiju u hrvatskoj stručnoj javnosti o potrošnji antibiotika u Hrvatskoj. U okviru ESAC programa odvojeno su se prikazivala bolnička i izvanbolnička potrošnja, što smo u Hrvatskoj nastavili pratiti i nakon prelaska ESAC projekta 2011.g. u ESAC-Net program Europskog centra za kontrolu bolesti (engl. "European Center for Disease Control", ECDC). S obzirom da ECDC objavljuje podatke samo za zemlje članice Europske unije Hrvatska nije u 2011.g. bila uključena u ESAC-Net, no nastavila je s prikupljanjem podataka sljedeći ESAC metodologiju. To podrazumijeva prikupljanje podataka o antimikrobnim lijekovima za sistemsku upotrebu, tzv. grupi J01 prema anatomsko-terapijsko-kemijskoj (ATK) klasifikaciji lijekova. Podaci o potrošnji antibiotika prikupljaju se na petoj, a objavljuju na četvrtoj i trećoj razini ATK klasifikacije. Podaci se izražavaju kao broj definiranih dnevnih doza (DDD) na tisuću stanovnika dnevno (engl. „thousand inhabitants daily", TID).

Za izvanbolničku potrošnju od samog početka praćenja podaci se prikupljaju kroz prikaz veledrogerija. Podaci o prodanim paketima pojedinih pakiranja antibiotika unose se u ABC kalkulator prilagođen hrvatskom tržištu i preko tog programa izračunava se broj potrošenih DDD. Nažalost, do danas Hrvatska nije uspjela pokrenuti detaljniju analizu izvanbolničke potrošnje antibiotika, koja bi omogućila analizu potrošnje antibiotika prema određenim dijagnozama ili prema demografskim podacima pacijenata. Očekuje se da će novi informatički sustav Hrvatskog zavoda za zdravstveno osiguranje (HZZO) omogućiti bolji uvid u navike propisivanja antibiotika čime će se moći pratiti slijede li liječnici nacionalne smjernice o propisivanju antibiotika kao i učinke različitih intervencija usmjerenih na poboljšanje propisivanja antibiotika.

Izvanbolnička potrošnja u 2011.g. čini 93% ukupne potrošnje antibiotika. Trend smanjenja potrošnje nastavlja se i u 2011.g. (slika 1). Registrirano je smanjenje potrošnje gotovo svih klasa antibiotika, osim penicilina s inhibitorima (ko-amoksiklav) (tablica 1). Uvođenje paralelnog praćenja izvanbolničke potrošnje antibiotika preko naplate recepata omogućilo bi ne samo detaljniju već i pouzdaniju analizu potrošnje antibiotika u Hrvatskoj.

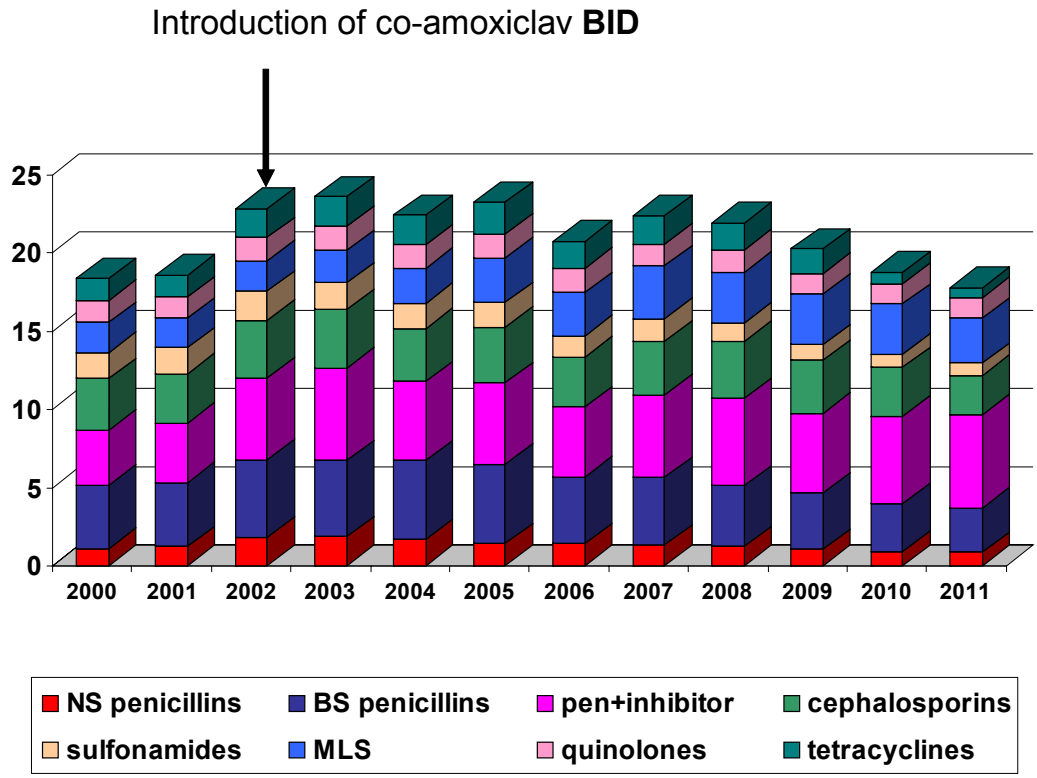
Outpatient antibiotic consumption in Croatia

By joining the European Surveillance of Antibiotic Consumption (ESAC) project in 2001 Croatia started collecting data on antibiotic consumption expressed as defined daily doses per thousand inhabitants daily (DDD/TID). Participation in the ESAC project gave Croatia an opportunity to compare national consumption with the one in other European countries and this also induced lots of discussion on antibiotic consumption among professionals in Croatia. In the framework of the ESAC project ambulatory and hospital antibiotic consumption data were presented separately and this was continued in Croatia after the transition of ESAC into ESAC-Net program of the European Center for Disease Control (ECDC) in 2011. As ECDC publishes data from the European Union member states only, Croatia did not participate in ESAC-Net in 2011. Nevertheless, we continued to collect consumption data using ESAC methodology. This implies data collection on antimicrobial drugs for systemic use, J01 group according to the Anatomical Therapeutic Chemical (ATC) Classification System. Antibiotic consumption data are collected at the 5th level and presented at the 4th and 3rd level of the ATC classification. Data are expressed as DDD/TID.

From the very begining of antibiotic consumption surveillance outpatient data were derived from the wholsalers reports. Package data are eneterd into the ABC calculator adapted to the Croatian market and through this program number of DDDs is calculated. Unfortunatelly, we were not able to start alternative antibiotic consumption data collection for ambulatory care. The present data source does not provide data that could be stratified according to diagnosis or patients demographics. It is expected that the new informatization system at the Croatian Health Insurance Institute (CHII) will be able to provide a more detailed analysis of antibiotic prescribing habits which will be a good indicator of implementation of the national guidelines on antibiotic prescribing. Such a system is also crucial for monitoring impact of various interventions aiming to improve antibiotic prescribing.

Outpatient antibiotic consumption in 2011 makes 93% of total antibiotic consumption in Croatia. A decreasing trend in ambulatory care consumption is continued (Figure 1). Decrease in consumption is recorded for almost all antibiotic classes, except for penicillins with inhibitors (co-amoxiclav) (table 1). Introduction of a paralel data collection system for outpatient consumption using reimbursement data would provide not only more detailed but also a more reliable analysis of outpatient antibiotic consumption in Croatia.

Slika - *Figure 1*
Izvanbolnička potrošnja antibiotika 2000 - 2011
Ambulatory antibiotic consumption 2000 - 2011



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	2011
JO1AA	Tetraciklini Tetracylines	1.82	1.90	1.91	2.01	1.74	1.81	1.73	1.57	1.46	1.39
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	2.84
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	0.88
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	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	5.93
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	0.84
	Cefalosporini II gen. II gen. cephalosporins	1.34	1.37	1.19	1.29	1.15	1.02	1.55	1.59	1.50	1.19
	Cefalosporini III gen. III gen. cephalosporins	0.35	0.44	0.39	0.42	0.42	0.56	0.55	0.61	0.59	0.53
JO1EE	Sulfonamides + trimethoprim	1.85	1.72	1.64	1.57	1.35	1.4	1.17	0.98	0.87	0.73
JO1F	Macrolides, lincosamides	1.92	2.07	2.27	2.82	2.73	3.40	3.24	3.24	3.19	2.89
JO1G	Aminoglycosides	0.04	0.01	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	1.32
JO1XE	Nitrofurantoin						0.47	0.63	0.68	0.69	0.60
UKUPNO / TOTAL		**22.86**	**23.61**	**22.66**	**23.29**	**20.81**	**22.92**	**22.60**	**20.95**	**20.22**	**19.16**

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	2011*
JO1AA	Tetracylines	0.12	0.15	0.08	0.09	0.07	0.06	0.06	0.06	0.05	0.07
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	0.06
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	0.04
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	0.03
JO1CR	Kombinacije s beta-laktamaza inhibitorima	0.64	0.79	0.40	0.36	0.27	0.22	0.25	0.23	0.22	0.51
JO1DA	Cefalosporini I gen. cephalosporins	0.20	0.17	0.09	0.11	0.10	0.11	0.09	0.10	0.09	0.11
	Cefalosporini II gen. cephalosporins	0.28	0.19	0.27	0.25	0.22	0.22	0.19	0.15	0.21	0.23
	Cefalosporini III + IV gen. cephalosporins	0.09	0.12	0.09	0.12	0.11	0.13	0.14	0.16	0.16	0.16
JO1DH	Carbapenems	0.02	0.02	0.02	0.02	0.02	0.04	0.04	0.04	0.04	0.07
JO1EE	Sulfonamides + trimethoprim	0.14	0.20	0.09	0.08	0.07	0.07	0.06	0.06	0.05	0.05
JO1F	Macrolides, lincosamides	0.14	0.16	0.10	0.12	0.10	0.11	0.11	0.12	0.11	0.15
JO1G	Aminoglycosides	0.15	0.12	0.10	0.11	0.10	0.09	0.10	0.10	0.09	0.12
JO1MA	Fluoroquinolones	0.18	0.22	0.15	0.18	0.17	0.19	0.19	0.21	0.21	0.23
JO1XA	Glycopeptides	0.02	0.02	0.02	0.02	0.02	0.03	0.03	0.03	0.03	0.04
JO1XD	Metronidazole	0.06	0.06	0.01	0.06	0.05	0.06	0.06	0.07	0.07	0.07
JO1XE	Nitrofurantoin						0.01	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**	**1.96**

* izvor podataka bolničke ljekarne/ data derived from hospital pharmacies

Potrošnja antibiotika u hrvatskim bolnicama

Od 2001. godine Hrvatska je sudjelovala u praćenju potrošnje antibiotika u okviru European surveillance of antibiotic consumption (ESAC) za što su bili korišteni podaci o potrošnji antibiotika dobiveni iz veledrogerija.

Od osnutka Interdisciplinarne sekcije za kontrolu rezistencije na antibiotike (ISKRA) 2006. godine, već petu godinu za redom, prati se potrošnja antibiotika u hrvatskim bolnicama paralelno iz dva izvora, tj. putem veledrogerija i prema podacima dobivenim iz bolničkih ljekarni. Usporedbom potrošnje antibiotika ovisno o izvoru podataka (veledrogerije/ bolničke ljekarne) u periodu od 2007. godine do 2011. godine (tablica 3, slika 2) uočava se da razlika između dvaju izvora podataka s godinama postaje sve očitija i u 2011. godini ta razlika iznosi 0,56 DDD/1000 stanovnika/dan. Kao što je navedeno u Publikacijama prethodnih godina, razlog tome je što se neki antibiotici distribuiraju u bolnice direktno, a ne preko veledrogerija. Najveće razlike se uočavaju u skupini peninicilna (J01C). Rezultati potrošnje antibiotika temeljeni na podacima dobivenim iz bolničkih ljekarni pouzdaniji su, točniji i precizniji te se od 2011.g. smatraju reprezentativnim podacima za Hrvatsku (tablica 2). Prelazak s jednog izvora podataka na drugi doveo je do administrativnog povečanja bolničke potrošnje u 2011.g., no u zadnjih pet godina paralelno smo prikazivali podatke iz obaju izvora i bili smo svjesni da su podaci o bolničkoj potrošnji podcjenjeni, naročito od 2008.g. nadalje.

Metodologija praćenja bolničke potrošnje antibiotika putem bolničkih ljekarni je dobro uhodana. Prati se skupina J01 - antimikrobni lijekovi za sistemsku upotrebu u skladu s anatomsko-terapijsko-kemijskom klasifikacijom lijekova (ATK klasifikacija). Podaci o potrošnji antibiotika prikupljaju se na petoj razini ATK klasifikacije lijekova, a rezultati se prikazuju na trećoj, odnosno na četvtoj razini. Diskretnije promjene u potrošnji, čak i onih klasa koje bilježe nisku potrošnju, mogu se uočiti ako se kao denominator primijene bolnički dani (100 bolničkih dana).

Tijekom godina praćenja uspostavljena je dobra suradnja s predstavnicima bolnica zaduženih za slanje podataka o potrošnji antibiotika. Podaci o potrošnji antibiotika izraženi u broju paketića/ampula upisuju se u ABC kalkulator koji se svake godine ažurira u skladu s aktualnom situacijom na našem tržištu. Manji broj bolnica dostavlja podatke već preračunate u DDD potrošenih antibiotika. Osim podataka o potrošnji antibiotika iznimno je važno dostaviti sve tražene podatke iz formulara koji dobije svaka bolnička ustanova uz ABC kalkulator priređen za tekuću godinu. Uz osnovne podatke o bolnici (broj kreveta, broj dječjih kreveta, jedinice intenzivnog liječenja (JIL) i vrste JIL-ova), potrebno je dostaviti podatke o broju bolničkoopskrbnih dana (BOD) te broju primitaka kako za čitavu bolnicu, tako i za JIL-ove.

Potrošnja antibiotika kroz dnevne bolnice je od početka bila uključena u ukupnu bolničku potrošnju, no po prvi puta u 2011. godini u denominatoru za bolničku potrošnju uključeni su i podaci o broju terapijskih dana dnevne bolnice. Takav denominator objektivnije prikazuje potrošnju antibiotika u odnosu na aktivnost bolnice. Kod nekih ustanova to je dovelo do smanjenja prikazanih DDD/100 BOD. Taj podatak su dostavile sve opće bolnice osim jedne (O 03) te sve kliničke ustanove, osim četiri (K 06; K 08; K 09; K13), od kojih je jedna (K13) navela da nema dnevnu bolnicu.

Nakon prikupljanja i obrade podataka o bolničkoj potrošnji antibiotika, svaka ustanova izvršila je provjeru vlastitih podataka te je svako značajnije odstupanje u potrošnji antibiotika u odnosu na prošlu godinu dodatno provjereno.

Podatke o bolničkoj potrošnji antibiotika za 2011. godinu dostavile su sve bolničke ustanove, ukupno njih 67. Potrošnja antibiotika u hrvatskim bolnicama za 2011. godinu iznosila je 44,34 DDD/100 BOD, što ukazuje na porast potrošnje u odnosu na 2010. godinu, kada je iznosila 41,76 DDD/100 BOD (tablica 4, slika 3).

Usporedbom potrošnje antibiotika u 2010. godini i 2011. godini uočava se porast potrošnje svih klasa antibiotika (J01A; J01C; J01D; J01 E; J01 F; J01G; J01X) osim kinolona (J01M), kod koje je uočen pad (tablica 5, slika 4).

Broj **kliničkih ustanova** smanjio se u 2011. godini s 15 na 13 iz razloga što su dvije, do tada samostalne klinike, ušle u sastav drugih kliničkih ustanova. Raspon potrošnje antibiotika u kliničkim ustanovama kreće se od 24,3 DDD/100 BOD do 114,9 DDD/100 BOD (tablica 6, slika 5), što je dijelom odraz različitih profila ustanova. U većini kliničkih ustanova (K01; K02; K03; K05; K06; K07; K11; K13) uočava se trend smanjene potrošnje antibiotika, dok je kod četiri kliničke ustanove (K04; K08; K09; K15) taj trend u porastu (slika 4). Najveća stabilnost u potrošnji antibiotika uočava se u kliničkoj ustanovi (K14), čija potrošnja u 4 godine praćenja iznosi manje od 40 DDD/100 BOD bez velikih oscilacija.

Broj **općih bolnica** ostao je jednak broju prethodne godine (22). Opće bolnice O 06 i O 16 premještene su u druge skupine bolnica u prethodnoj godini zbog drugačije kategorizacije (O 06 opća bolnica $\Rightarrow$ specijalna bolnica; O 16 opća bolnica $\Rightarrow$ klinička bolnica;).
Raspon potrošnje antibiotika u toj, po profilu djelatnosti, najhomogenijoj skupini bolnica kreće se od 33,2 (O 24) do 89,3 DDD/100 BOD (O 07), što ukazuje na veliku razliku u propisivanju antibiotika ovisno o bolnici (tablica 7, slika 6). Bolnica s najvećom potrošnjom bilježi čak i do dva i pol puta veću potrošnju u odnosu na bolnicu s najnižom potrošnjom. Medijan potrošnje antibiotika u općim bolnicama u 2011. godini iznosi 55,1 DDD/100 BOD, što je niža vrijednost u odnosu na prethodnu godinu kada je iznosio 58,8 DDD/100 BOD. Samo jedna bolnica bilježi potrošnju ispod 40 DDD/100 BOD. Potrošnja antibiotika u sedam općih bolnica kreće se između 41 i 50 DDD/100 BOD. Šest bolnica se nalazi u rasponu između 51 i 60 DDD/100 BOD. Isti broj bolnica (6) bilježi potrošnju antibiotika između 61 do 70 DDD/100 BOD. Jedna bolnica je u rasponu od 71 do 80 DDD/100 BOD, a jedna iznad 81 DDD/100 BOD.

Kod 16 općih bolnica uočava se pad u potrošnji antibiotika (O 02; O 03; O 04; O 05; O 08; O 09; O 11; O 12; O 15; O 17; O 18; O 19; O 20; O 22; O 23; O 24), dok šest bilježi porast (O 01; O 07; O 10; O 13; O 14; O 21) (slika 5).

Iako je broj **psihijatrijskih ustanova** povećan za jednu tijekom godine, ta ustanova još nije uključena u praćenje potrošnje antibiotika za 2011. godinu, tako da je broj uključenih psihijatrijskih ustanova u praćenje bolničke potrošnje antibiotika ostao 8. To je skupina bolnica s najmanjom potrošnjom koja se u 2011. godini kretala od 3,9 do 28,1 DDD/100 BOD (tablica 8, slika 7). Posebno se uočava značajan porast potrošnje antibiotika u bolnicama P 01 i P 07, gotovo dvostruki, dok je u ostalim psihijatijskim ustanovama na razini prethodnih godina.

Skupina **specijalnih bolnica** (ukupno 22) podijeljena je u 2 podskupine. Prvu čine bolnice namijenjene liječenju (akutne/kronične) koje troše znatno više antibiotika od druge podskupine u kojoj se nalaze bolnice namijenjene rehabilitaciji. Podjela je izvršena prema kriteriju tipa, odnosno namjene bolnice. Po profilu djelatnosti to je najheterogenija skupina bolnica s najvećim rasponom u potrošnji antibiotika od 0 - 55,8 DDD/100 BOD (tablica 9, slika 8). U prvoj podskupini specijalnih bolnica (namijenjene liječenju) šest bolnica bilježi pad (S 01; S 02; S 03; S 04; S 13; S 20) u potrošnji antibiotika, dok tri bolnice imaju uočen porast potrošnje (S 19; S 21; S 22). U drugoj podskupini specijalnih bolnica (namijenjene rehabilitaciji), usprkos tome što je to skupina s relativno niskom potrošnjom antibiotika, kod sedam bolnica (S 06; S07; S09; S10; S12; S15; S18) se uočava trend porasta potrošnje.

Pet godina praćenja, u ovom slučaju potrošnje antibiotika, solidno je razdoblje u kojem se iz godine u godinu gradio i razvijao sustav mreže za praćenje, «dotjerivala» metodologija praćenja te kvaliteta i pouzdanost podataka. Dobiveni podaci pružili su nam jasnu sliku potrošnje antibiotika u Hrvatskoj, hrvatskim bolnicama te trendove u ukupnoj potrošnji i u potrošnji pojedinih klasa antibiotika, kako na razini čitave zemlje, tako i za svaku pojedinu bolničku ustanovu.

Za svaku bolnicu podaci o potrošnji antibiotika su posebna vrijednost u smislu mogućnosti analize potrošnje i praćenja indikatora racionalnog propisivanja kroz analizu potrošnje pojedinih klasa, te trendova u propisivanju. Uočene velike razlike u potrošnji antibiotika unutar pojedinih grupa bolnica (klinike, opće, specijalne i psihijatrijske) ukazuju na potrebu i mogućnost korekcije u propisivanju i potrošnji antibiotika, a sve sa ciljem racionalizacije propisivanja antibiotske terapije.

Antibiotic Consumption in Croatian Hospitals

Since 2001 Croatia participated in the European Surveillance of Antibiotic Consumption (ESAC) with data obtained from the wholesalers.

Since the establishment of the Interdisciplinary Section for Antibiotic Resistance Control (ISKRA) in 2006, for the fifth consecutive year, we are monitoring antibiotic consumption in Croatian hospitals, simultaneously from two different sources, from the wholesalers and from hospital pharmacies. By comparing antibiotic consumption data obtained from the two sources (wholesalers/hospital pharmacies) during the period from 2007 to 2011 (table 3, figure 2) we have observed that discrepancy between the data sources is becoming larger with years and has reached a difference in consumption data of 0.56 DDD/1000 inhabitants per day in 2011. As stated in the Publication from previous years, the reason for this is that some antibiotics are distributed directly to hospitals rather than through wholesalers. The largest differences are observed in the J01C (Penicillins) class. Antibiotic consumption data obtained from hospital pharmacies are more reliable, accurate and precise and therefore from 2011 on these data are considered to be representative data for Croatia (table 2). Transition from one source of data to another resulted in artificial rise in antibiotic consumption. However, for the last five years we were reporting data from both sources and were aware that hospital consumption data were somewhat underestimated when judged by wholesales data, especially after 2008 on.

Methodology for monitoring hospital antibiotic consumption through hospital pharmacies is well established. Data are collected for the group J01 - antimicrobial drugs for systemic use as defined by the Anatomical Therapeutic Chemical classification of medicines (ATC classification). Antibiotic consumption data are collected at the fifth level of ATC classification of drugs, and the results are displayed on the third or fourth level. Discrete changes in consumption, even in those classes that record low consumption, may be observed if bed days (hundred bed days) are used as a denominator.

Over the years a good cooperation with representatives of the hospitals responsible for providing data on antibiotic consumption is established. Antibiotic consumption data expressed in the number of vial/ampoule is entered into the ABC calculator that is updated annually in accordance with the current situation on the Croatian market. A smaller number of hospitals submitted data already converted into DDDs. In addition to data on antibiotic consumption every hospital is requested to submit a demographics form that each hospital receives together with an ABC calculator prepared for the current year. Along with basic information about the hospital (the number of beds, the number of children's beds, number and type of intensive care units (ICUs), it is necessary to provide data on the number of bed days (BD) and the number of hospital admissions for the entire hospital and separately for the ICU's.

From the very begining of surveillance day care antibiotic consumption was included in total hospital consumption but for the first time in 2011 number of therapeutic days in the day care was included in the number of hospital bed days providing a more realistic denominator for antibiotic consumption related to hospital activity. That way a number of DDD/100 BD decreased for some hospitals. This information was submitted by all general hospitals except one (O 03) and by all clinical facilities except for the four institutions (K 06; K 08; K 09; K 13), one of which (K13) stated that it does not have a daycare facility.

After collecting and processing data on hospital antibiotic consumption, each institution got its own data for scrutiny and any significant variation in antibiotic consumption in comparison to last year was carefully investigated.

In 2011 data on hospital antibiotic consumption were submitted by all hospitals, a total of 67. Consumption of antibiotics in Croatian hospitals for 2011 was 44.34 DDD/100 BD, indicating an increase in consumption compared to the 2010, when it was 41.76 DDD/100 BD (Table 4; Figure 3).

Comparing antibiotic consumption in 2010 and 2011, an increase in consumption for all antibiotic classes (J01A, J01C; J01D; J01 E, J01 F; J01G; J01X) is observed, except for the quinolones (J01M) whose consumption slightly decreased (table 5, figure 4).

Number of **clinical facilities** decreased in 2011 from 15 to 13 due to the merger of two previously independent clinics into joint clinical institutions. The range of consumption of antibiotics in clinics ranges from 24.3 to 114.9 BD DDD/100 (table 6, figure 5), which is partly a reflection of difference in institution profiles. In most clinical institutions (K 01, K 02, K 03, K 05; K 06; K 07; K 11; K 13) a trend of reduced antibiotic consumption is observed, and in four clinical institutions (K 04; K 08;K 09;K 15) this trend is increasing (figure 4). The greatest stability in antibiotic consumption is observed in clinical institution (K 14), whose consumption in the 4 years of follow up was less than 40 DDD/100 BD, without large oscillations.

Number of **general hospitals** remained the same as last year (22). General hospitals O 06 and O 16 were moved in the previous year to another group of hospitals due to the different categorization (O 06 general hospital $\Rightarrow$ special hospital, O 16 general hospitals $\Rightarrow$ university hospital). Antibiotic consumption in this, by patient profile most homogenous group of hospitals, ranged from 33.2 (O 24) to 89 DDD/100 BD (O 07), indicating a large variation in antibiotic prescribing among hospitals (table 7, figure 6). The hospital with the largest consumption has up to two and a half times higher consumption compared to the hospital with the lowest consumption. Median of antibiotic consumption in general hospitals in 2011 amounted to 55.1 DDD/100 BD, which is a lower value compared to the previous year when it was 58.8 DDD/100 BD. Only one hospital reported spending less than 40 DDD/100 BD. Consumption of antibiotics in seven general hospitals ranges between 41 and 50 DDD/100 BD. Six hospitals are located in the range between 51 and 60 DDD/100 BD. The same number of hospitals (6) reported antibiotic consumption between 61-70 DDD/100 BD. One hospital is in the range of 71-80 DDD/100 BD and one above 81 DDD/100 BD.

The decrease in antibiotic consumption is shown in 16 general hospitals (O 02; O 03; O 04; O 05; O 08; O 09; O 11; O 12; O 15; O 17; O 18; O 19; O 20; O 22; O 23; O 24), while in six hospitals consumption increased (O 01; O 07; O10; O13; O14; O21) (figure 5).

The number of **psychiatric institutions** has increased by one, but this new institution is not included in antibiotic consumption surveillance for 2011. Therefore the number of psychiatric institutions involved in hospital consumption monitoring remained eight. This is a group of hospitals with the lowest consumption, which in 2011 year ranged from 3.9 to 28.1 DDD/100 BD (table 8, figure 7). Significant increase is especially noted in hospitals P 01 and P 07 - almost double the last year value, while in other psychiatric institutions consumption rates remained the same.

A group of **specialized hospitals** (total 22) is divided into two subgroups, hospitals designed to treat acute/chronic illnesses and hospitals for rehabilitation. The acute/chronic care hospitals spend significantly more antibiotics than the rehabilitation hospitals. Altogether this group is the most heterogeneous group with the largest variation in antibiotic consumption rangeing from 0 to 55.8 DDD/100 BD (table 9, figure 8). In the first subgroup six hospitals (S 01; S 02; S 03; S 04; S 13; S 20) reported a decrease, while three hospitals (S 19; S21; S22) noticed an increase in antibiotic consumption. In another subgroup of special hospitals, despite the fact that this is a group with relatively low consumption of antibiotics, an increasing trend is observed in seven hospitals (S 06; S 07; S 09; S10; S 15; S 18).

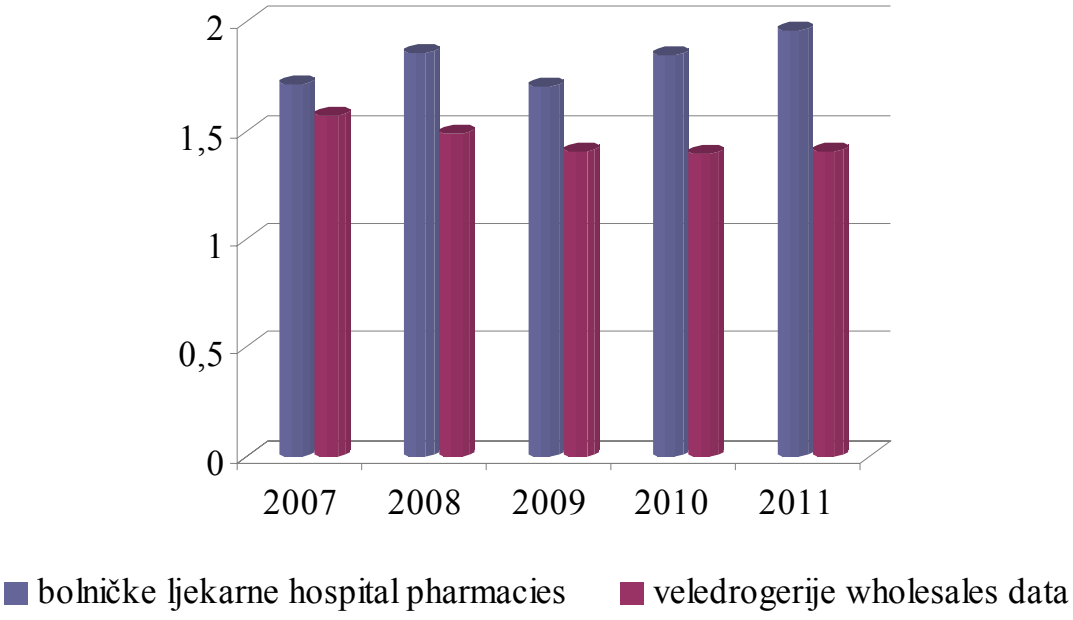
Five years of monitoring, in this case antibiotic consumption, proved to be a period long enough to develop a reliable surveillance network, to implement standardized surveillance methodology and to obtain high quality data. The analysis of these data gives us a clear picture of hospital antibiotic consumption in Croatia, and more specifically shows us the trends in total consumption and consumption of certain antibiotic classes, both at the national level and at the individual hospital level.

Data at the hospital level provide an opportunity for individual hospitals to analyze trends in consumption and monitor indicators of rational antibiotic prescribing. The large variation in antibiotic consumption observed among hospitals of the same category (clinics, general, special and psychiatric hospitals) indicate that there is a need and room for improvement in antibiotic prescribing.

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
2011	1,96	1,4

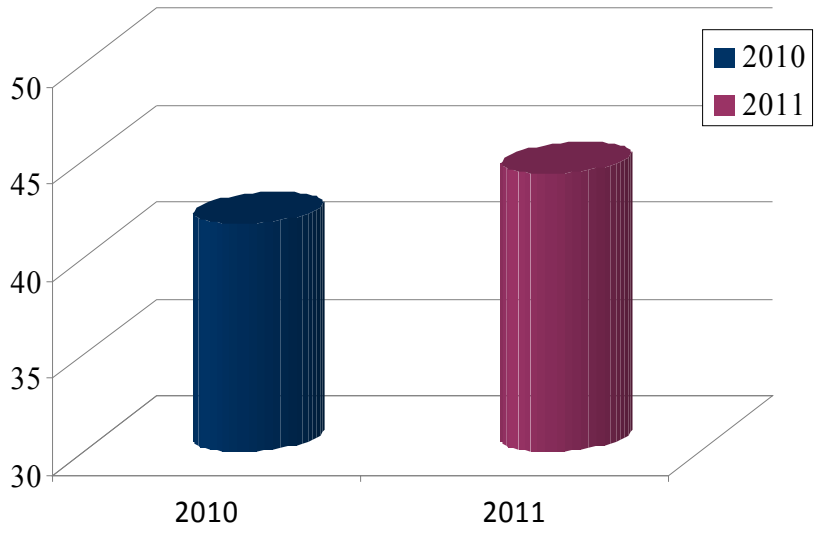
Slika - *Figure 2*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija
Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales data



Tablica - *Table 4*
Bolnička potrošnja antibiotika (DDD/100 BOD)
H*ospital antibiotic consumption (DDD/100 BD)*

godina year	DDD/100 BOD DDD/100 BD
2010	41,76
2011	44,34

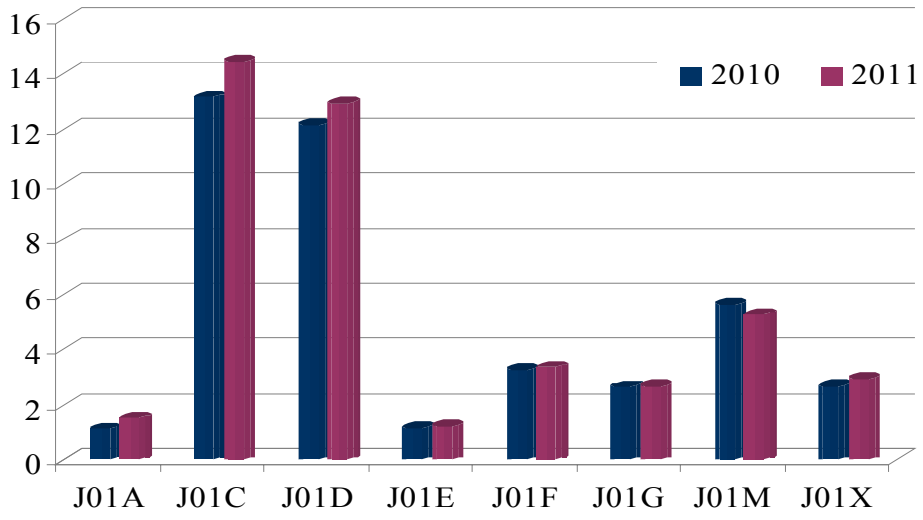
Slika - *Figure 3*
Bolnička potrošnja antibiotika (DDD/100BOD)
Hospital antibiotic consumption (DDD/100 BD)



Tablica - *Table 5*
Bolnička potrošnja antibiotika (DDD/100 BOD) po klasama, izvor podataka - bolničke ljekarne
Hospital antibiotic consumption (DDD/100 BD) by class, origin of data - hospital pharmacies

klasa/class	godina/year	
	2010	2011
J01A	1,12	1,51
J01C	13,16	14,45
J01D	12,13	12,93
J01E	1,16	1,21
J01F	3,26	3,36
J01G	2,65	2,67
J01M	5,62	5,26
J01X	2,66	2,95

Slika - *Figure 4*
Bolnička potrošnja antibiotika (DDD/100 BOD) po klasama, izvor podataka - bolničke ljekarne
Hospital antibiotic consumption (DDD/100 BD) by class, origin of data - hospital pharmacies

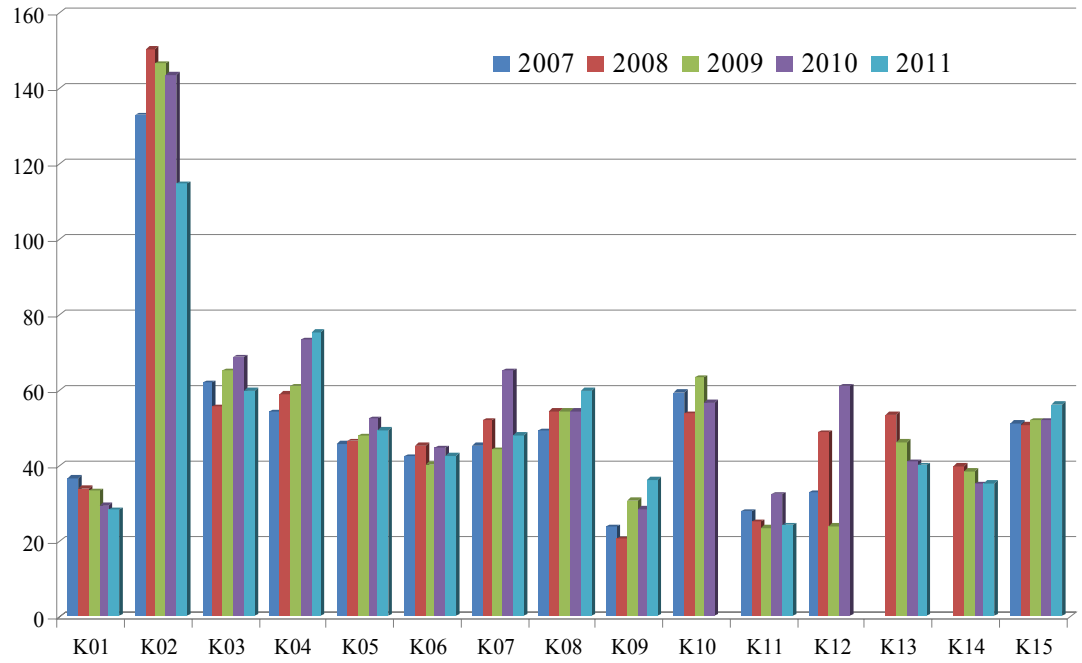


Tablica - *Table 6*
Kliničke ustanove - potrošnja antibiotika, 2011.
Clinical insitutions – antibiotic consumption, 2011

USTANOVA *INSTITUTION*	DDD/100 BOD, *DDD/100 BD*								
	UKUPNO / TOTAL	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
K 01	28,3	0,1	7,7	8,7	1,1	4,4	3,6	1	1,7
K 02	114,9	2,1	54,5	24,3	2,1	10,8	3	10,6	7,4
K 03	60	0,2	22,1	15,5	2	3,2	4,4	5,9	6,5
K 04	75,4	1,6	29,9	17	2,3	5,2	2,4	10,5	6,3
K 05	49,5	1,4	16,7	11,8	1,2	3,5	3,5	8,2	3,1
K 06	42,7	0,7	8,8	18	1	2,1	2,9	5,1	4,2
K 07	48,1	0,6	13,7	14,5	1,5	4,5	2,7	7,1	3,5
K 08	60	1,9	15,2	19,6	1,8	3,7	2,3	9,9	5,6
K 09	36,2	0	3,9	27,6	0	0,3	1,2	2,9	0,3
K 10*									
K 11	24,3	0,1	9,1	10,3	0,6	0,4	1	0,6	2,3
K 12*									
K 13	40,1	0,4	15,3	12,2	3,7	3,4	2,2	1,1	1,9
K 14	35,3	0,4	10,6	16,5	0	2,4	2,1	0,7	2,6
K 15	56,4	0,7	21,5	14,5	0	3,8	3,2	8,4	4,2

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

Slika - *Figure 5*
Kliničke ustanove - potrošnja antibiotika, 2011., DDD/100 BOD
Clinical insitutions – antibiotic consumption, 2011, DDD/100 BD

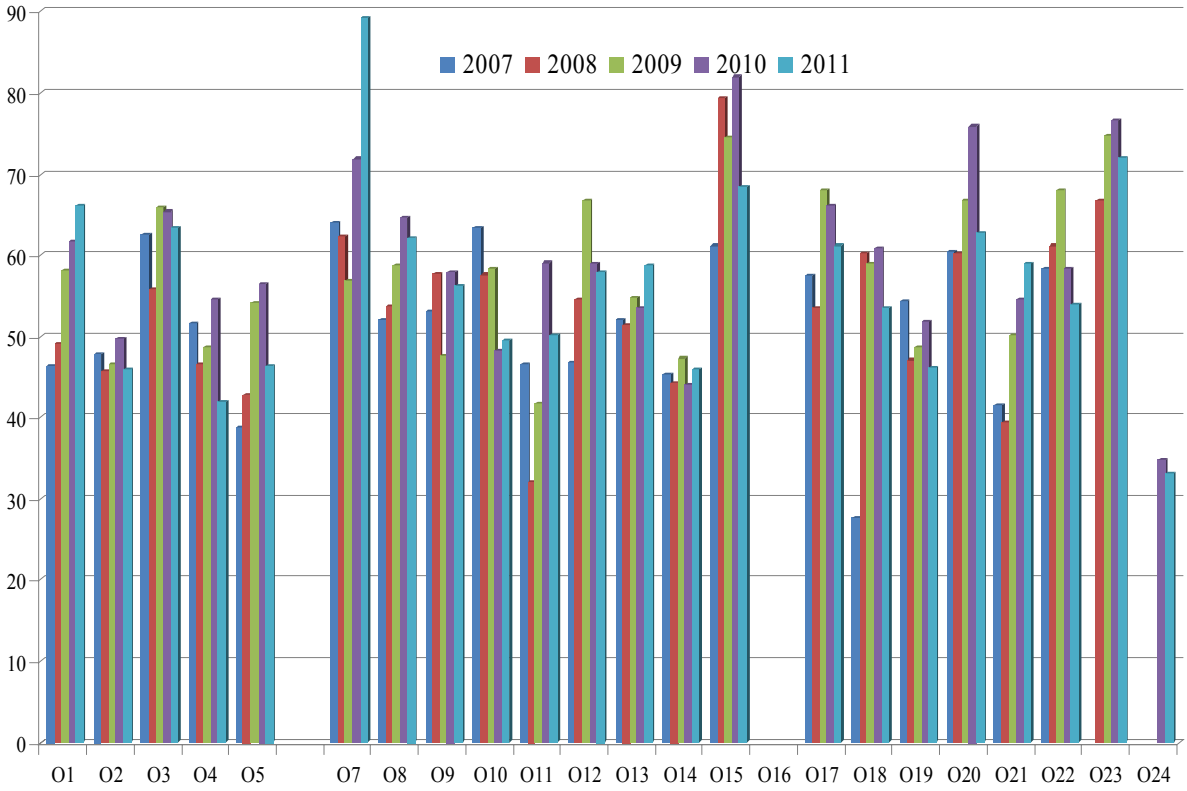


Tablica - *Table 7*
Opće bolnice - potrošnja antibiotika, 2011.
General hospitals – antibiotic consumption, 2011

USTANOVA *INSTITUTION*	DDD/100 BOD, *DDD/100 BD*								
	UKUPNO / *TOTAL*	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
O 01	66,1	2,8	0	16,3	0,2	6,5	6,8	3,1	5,1
O 02	46	0,9	25,2	9,9	0,4	1,6	2,5	3,4	2,2
O 03	63,4	4,7	12,2	26,2	1	9	3,6	3,1	3,7
O 04	41,9	2,5	8,4	13,8	0,9	2,6	5,7	5,8	2,2
O 05	46,4	4,1	20,6	6	0,9	3,7	4,6	5	1,5
O 06*									
O 07	89,3	1,2	29	28,9	2,2	10,1	9,2	6,1	2,5
O 08	62,1	2,7	24,2	11,9	2,4	3,6	5,6	7,4	4,4
O 09	56,3	0,3	16,9	20	0,9	3	5,7	6,1	3,4
O 10	49,6	0,5	12,4	21,8	0,5	3,5	3,7	2,5	4,7
O 11	50,2	1,3	19,9	13,3	1,2	4,3	2,6	5,7	1,9
O 12	57,9	3,4	15,1	23,2	0,8	4,2	1,8	7,3	2,1
O 13	58,8	0,7	17,8	21,5	2	6,5	2,3	4,6	3,1
O 14	46	4	18,1	9,9	3,2	2,8	2,9	2,8	2,3
O 15	68,5	3,5	24,3	19,8	0,7	4	5,9	4,7	5,4
O 16**									
O 17	61,2	1,5	21	19,7	0,4	5,8	3,5	4,4	4,9
O 18	53,6	2,7	24	11,5	0,6	2,7	2,8	6	3,3
O 19	46,2	1	17,5	11,7	1,2	2,8	4,2	5,1	2,8
O 20	62,8	2,9	9,9	28,4	0,4	3,3	4,4	9,3	4,2
O 21	59	1,1	25,3	11,9	1,8	7	4,3	6,3	1,2
O 22	53,9	1	13,1	19,1	0,9	3,5	4,1	9	3,1
O 23	72	2,4	29,6	18,5	0,6	6,8	5,4	4,7	4,1
O 24	33,2	1,1	11,5	5,7	1,2	1	3,3	5,2	4,1

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

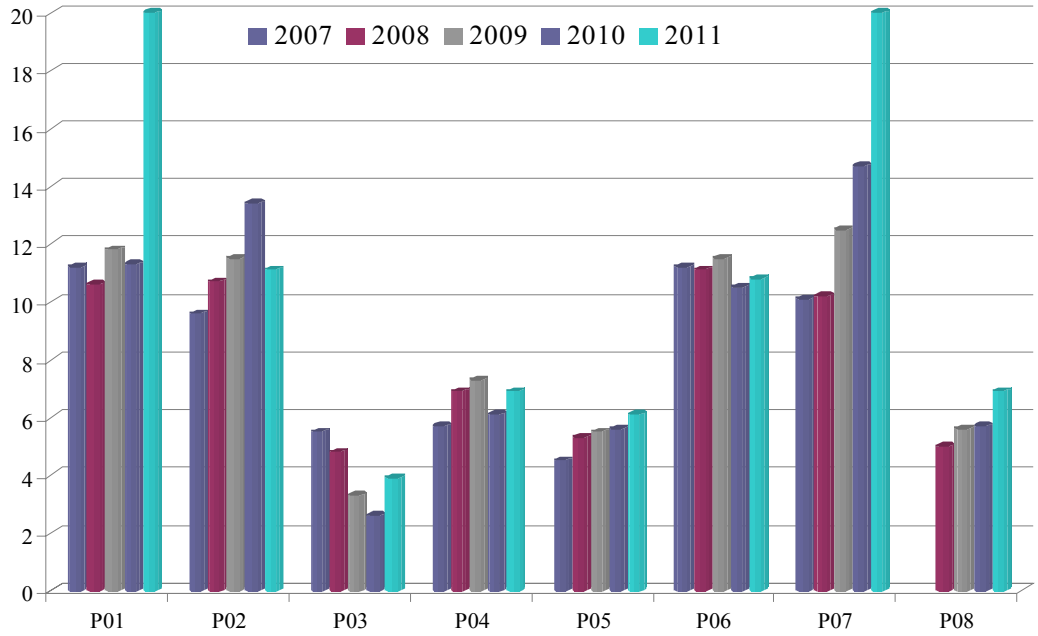
Slika - *Figure 6*
Opće bolnice - potrošnja antibiotika, 2007.-2011., DDD/100 BOD
General hospitals – antibiotic consumption, 2007-2011, *DDD/100 BD*



Tablica - *Table 8*
Psihijatrijske ustanove - potrošnja antibiotika, 2011.
Psychiatric institutions - antibiotic consumption, 2011

USTANOVA *INSTITUTION*	DDD/100 BOD, *DDD/100 BD*								
	UKUPNO / *TOTAL*	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
P 01	20,2	9	5,7	2	0,8	1,3	0,1	0,6	0,6
P 02	11,1	0,1	5,4	2,1	0,7	0,6	0,2	1,6	0,4
P 03	3,9	0	2,8	0,9	0	0,3	0	0	0
P 04	6,9	0,4	3,4	1,1	0,6	0,7	0,1	0,6	0
P 05	6,1	0,2	3,2	1,4	0,1	0,4	0,1	0,7	0
P 06	10,8	0,2	5,9	0,9	0,4	1	0,5	1,7	0,2
P 07	28,1	0,3	5	15	0,5	1,6	3,2	2,2	0,5
P 08	6,9	0,6	2,4	0,7	0,8	0,1	0,3	1,3	0,7

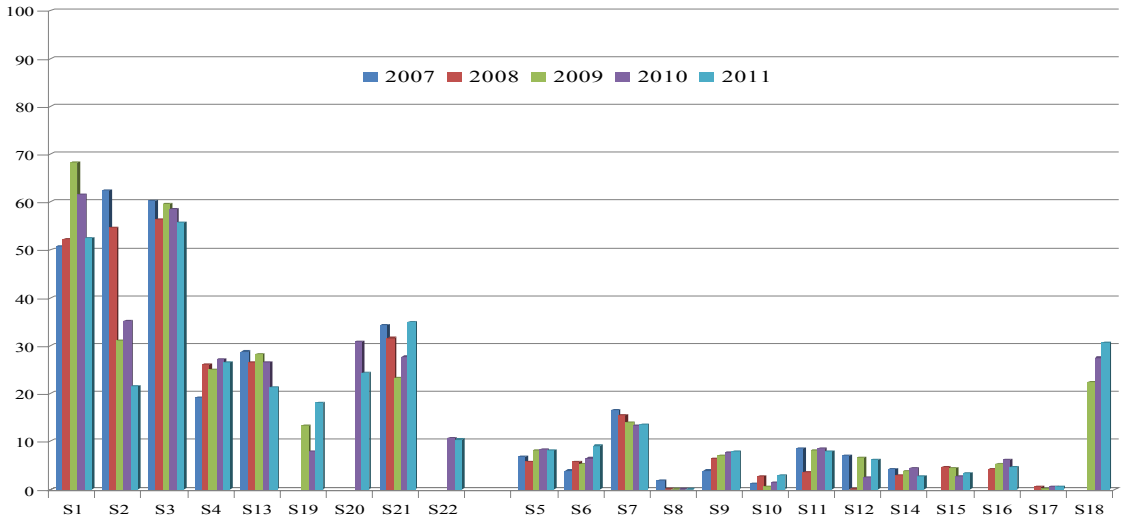
Slika - *Figure 7*
Psihijatrijske ustanove - potrošnja antibiotika, 2007.-2011., DDD/100 BOD
Psychiatric institutions – antibiotic consumption, 2007-2011, DDD/100 BD



Tablica - *Table 9*
Specijalne bolnice - potrošnja antibiotika, 2011.
Specialised hospitals - antibiotic consumption, 2011

USTANOVA *INSTITUTION*	DDD/100 BOD, *DDD/100 BD*								
	UKUPNO / *TOTAL*	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
S 01	52,4	0,4	24,4	2,5	1,9	4	6,9	11,5	1
S 02	21,6	0	7,6	6	0,2	6,2	0,6	0,8	0,3
S 03	55,8	2,4	21,3	9,6	2,7	3,3	7,2	9,1	0,4
S 04	26,5	0,6	11,2	5,1	2,9	0,6	1,8	3,1	1,1
S 13	21,3	6,9	2,4	4	1,4	0,6	1,6	2,1	2,4
S 18	30,6	1,5	12,8	9	0,2	1,1	0,5	4,9	0,6
S 19	18	0,2	6,8	4	2,9	0,4	0,7	2,3	0,6
S 20	24,4	0	7,5	7,9	0	0,7	1	2	5,2
S 21	34,9	0	16,1	8,7	0,2	1,9	0,6	4,7	2,7
S 22	10,4	0	1,1	7,1	0	1,4	0,6	0	0,3
S 05	8,2	0	3,9	1,5	0,5	0,5	0,2	1,3	0,3
S 06	9,1	0	3,1	1,1	1,3	0,3	0,1	2,8	0,5
S 07	13,6	0	3,9	3,2	0,6	1,4	0,7	3,1	0,6
S 08	0	0	0	0	0	0	0	0	0
S 09	7,9	0,1	3,5	0,8	0,4	1,3	1,3	0,4	0
S 10	2,9	0,2	0,8	0,4	0,6	0,1	0	0,5	0,2
S 11	7,9	0,3	2,9	2,3	0,4	0,5	0	1,4	0,2
S 12	6,1	0,7	4,6	0	0,3	0,4	0	0,1	0
S 14	2,7	0,2	1,2	0,6	0	0,4	0	0,3	0
S 15	3,3	0	1,7	0,9	0,1	0,4	0	0	0,2
S 16	4,6	0,4	2,6	0,5	0,4	0,1	0	0,5	0,2
S 17	0,5	0	0,3	0,1	0	0	0	0	0

Slika - *Figure 8*
Specijalne bolnice - potrošnja antibiotika, 2007.-2011., DDD/100 BOD
Specialised hospitals - antibiotic consumption, 2007-2011, DDD/100 BD



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, 2011.
EXTERNAL QUALITY CONTROL, 2011

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Reference Centre for Antibiotic Resistance Surveillance of the Ministry of Health and Social Welfare, Republic of Croatia

Vanjska kontrola kvalitete
External Quality Control

Opis sojeva za kontrolu: <u>proljeće 2011</u>

Kao proljetna kontrola testiranja osjetljivosti na antibiotike obrađeni su podaci za sojeve koji su testirani u okviru EARS-Net projekta, UK National External Quality Assessment Service for Microbiology (UK NEQAS) distribucija 2803 od 3. svibnja 2011. godine. Rezultati su interpretirani prema EUCAST verziji 1.3, s obzirom da su to bili dogovoreni i službeni standardi za Hrvatsku u 2011. godini.

Soj 0270: ***Escherichia coli****:* soj producira ESBL CTX-M-15 i granično je osjetljiv na amikacin (4-8 mg/L) i tazobaktam (8-16 mg/L). Svi hrvatski laboratoriji (30/30) su točno identificirali soj. Samo jedan laboratorij je proglasio soj rezistentnim na amikacin (velika greška), a još pet laboratorija intermedijarno osjetljivim na amikacin. Šest laboratorija (6/30) je utvrdilo smanjenu osjeljivost na piperacilin/tazobaktam. Hrvatski laboratoriji kao i europski laboratoriji nisu imali problema u prepoznavanju prisutnosti ESBL kod ovog soja (podatci službenog UKNEQAS izvješća).

Soj 0271: ***Klebsiella pneumoniae****:* soj producira karbapenemazu klase A, KPC i beta-laktamazu proširenog spektra, ESBL SHV-12. Detekcija ESBL-a otežana je prisutnošću KPC i težom interpretaciojm testa sinergije s klavulanatom. Vrijednosti za III. generaciju cefalosporina bile samo blago reducirane. Iako soj producira karbapenemazu vrijednost MIK-a mikrodilucijskom metodom za imipenem je niska (0,5-1 mg/L), a za meropenem je 4 mg/L. Također, soj producira AAC(6')I aminoglikozidazu i rezistentan je na tobramicin (>128 μg/m), osjetljiv na gentamicin (1 mg/L) i granično osjetljiv na amikacin (16 mg/L: *EUCAST (I); CLSI (S)*). Niti jedan od hrvatskih laboratorija nije odredio točno osjetljivost ovog soja na sve antibiotike. Produkciju ESBL nije prepoznalo 19/ 30 hrvatskih laboratorija. Iako soj ima niski MIK za imipenem, UK NEQAS očekivani rezultat je bio rezistencija na imipenem, što rezultat dobiven disk difuzijom u 25/30 hrvatskih laboratorija. Samo 6/30 hrvatskih laboratorija prepoznalo je smanjenu osjetljivost na amikacin, a čak 23/30 laboratorija su soj proglasili rezistentnim na amikacin.

Soj 0272: ***Streptococcus pneumoniae****:* soj je smanjeno osjetljiv na penicilin (MIK 0,5 mg/L) i ciproflokacin. Naglasak je bio na kliničkoj interpretaciji za penicilin zbog prilagodbe terapijske doze penicilina dobivenoj vrijednosti MIK-a, te na interpretaciji vrijednosti diska norfloksacina od 10 μg koji se koristi za provjeru osjetljivosti soja na kinolone. Osamnaest hrvatskih laboratorija točno je odredilo osjetljivost ovog soja na sve antibiotike. Točno je smanjenu osjetljivost na penicilin detektiralo 22/30 laboratorija, a točnu interpretaciju za primjenu doze penicilina za pneumoniju imalo je 25 od 30 laboratorija, dok je za meningitis točnu interpretaciju primjene penicilina imalo 26/30 laboratorija. Većina laboratorija imala je problema s upisivanjem vrijednosti za norfloksacin, te je stoga osjetljivost na kinolone procijenjena na temelju upisa vrijednosti za ciprofloksacin. Čak sedam laboratorija nije upisalo vrijednost ni za norfloksacin niti za ciprofloksacin, a 12/30 laboratorija je točno utvrdilo smanjenu osjetljivost na ciprofloksacin.

Soj 0273: ***Enterococcus faecium****:* soj ima *vanB* posredovanu rezistenciju te je rezistentan na vankomicin (MIK 8-16 mg/L), ali ne i na teikoplanin. Također je rezistentan na ampicilin ali nema visoku rezistenciju na gentamicin. Jedan hrvatski laboratorij je soj identificirao kao *Enterococcus gallinarum*. Većina laboratorija (29/30) je prepoznala v*anB* posredovanu rezistenciju. Samo 2/30 laboratorija su netočno utvrdila visoku rezistenciju soja na gentamicin.

Soj 0274: ***Pseudomonas aeruginosa****:* soj je trebalo interpretirati kao rezistentan samo na gentamicin. Svi hrvatski laboratoriji (30/30) su točno utvrdili rezistenciju soja na gentamicin. Jedan je laboratorij napravio veliku grešku utvrdivši da je soj rezistentan na imipenem i intermedijarno osjetljiv na meropenem.

Soj 0275: ***Staphylococcus aureus****:* soj je MRSA s inducibilnom rezistencijom na klindamicin (MLSB inducibilna rezistencija) i naglasak je bio na interpretaciji i komentaru koji bi trebao pratiti nalaz za kliničara da terapija klindamicinom može biti neuspješna zbog mogućnosti selekcije klindamicin rezistentnih mutanti za vrijeme terapije. Hrvatski laboratoriji su većinom (29/30) točno interpretirali osjetljivost ovog soja na klindamicin. Jedan laboratorij je primjenom i cefoksitinskog i oksacilinskog diska krivo ustvrdio osjetljivost soja na meticilin, što predstavlja vrlo veliku grešku.

Challenge strains: spring 2011

For the spring challenge EARS-Net UK National External Quality Assessment Service for Microbiology (UK NEQAS) 2803 test strains, distributed on 3rd May 2011, were used. Results were interpreted according to the EUCAST standards, version 1.3 as these were the official standards for Croatia in 2011.

Strain 0270: ***Escherichia coli****:* this strain produces ESBL CTX-M-15 and shows borderline sensitivity to amikacin (4-8 mg/L) and piperacillin-tazobactam (8-16 mg/L). All the Croatian laboratories (30/30) identified the strain correctly. Only one laboratory declared strain as resistant to amikacin (major error), and five laboratories declared intermediate sensitivity to amikacin. Six laboratories (6/30) detected intermediate sensitivity to piperacillin-tazobactam. Croatian as well as European laboratories had no problem in detection of ESBL (data from the EUCAST official report).

Strain 0271: ***Klebsiella pneumoniae****:* this strain produces carbapenemase KPC, class A β-lactamase and at the same time produces extended spectrum beta-laktamase, ESBL SHV-12. ESBL detection was problematic due to the presence of carbapenemase and because in disk diffusion III generation cephalosporins were only of slightly reduced values so that clavulanat synergy tests were difficult to interpret. Although the strain produces carbapenemase MIC value for imipenem was low (0, 5-1 mg/L) and for meropenem was 4 mg/L. Strain also produces AAC (6') I aminoglycosidas,e and is resistant to tobramycin (>128 μg/m), sensitive to gentamicin (1 mg/L) and borderline sensitive to amikacin (16 mg/L: EUCAST (I); CLSI (S)). None of the Croatian laboratories reported correct sensitivity to all antibiotics for this strain. ESBL production was not detected by 19 of 30 Croatian laboratories. Although this strain has a low MIC for imipenem the UK NEQAS intended result was imipenem resistant which is the result obtained in 25 of 30 Croatian laboratories. Only 6/30 Croatian laboratories recognized reduced susceptibility to amikacin and 25/30 laboratories reported strain as resistant to amikacin.

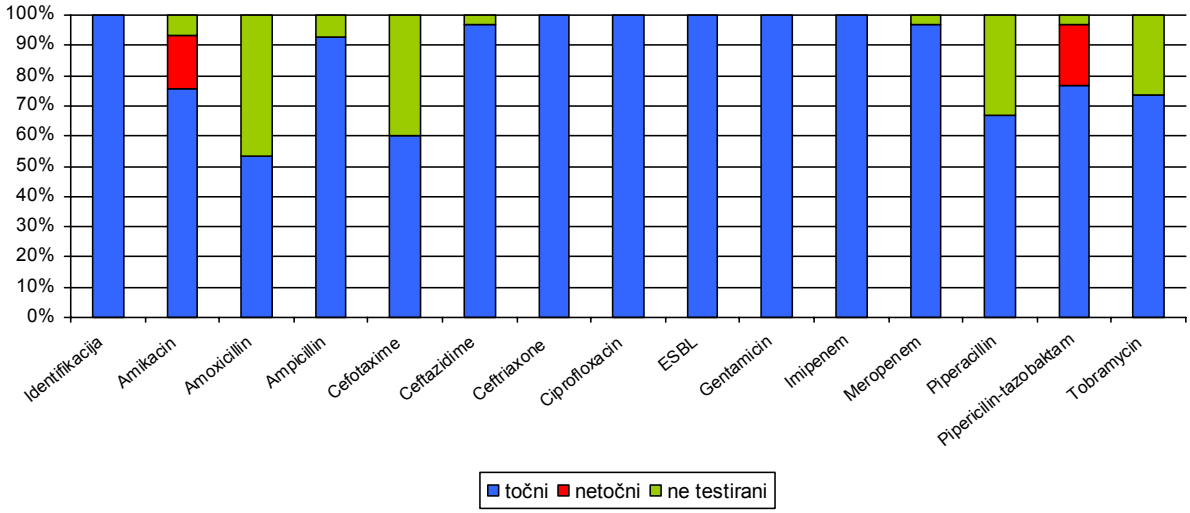
Strain 0272: ***Streptococcus pneumoniae****:* this strain shows reduced sensitivity to penicillin (MIC 0.5 mg/L) and ciprofloxacin. The point of this challenge was clinical interpretation of penicillin MIC according to clinical indication and dosing and interpretation of norfloxacin 10 μg disc screening test for quinolone resistance. Eighteen Croatian laboratories correctly reported sensitivity of this strain to all antibiotics. Reduced sensitivity to penicillin correctly detected 22 of 30 laboratories, and correct interpretation for therapeutic dose of penicillin for pneumonia was reported by 25 of 30 laboratories. At the same time correct interpretation for penicillin in meningitis cases was reported by 26/30 laboratories. The majority of laboratories had problem with norfloxacin reporting and quinolone susceptibility was estimated according to ciprofloxacin values. Seven laboratories did not report values for norfloxacin and ciprofloxacin at all and 12/30 laboratories correctly reported reduced sensitivity to ciprofloxacin.

Strain 0273: ***Enterococcus faecium****:* this strain has *vanB* resistance phenotype and is resistant to vancomycin (MIC 8-16 mg/L), but not to teicoplanin. The strain is also resistant to ampicillin, but does not show high level resistance to gentamicin. One Croatian laboratory identified strain as *Enterococcus gallinarum*. The majority of Croatian laboratories (29/30) detected *vanB* resistance phenotype. Only 2/30 laboratories reported high level resistance to gentamicin.

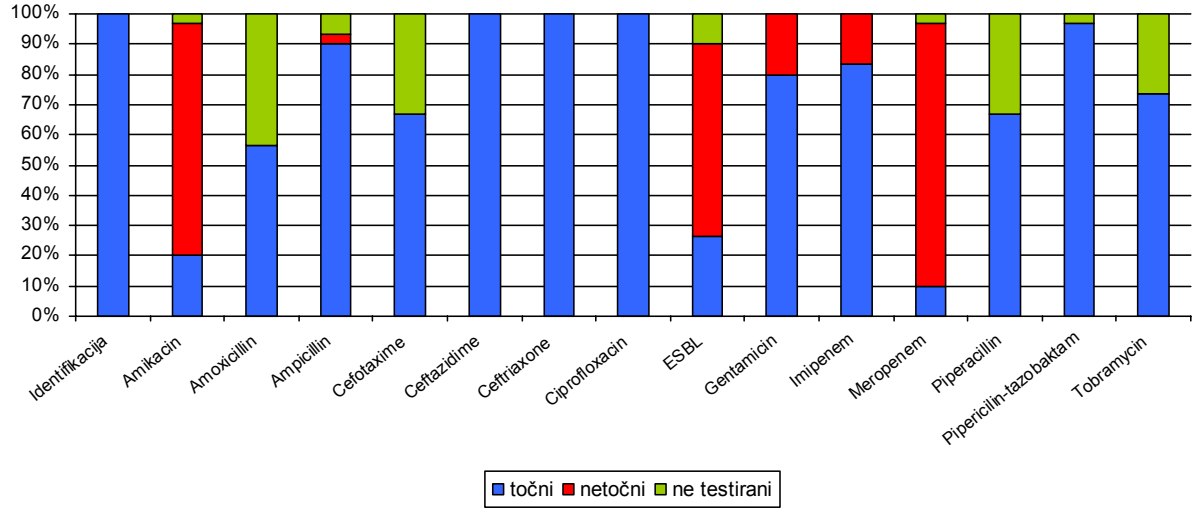
Strain 0274: ***Pseudomonas aeruginosa****:* this strain should be interpreted as resistant to gentamicin only. All Croatian laboratories (30/30) correctly detected resistance to gentamicin. One laboratory made major error and reported imipenem as resistant and meropenem as intermediate.

Strain 0275: ***Staphylococcus aureus****:* this strain is MRSA with inducible resistance to clindamycin (MLSB inducible resistance). The main point of this challenge was clinical interpretation for clindamycin and a necessity to include a comment for clinicians stating that clindamycin therapy for this strain may be unsuccessful because resistant mutants can easily be selected during therapy. Croatian laboratories generally did not have problem with clindamycin testing and interpretation (29/30 reported correctly). One laboratory reported this strain to be sensitive to methicillin using both cefoxitin and oxacillin disk which is a very major mistake.

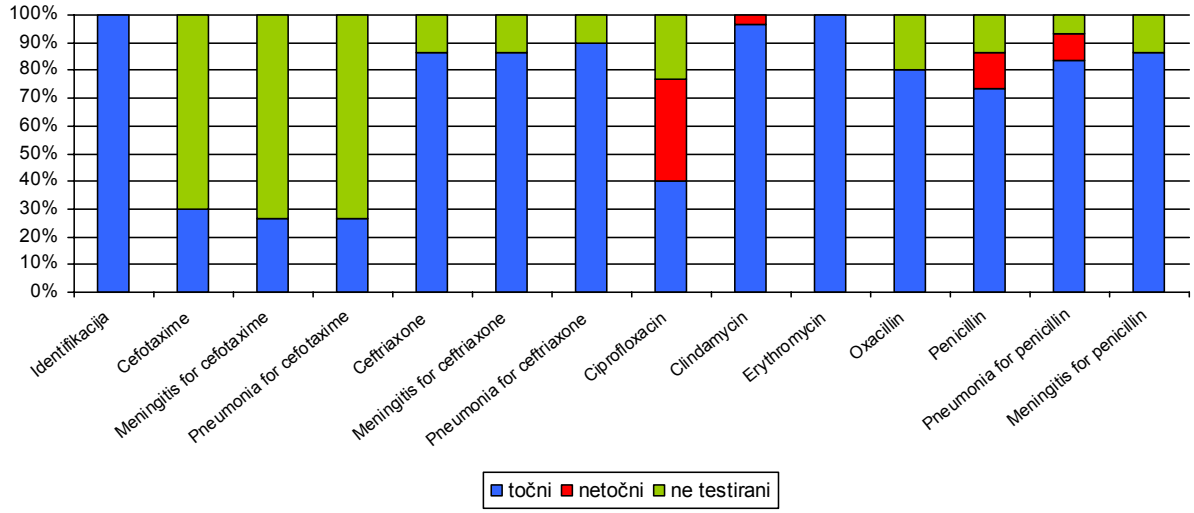
Slika-*Figure 1.*
NEQAS soj 0270: ***E.coli* ESBL** - granično osjetljiva na amikacin i pipercilin-tazobaktam
NEQAS strain 0270: ***E.coli ESBL*** *Amikacin and piperacillin-tazobactam borderline sensitivity*
NEQAS: Amikacin MIC 4-8 mg/L (S), piperacillin-tazobactam MIC 8-16 mg/L (S/I)



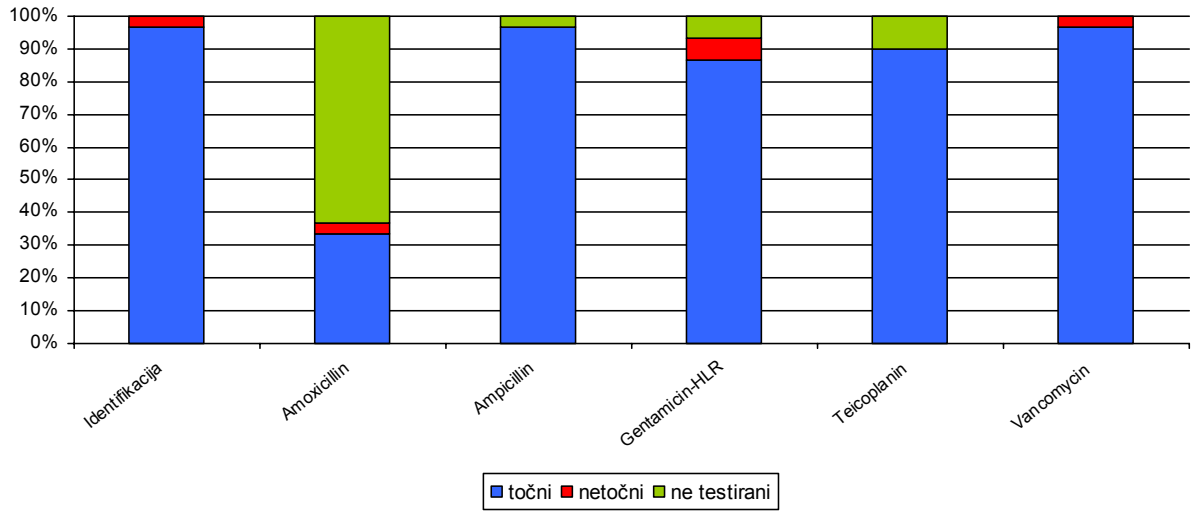
Slika-*Figure 2.*
NEQAS soj 0271: ***K.pneumoniae* KPC i ESBL**
NEQAS strain 0271: ***K.pneumoniae KPC* and *ESBL positive***
NEQAS: Meropenem (I), Imipenem (R), tobramycin (R), gentamicin (S)



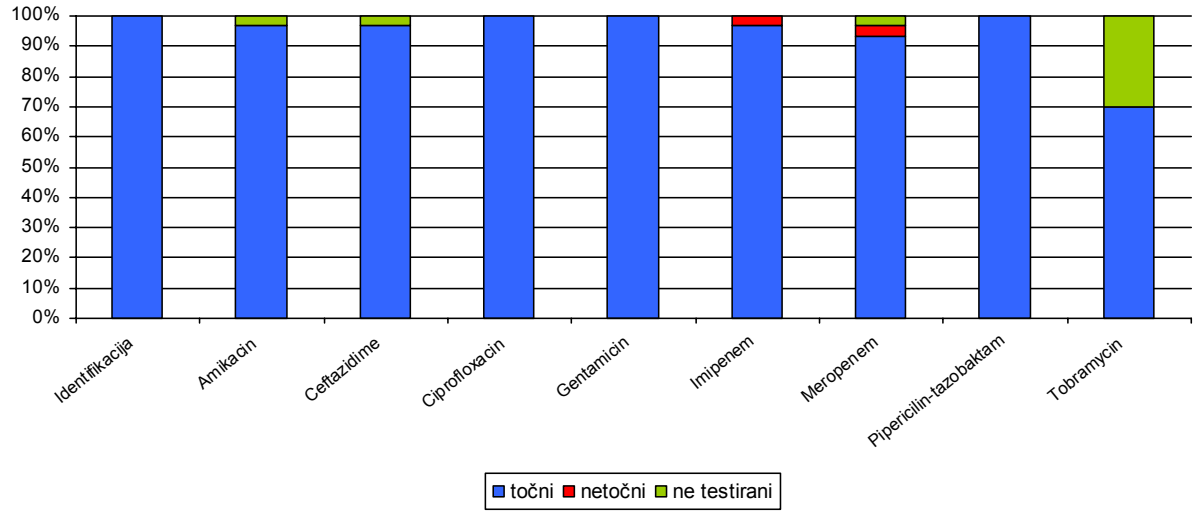
Slika-*Figure 3.*
NEQAS soj 0272: ***S.pneumoniae*** - penicilin (I), kinoloni (I)
NEQAS strain 0272: ***S.pneumoniae -*** *Penicillin (I), Quinolon (I)*
NEQAS: Penicillin MIC 0,5 mg/L



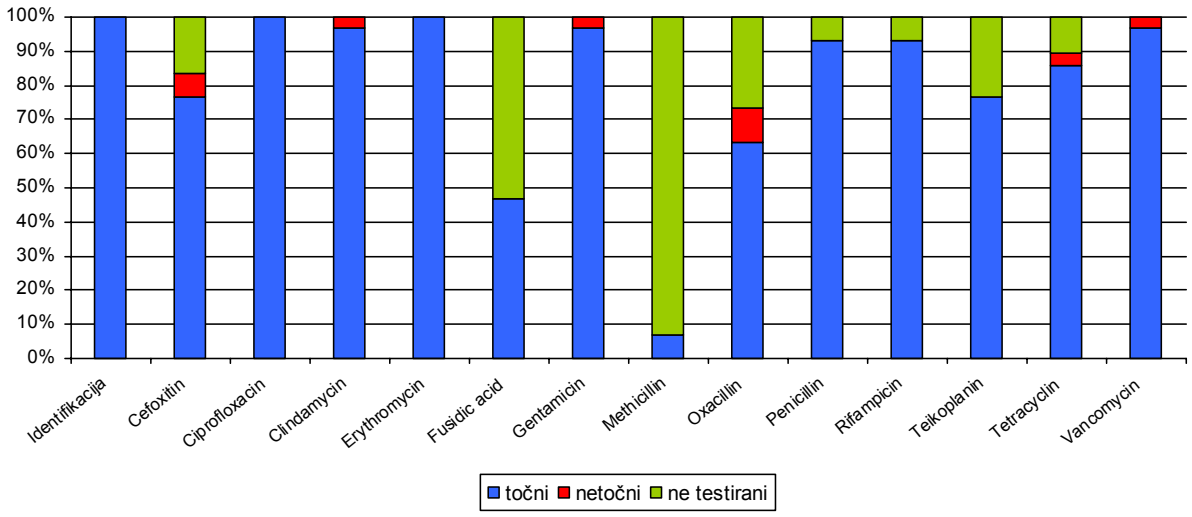
Slika-*Figure 4.*
NEQAS soj 0273: ***E.faecium*** - vankomicin R
NEQAS strain 0273: ***E.faecium -*** *Vancomycin R*
NEQAS: Vankomicin/Vancomycin MIK/MIC 8-16 mg/L



Slika-*Figure 5*
NEQAS soj 0274: ***P.aeruginosa*** – gentamicin R
NEQAS strain 0274: ***P.aeruginosa -*** *gentamicin R*



Slika-*Figure 6.*
NEQAS soj 0275: ***S.aureus MRSA*** – cefoksitin R, klindamicin –inducibilna rezistencija
NEQAS strain 0275: ***S.aureus MRSA -*** *cefoxitin R, clindamycin –inducible resistance*



Opis sojeva za kontrolu: **jesen 2011.**

Soj 01 / 11 je *Staphylococcus epidermidis* koji je već bio uključen u vanjsku kontrolu kao WHO 36. Soj je rezistentan na penicilin, oksacilin, kotrimoksazol, gentamicin i levofloksacin a osjetljiv na eritromicin, klindamicin, tetraciklin i rifampin. MIK vankomicina za ovaj mikroorganizam je 8 mg/L, što se prije interpretiralo kao intermedijarna osjetljivost na vankomicin, a po EUCAST standardima se smatra rezistentnim na vankomicin.
U Hrvatskoj od 35 laboratorija 32 su ispravno identificirali soj kao *Staphylococcus epidermidis*. Trideset tri laborotorija su detektirali točno rezistenciju na vankomicin. Jedan laboratorij nije određivao MIK na vankomicin, a 1 laboratorij je krivo proglasio soj osjetljivim na vankomicin.

Test soj 02 / 11 je *Klebsiella pneumoniae* koja proizvodi SHV-18 beta-laktamazu proširenog spektra (ESBL) te pokazuje jasnu rezistenciju na ceftazidim (MIK 64.0 mg/L) i nižu rezistenciju na ceftriakson (MIK 8.0 mg/L). Soj je već bio uključen u vanjsku kontrolu kao WHO 37, ali se tada soj s MIK-om od 8.0 mg/L smatrao intermedijarno osjetljivim uz obaveznu promjenu interpretacije u rezistentno zbog produkcije ESBL. Prema EUCAST preporukama cefalosporini se kod ESBL sojeva izdaju prema dobivenom rezultatu uz komentar da se radi o ESBL soju samo radi primjene mjera kontaktne izolacije.
U Hrvatskoj su 34 od 35 laboratorija ispravno detektirali ESBL produkciju. Četiri laboratorija su korigirali dobivenu intermedijarnu vrijednost za ceftriakson i interpretirali ju kao rezistentnu zbog produkcije ESBL-a, što ukazuje da još nisu usvojili u potpunosti EUCAST standarde koji su u 2011.g. postali obavezni.
Soj producira i ANT(2“) aminoglikozid adeniltransferazu zbog koje je rezistentan ili intermedijaran na gentamicin, ali ne i amikacin. Samo jedan laboratorij je gentamicin izdao kao osejtljiv. Soj je osjetljiv na piperacilin/tazobaktam no 10 laboratorija je detektiralo intermedijarnu osjetljivost.

Challenge strains: autumn 2011

Test strain 01 / 11 is *Staphylococcus epidermidis* previously included in external contorol as WHO 36. This strain is penicillin, oxacillin, co-trimoxazol, gentamicin and levofloxacin resistant and erythromycin, clindamycin, tetracycline and rifampincin susceptible. Vancomycin MIC for this microorganisam is 8 mg/L which was previously interpreted as intermediate resistance to vancomycin but according to EUCAST standards this is considered to be vancomycin resistant.
Thirty-two out of 35 Croatian laboratories correctly identified this strain as *Staphylococcus epidermidis* . Thirty-three laboratories correctly detected resistance to vancomycin. One laboratory did not test vancomycin MIC and one laboratory wrongly reported strain as susceptible to vancomycin.

Test strain 02 / 11 is *Klebsiella pneumoniae* which produces SHV-18 extended spectrum beta-lactamase (ESBL) with obvious resistance to ceftazidim (MIC 64.0 mg/L) and lower resistance to ceftriaxon (MIC 8.0 mg/L). This strain was previously included in external quality control as WHO 37 but at that time an isolate with ceftriaxone MIC of 8 mg/L was regarded as intermediate with obligatory correction into resistant due to the ESBL production. According to EUCAST sensitivity to cephalosporins in ESBL producers is reported as found and ESBL production is reported for the infection control purpose only.
Thirty-four out of 35 Croatian laboratories correctly detected ESBL production. Four laboratories corrected intermediate result for ceftriaxon into resistant because this isolated was an ESBL producer. This indicates that these laboratories did no adopt EUCAST standards completely, which is an obligation since 2011.
This strain also produces ANT(2“) aminoglycoside adeniltranspherase and therefore is resistant or intermediately susceptible to gentamicin, but not to amikacin. One laboratoy reported gentamicin as susceptible. This strain is susceptible to piperacillin/tazobactam but 10 laboratories reported intermediate susceptibility.

POGLAVLJE/CHAPTER 6.

MULTIPLO REZISTENTNI *ACINETOBACTER BAUMANNII U* SJEVEROZAPADNOJ HRVATSKOJ I ISTRI
MULTIPLY RESISTANT ACINETOBACTER BAUMANNII IN NORTHWESTERN CROATIA AND ISTRIA

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Članovi Odbora za praćenje rezistencije bakterija na antibiotike u Republici Hrvatskoj

Multiplo rezistentni *Acinetobacter baumannii* u sjeverozapadnoj Hrvatskoj i Istri
Multiply resistant Acinetobacter baumannii in northwestern Croatia and Istria

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Multiplo rezistentni *Acinetobacter baumannii* u sjeverozapadnoj Hrvatskoj i Istri

U sklopu praćenja rezistencija bakterija Odbora za praćenje rezistencije na antibiotike pri Akademiji medicinskih znanosti Hrvatske tijekom zadnja tri mjeseca 2009. g. skupljani su izolati *Acinetobacter baumannii* radi analize rezistencije kod te bakterijske vrste. U Kliničkom zavodu za kliničku i molekularnu mikrobiologiju KBC Zagreb je obrađeno 185 izolata *Acinetobacter baumannii* prikupljenih iz 13 centara iz sjeverozapadne Hrvatske i Istre.

Uzorci su prikupljani iz Klinike za traumatologiju u Zagrebu, Hrvatskog zavoda za javno zdravstvo, Klinike za infektivne bolesti „Dr. Fran Mihaljević“, Kliničke bolnice Merkur, Kliničkog bolničkog Centra Zagreb, Opće bolnice Bjelovar, Opće bolnice Čakovec, Opće bolnice Koprivnica, Opće bolnice Sisak, Opće bolnice Varaždin, Opće bolnice Vinkovci, Specijalne bolnice za rehabilitaciju Krapinske Toplice i Opće bolnice Pula.

Preko 90% izolata bili su multirezistentni, a 39% je pokazivalo rezistenciju na imipenem te 35% na meropenem. Produkcija stečenih oksacilinaza je utvrđena u 36 izolata. U 4 izolata utvrđena je OXA-23 β-laktamaza, u 14 OXA-58 i u 18 OXA-24. Sojevi sa stečenim oksacilinazama su iz centara sjeverne Hrvatske i sa značajno su većom stopom rezistencije na karbapeneme u odnosu na grupu koja ima samo prirođenu OXA-51 oksacilinazu. Prisutnost insercijske sekvencije IS*Aba*I dokazana je u svih 36 izolata sa stečenim oksacilinazama, a u 118 izolata koji su imali samo prirođenu OXA-51 oksacilinazu IS*Aba*I je utjecala na smanjenu osjetljivost prema karbapenemima. Invazivnih izolata *A. baumannii* (iz hemokultura i likvora) je bilo 26 (14%), a nije utvrđena značajna razlika u stopama rezistencije i prisutnošću stečenih oksacilinaza u odnosu na neinvazivne izolate. Invazivni izolati su pokazivali veliku različitost PFGE profila i svrstani su u pet klonova.

Studija je pokazala veliku različitost oksacilinaza kao i vrlo različite genotipove izolata *A. baumannii* iz Hrvatske. Tim istraživanjem smo unaprijedili znanje o molekularnoj epidemiologiji infekcija uzrokovanih acinetobakterom u Hrvatskoj, utvrdili smo razlike u klonalnoj distribuciji izolata i mehanizama rezistencije acinetobaktera, a prvi put je opisana OXA-23 grupa β-laktamaza u Hrvatskoj.

Osjetljivost na antibiotike izolata *Acinetobacter baumannii*
Antibiotic susceptibilities of Acinetobacter baumannii isolates

Antibiotik i prijelomna točka po CLSI-u **Antibiotic (CLSI breakpoint)**	**MIK raspon** **MIC range** **mg/L**	**MIK $_{50}$** **MIC $_{50}$** **mg/L**	**MIK$_{90}$** **MIC$_{90}$** **mg/L**	**Broj i postotak (%) rezistentnih izolata** **Resistant isolates**
Ceftriakson / Ceftriaxone (≥ 64)	1 – ≥ 256	256	256	178/185 (96)
Cefotaksim / Cefotaxime (≥ 64)	1 – ≥ 256	128	256	170/185 (92)
Ceftazidim / Ceftazidime (≥ 32)	≤ 0.12 – ≥ 256	64	256	168/185 (91)
Piperacilin / Piperacillin (≥ 128)	1 – ≥ 256	256	256	172/185 (93)
Piperacilin/tazobaktam (≥ 128/4) Piperacilln/tazobactam	4 – ≥ 256	≥ 128	256	136/185 (74)
Gentamicin / Gentamicin (≥ 16)	≤ 0.12 – ≥ 256	128	256	169/185 (91)
Meropenem / Meropenem (≥ 16)	≤ 0.06 – ≥ 128	4	64	64/185 (35)
Imipenem / Imipenem (≥ 16)	≤ 0.06 – ≥ 128	4	64	71/185 (39)
Kolistin / Colistin (≥ 4)	0.5 – 2	1	2	0/185 (0)
Ampicilin/sulbaktam (≥ 32/16) Ampicillin/sulbactam	≤ 0.12 – ≥ 256	8	≥ 256	73/185 (39)
Ciprofloksacin /Ciprofloxacin (≥ 4)	≤ 0.12 – ≥ 256	64	≥ 256	179/185 (97)
Cefepim / Cefepime (≥ 32)	≤ 0.12 – 256	32	128	125/185 (68)
Amikacin / Amikacin (≥ 64)	≤ 0.5 – ≥ 256	32	128	106/185 (57)

Multiply resistant *Acinetobacter baumannii* in northwestern Croatia and Istria

In the frame of the Croatian Committee for Antibiotic Resistance Surveillance of the Croatian Academy of Medical Sciences during the last three months in 2009 *Acinetobacter baumannii* isolates were collected from 13 centers from northwestern Croatia and Istria in order to analyze in more details resistance in this bacterial species. All the 185 strains collected were analyzed in the Department of Clinical and Molecular Microbiology at the Clinical Hospital Centre Zagreb.

Isolates were collected from the following institutions: Klinika za traumatologiju, Zagreb, Hrvatski zavod za javno zdravstvo, Klinika za infektivne bolesti „Dr. Fran Mihaljević“, Zagreb, Klinička bolnica Merkur, Zagreb, Klinički bolnički centar Zagreb, Opća bolnica Bjelovar, Opća bolnica Čakovec, Opća bolnica Koprivnica, Opća bolnica Sisak, Opća bolnica Varaždin, Opća bolnica Vinkovci, Specijalna bolnica za rehabilitaciju Krapinske Toplice and Opća bolnica Pula.

Over 90% of isolates were multiresistant, 39% of the isolates were resistant to imipenem and 35% to meropenem. Acquired oxacillinases were found in 36 isolates. Four strains were found to produce OXA-23 β-lactamase, eighteen OXA-24 and fourteen OXA-58. All strains with acquired oxacillinases originated from Northern Croatia. The isolates showed significantly higher resistance rates to carbapenems compared to strains possessing only naturally occurring OXA-51 group of oxacillinases. All 36 isolates with acquired oxacillinases were positive for IS*Aba*I. 118 isolates possessing only the naturally occuring OXA-51 β-lactamase were shown to have IS*Aba*I. The presence of for IS*Aba*I located upstream of $bla_{\text{OXA-51}}$ gene is shown to facilitate the expression of the gene and thus is responsible for elevated carbapenem MICs. Fourteen major clones were found. Twenty-six (14%) isolates were invasive. No significant differences in carbapenem resistance rates and proportion of acquired oxacillinases were observed between invasive and non-invasive strains. Invasive isolates showed a great diversity of PFGE profile and were assigned into five clones.

Our study showed a great diversity of oxacillinases as well as different genotypes of *A. baumannii* isolates from Croatia. With this study we have contributed to knowledge about the molecular epidemiology of infections caused by *A.baumannii* in Croatia, we found differences in the distribution of clonal isolates and resistance mechanisms in *A. baumannii*. In this study OXA-23 β-lactamase in *A. baumannii* was described for the first time in Croatia.