# Uporaba antibiotika i rezistencija na antibiotike u djece školske dobi

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# UPORABA ANTIBIOTIKA I REZISTENCIJA NA ANTIBIOTIKE U DJECE ŠKOLSKE DOBI

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## 2. POPIS OZNAKA I KRATICA

AMZH = Akademija medicinskih znanosti Hrvatske

EAAD = Europski dan svjesnosti o antibioticima (engl. European Antibiotic Awareness Day)

ECDC = Europski centar za prevenciju i kontrolu bolesti (engl. European Centre for Disease Prevention and Control)

ESBL = β-laktamaze proširenog spektra (engl. Extended-spectrum beta-lactamases)

EUCAST = Europski odbor za testiranje antimikrobne osjetljivosti (engl. European Committee on Antimicrobial Susceptibility Testing)

ISKRA = Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike (Ministarstvo zdravstva Republike Hrvatske)

MH-F = Mueller-Hinton Fastidious agar

MIK = minimalna inhibitorna koncentracija

MRSA = meticilin rezistentni *Staphylococcus aureus* (engl. Meticillin-resistant *Staphylococcus aureus*)

NZZJZ = Nastavni zavod za javno zdravstvo

PGŽ = Primorsko-goranska županija

SZO = Svjetska zdravstvena organizacija

SAD = Sjedinjene Američke Države

WAAW = Svjetski tjedan svjesnosti o antibioticima (engl. World Antibiotic Awareness Week)

# 3. PREGLED OBJEDINJENIH RADOVA

Ova doktorska disertacija temelji se na trima objedinjenim znanstvenim radovima:

1. Farkaš M, Čulina T, Sišul J, Pelčić G, Mavrinac M, Mićović V, Tambić Andrašević A. Impact of antibiotic consumption on the carriage of antibiotic-resistant bacteria by school children. Eur J Public Health 2020;30:265-9.

2. Farkaš M, Glažar Ivče D, Stojanović S, Mavrinac M, Mićović V, Tambić Andrašević A. Parental Knowledge and Awareness Linked to Antibiotic Use and Resistance: Comparison of Urban and Rural Population in Croatia. Microb Drug Resist 2019;25:1430-6.

3. Farkaš M., Ivančić Jokić N, Mavrinac M, Tambić Andrašević A. 2021. Antibiotic Prescribing Habits and Antimicrobial Resistance Awareness of Dental Practitioners in Primorsko-Goranska County, Croatia. Microb Drug Resist 2021;27:1482-8.

## 3.1. UVOD

### 3.1.1. Antibiotici - važna uloga u suvremenoj medicini

Visoke stope propisivanja antibiotika su veliki izazov za javno zdravstvo i kliničku medicinu u Hrvatskoj i svijetu. Zadnja dva desetljeća svjesni smo sve bržeg razvoja otpornosti (rezistencije) bakterija na antibiotike i sve sporije pojave novih antibiotika (1-3).
Antibiotici su lijekovi koji djeluju selektivno toksično na bakterije, posjeduju više mehanizama djelovanja poput ometanja sinteze staničnog zida, ometanja funkcije citoplazmatske opne, ometanja sinteze proteina i ometanja sinteze nukleinskih kiselina (4). Uvođenjem penicilina u kliničku praksu početkom 40-tih godina 20. stoljeća do danas, mnoga područja medicine su napredovala zahvaljujući antibioticima. Suvremena medicina postajala je sve invazivnija i odvažnija u mnogim dijagnostičkim i terapijskim postupcima znajući da postoji adekvatna profilaktička i terapijska djelotvornost antibiotika. Posljedično tomu, suvremena medicina nije održiva bez učinkovitih antibiotika. Svojim ponašanjem dovodimo u pitanje živote mnogih, posebno osjetljive populacije poput transplantiranih pacijenata, pacijenata u jedinicama intenzivnog liječenja, nedonoščadi, ukoliko pojedinci nastave ignorirati problem antimikrobne rezistencije i činjenice da je problem zajednički, svakoga od nas (1).

Antibiotici su posebni lijekovi, jer njihovom konzumacijom ne utječemo samo na pojedinca, već na cijelu zajednicu. Svakodnevno izmjenjujemo svoje bakterije s okolinom i moramo naučiti živjeti s njima, uz osobnu odgovornost da nam je obaveza što duže sačuvati djelotvornost postojećih antibiotika, dok čekamo pojavu novih antibiotika i druge načine liječenja infektivnih bolesti (1, 3).

### 3.1.2. Rezistencija bakterija na antibiotike - globalni problem suvremene medicine

Prekomjerna i neprimjerena uporaba antibiotika je jedan od glavnih pokretača za pojavu i širenje rezistencije bakterija na antibiotike, koja je ozbiljna globalna prijetnja javnom zdravstvu i kliničkoj medicini (3, 5, 6).

Rezistencija bakterija na antibiotike je prirodni fenomen kojim se bakterije adaptiraju na uvjete iz okoliša. Daleke 1945. g., *sir* Alexander Fleming je upozorio na problem razvoja rezistencije bakterija na antibiotike, i zaista otkriće penicilina i kasnije drugih antibiotika slijedila je i njihova antimikrobna rezistencija (7, 8). Bakterije koriste različite mehanizme rezistencije koji uključuju promjenu ciljnog mjesta, inaktivaciju antibiotika stvaranjem enzima, smanjenu propusnost stijenke za ulaženje antibiotika ili aktivno izbacivanje antibiotika iz stanice (4). Međutim, velika većina društvene zajednice (od zdravstvenih djelatnika, građana i šire) je ignorirala ovaj rastući problem,

koji se najbolje opisuje kao „tihi tsunami“. Mnogi još uvijek nisu svjesni predviđanja da će u drugoj polovici 21. stoljeća od infekcija uzrokovanih multiplorezistentnim uzročnicima godišnje umirati 10 milijuna ljudi diljem svijeta. Za racionalnu primjenu antibiotika odgovorni su i oni koji antibiotike propisuju i oni koji ih konzumiraju (1, 3, 8).

Zadnjih godina svjedočimo velikom problemu pojave, kontrole i liječenja multiplorezistentnih bakterija (rezistentnih na više skupina antibiotika), kako u radu kliničkog mikrobiološkog laboratorija tako i u radu kliničara s pacijentom u bolnicama, ali i sve većem širenju takvih sojeva u izvanbolničku sredinu. Unatoč visokoj stopi izvanbolničke potrošnje antibiotika, antimikrobna rezistencija se najviše uočava u bolničkoj skrbi, naročito jedinicama intenzivnog liječenja, pojavom sojeva poput meticilin rezistentnog *Staphylococcus aureus* (MRSA) te gram-negativnih bakterija koje proizvode β-laktamaze proširenog spektra (ESBL) i/ili karbapenemaze (3, 9-11).

### 3.1.3. Praćenje širenja i kontrola rezistencije bakterija na antibiotike u Hrvatskoj

Hrvatska je već prije nekoliko desetljeća zahvaljujući brojnim stručnjacima, prepoznala problem antimikrobne rezistencije kao veliku prijetnju suvremenoj medicini na nacionalnoj i globalnoj razini (1). Davne 1996. g. započelo je sustavno praćenje rezistencije bakterija na antibiotike u Hrvatskoj, za što je zaslužan Odbor za praćenje rezistencije bakterija na antibiotike, koji je osnovan pri Kolegiju javnog zdravstva Akademije medicinskih znanosti Hrvatske (AMZH). Idejna začetnica i osnivačica Odbora prim.dr.sc. Tera Tambić već tada je prepoznala važnost praćenja rezistencije bakterija na antibiotike u Republici Hrvatskoj (12, 13).

Referentni centar Ministarstva zdravstva za praćenje rezistencije bakterija na antibiotike osnovan je 2003. g. pri Klinici za infektivne bolesti „Dr. Fran Mihaljević“, s važnom ulogom pružanja laboratorijske podrške u testiranju sve zahtjevnijih, neuobičajenih, multiplorezistentnih sojeva i ostale podrške mikrobiološkim laboratorijima u cijeloj Hrvatskoj. Nadalje, 2006. g. osnovana je Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike (ISKRA) pri Ministarstvu zdravstva Republike Hrvatske, koja koordinira sve aktivnosti predviđene Nacionalnim programom za kontrolu širenja otpornosti bakterija na antibiotike na području kontrole rezistencije na antibiotike u humanoj medicini, veterini i poljoprivredi. U skladu sa strategijama i preporukama Svjetske zdravstvene organizacije (SZO) i Europske komisije, u Hrvatskoj se provodi kontinuirano praćenje rezistencije i potrošnje antibiotika, razvoj smjernica za racionalnu uporabu antibiotika, edukacija zdravstvenih djelatnika te edukacija građana kroz javne kampanje sa svrhom podizanja svjesnosti o antibioticima (3, 7).

U cilju skretanja pozornosti na ovaj gorući javnozdravstveni problem, 2008. g. Europski centar za prevenciju i kontrolu bolesti (ECDC) proglasio je 18. studeni Europskim danom svjesnosti o

antibioticima (EAAD), a 2015. g. SZO taj cijeli tjedan Svjetskim tjednom svjesnosti o antibioticima (WAAW). Simpozij povodom Europskog dana svjesnosti o antibioticima, i kasnije Svjetskog tjedna svjesnosti o antibioticima organizira se svake godine u Zagrebu, prateći sve aktualnosti u svezi s uporabom antibiotika i problemom antimikrobne rezistencije (3).

### 3.1.4. Potrošnja antibiotika u izvanbolničkoj skrbi

Potrošnja antibiotika je najveća u izvanbolničkoj skrbi u Hrvatskoj i svijetu (3, 10). Više od 90% antibiotika u Hrvatskoj se potroši u izvanbolničkom sektoru, a liječnici dentalne medicine značajno doprinose ukupnom propisivanju antibiotika (7-11% potrošnje u primarnoj zdravstvenoj zaštiti) (14-17).

Prema istraživanjima u Hrvatskoj, na listi najpropisivanijih antibiotika prvo mjesto i dalje uvjerljivo zauzima amoksicilin s klavulanskom kiselinom, slijede amoksicilin, cefuroksimaksetil, azitromicin te doksiciklin. U zemljama koje antibiotike ne troše racionalno, pa i u Hrvatskoj, uočava se veliki porast potrošnje u zimskim mjesecima, kada su infekcije gornjeg dišnog sustava učestalije, s obzirom na najčešće virusnu etiologiju ovih infekcija, što znači da se antibiotici uvelike troše i kod virusnih infekcija (14, 15).

Iako u Hrvatskoj postoje nacionalne ISKRA smjernice za grlobolju, koje kao lijek izbora navode fenoksimetilpenicilin i dalje se nastavlja trend najčešćeg propisivanja širokospektralnih penicilina, naročito amoksicilina s klavulanskom kiselinom (14, 15, 18). Činjenica je da se u mnogim zemljama antibiotici najviše koriste u djece predškolske dobi (19-22) te da je odabir antibiotika često neprimjeren. Najčešće se neracionalno propisuju širokospektralni antibiotici za stanja gdje bi i uskospektralni antibiotici bili učinkoviti. Infekcije gornjeg dišnog sustava su najčešća indikacija za nepotrebno propisivanje antibiotika te čine najznačajnije područje za unapređenje propisivanja antibiotika (3, 19). Nadalje, liječnici dentalne medicine u svom svakodnevnom radu vrlo često propisuju antibiotike za stanja gdje je kirurški zahvat prvi izbor te mogu služiti kao važan posrednik u pojavi i širenju bakterija rezistentnih na antibiotike u zajednici (23-25).

### 3.1.5. Kontrola širenja rezistentnih bakterija

#### 3.1.5.1. Rezervoari i putovi prenošenja rezistentnih bakterija

Kolonizirani ili inficirani pacijenti su važan rezervoar za prenošenje rezistentnih bakterijskih sojeva. Dodatni problem u kontroli pojave i širenja predstavlja činjenica da multiplorezistentni bakterijski

sojevi često koloniziraju pacijente i zdrave osobe, a da pri tome uglavnom nisu klinički vidljivi (3, 26).

Kolonizirani zdravstveni djelatnici i zdrave osobe najčešće na svojim rukama mogu prenositi rezistentne bakterije ukoliko se ne pridržavaju osnovnih higijenskih mjera (3, 26, 27). Kao važan rezervoar treba spomenuti kontaminiranu okolinu, a primjer su infekcije dišnog sustava kod kojih govorom, kihanjem i kašljanjem bakterijske čestice padaju na okolne površine i predmete (26).

### 3.1.5.2. Mjere za sprječavanje i suzbijanje širenja rezistentnih bakterija

Provođenje i poboljšanje higijenskih mjera desetljećima se navodi kao jedna od najvažnijih mjera za sprječavanje i suzbijanje antimikrobne rezistencije (1, 2, 26). Pravilna higijena ruku (pranje ruku i utrljavanje alkohola) dokazano je najdjelotvorniji način u prevenciji pojave i širenja infekcije i osnovni dio standardnih mjera predostrožnosti. Ostale mjere uključuju uporabu zaštitnih sredstava (maske, rukavice) kod rizika dodira s tjelesnim tekućinama te standardne higijenske mjere čišćenja i pospremanja. Kod pacijenata inficiranih ili koloniziranih multiplorezistentnim bakterijama dodatno treba primijeniti i mjere kontaktne izolacije. U sprječavanju širenja multiplorezistentnih bakterija bitnu ulogu ima i racionalizacija potrošnje antibiotika koja se može postići kroz edukaciju zdravstvenih djelatnika (nacionalne smjernice o propisivanju antimikrobne terapije, edukacija u sklopu stručnog usavršavanja), edukaciju građana kroz javne kampanje za promicanje ispravne uporabe antibiotika i edukaciju pacijenata intenzivnijom komunikacijom zdravstvenih djelatnika s pacijentima o problemu antimikrobne rezistencije (3, 18, 26-28).

### 3.1.6. Cilj objedinjenih radova

Opći cilj objedinjenih radova je detektirati prisutnost rezistentnih bakterijskih respiratornih patogena u djece školske dobi i istražiti stavove o primjeni antimikrobne terapije u roditelja i liječnika dentalne medicine u Primorsko-goranskoj županiji (PGŽ).

Specifični ciljevi objedinjenih radova:
1. Ispitati primjenu antibiotika u djece školske dobi.

2. Utvrditi povezanost između uporabe antibiotika i kliconoštva bakterijskih respiratornih patogena (*Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* i *Haemophilus influenzae*), posebno sojeva rezistentnih na antibiotike.

3. Utvrditi postoji li razlika između roditelja urbane i ruralne sredine u PGŽ u znanju, stavovima i praksi o uporabi antibiotika i svjesnosti o rezistenciji bakterija na antibiotike.

4. Utvrditi postoji li razlika između liječnika dentalne medicine dviju sredina u PGŽ u znanju, stavovima i praksi o uporabi antibiotika i svjesnosti o rezistenciji bakterija na antibiotike.

5. Podizanje svijesti o racionalnoj uporabi antibiotika u izvanbolničkoj populaciji.

## 3.2. PREGLED METODOLOGIJE OBJEDINJENIH RADOVA

### 3.2.1. Rad 1.: Kliconoštvo i osjetljivost na antibiotike najčešćih bakterijskih respiratornih patogena u školske djece

Istraživanje je provedeno u razdoblju od 29. siječnja do 16. lipnja i od 22. rujna do 4. studenog 2014. godine. U studiju su bile uključene dvije skupine djece u dobi od 6 do 15 godina, iz 31 osnovne škole Grada Rijeke i okolice, kojima su bakteriološki obrađeni obrisci ždrijela i nazofarinksa u mikrobiološkom laboratoriju Nastavnog zavoda za javno zdravstvo (NZZJZ) PGŽ u Rijeci. Prvu skupinu je sačinjavalo 225 zdrave djece, bez znakova infekcije dišnog sustava unazad zadnja dva tjedna. Drugu skupinu je uključivalo 225 izvanbolničkih pacijenata sa simptomima infekcije gornjeg dišnog sustava (poput povišene temperature, kihanja, šmrcanja, sekreta iz nosa, grlobolje, promuklosti, kašlja itd.), iz pedijatrijskih ordinacija, ordinacija opće i obiteljske medicine (privatne i Dom zdravlja PGŽ) Grada Rijeke i okolice. Obje skupine su bile sličnog socioekonomskog statusa. U istraživanje nisu bila uključena djeca s imunokompromitiranim stanjima (npr. na imunosupresivnoj terapiji i sl.) zbog njihove pojačane osjetljivosti prema infekcijama (naročite infekcije dišnog sustava).

Prije početka uzorkovanja obrisaka ždrijela i nazofarinksa kod djece, roditelji (zakonski zastupnici ili skrbnici) su potpisali suglasnost za sudjelovanje u istraživanju i ispunili upitnik o sociodemografskim podatcima i uporabi antibiotika u školske djece unazad zadnjih šest mjeseci. Iz upitnika su analizirani i podatci o infekciji dišnog sustava (simptomi), dijagnoza infekcije i uzimanje antibiotika unazad zadnjih šest mjeseci. Uzorci zdrave djece prikupljeni su u suradnji s liječnikom školske i sveučilišne medicine NZZJZ PGŽ u Rijeci, a uzorci bolesne djece u ranije navedenim ordinacijama (pedijatrijske, opće i obiteljske medicine). Obrisci ždrijela i nazofarinksa transportirani su u Amies transportnoj podlozi (Venturi Transystem, Copan Italia S.p.A, Brescia, Italija) i dostavljeni u laboratorij unutar 12 sati od uzimanja. Uzorci su odmah nasađeni na Columbia agar s dodatkom 5% ovčje krvi (bioMérieux, Marcy I' Etoile, Francuska) i povučena crta *Staphylococcus aureus*. Ploče su inkubirane aerobno na 36˚C uz 5% CO2, a očitavane nakon 24 h i 48 h. Izolati *Streptococcus pyogenes* identificirani su prisustvom β-hemolize, gram preparatom, testom katalaze, bacitracinskim testom (BBL, Becton, Dickinson and Company, Sparks, MD, SAD) i latex aglutinacijskim testom (Slidex Strepto Plus, bioMérieux, Marcy I' Etoile, Francuska). Izolati *Streptococcus pneumoniae* dokazani su prisustvom α-hemolize, gram preparatom, testom katalaze, optohinskim testom (BBL, Becton, Dickinson and Company, Sparks, MD, SAD) i testom topivosti u žučnim solima. Izolati *Moraxella catarrhalis* identificirani su izgledom kolonija (γ-hemoliza), gram preparatom, testom oksidaze (Bio-Rad, Marnes-la Coquette, Francuska), testom katalaze,

testom redukcije nitrata (nitrate agar, HiMedia Laboratories Pvt. Ltd., Mumbai, Indija), testom produkcije deoksiribonukleaze (DNAse) (DNAse agar, Oxoid Ltd., Basingstoke, Hampshire, Engleska) te pojavom „znaka hokejaškog paka“. Izolati *Haemophilus influenzae* dokazani su izgledom kolonija (γ-hemoliza), gram preparatom, testom katalaze, satelit testom i detekcijom potrebe za X i V faktorima rasta (Oxoid Ltd., Basingstoke, Hampshire, Engleska).

Osjetljivost na antibiotike testirana je metodom disk difuzije i određivanjem minimalnih inhibitornih koncentracija (MIK) sukladno standardima Europskog odbora za testiranje antimikrobne osjetljivosti (EUCAST) (29), koristeći Mueller-Hinton Fastidious agar (MH-F) (bioMérieux, Marcy I' Etoile, Francuska) te antibiotske diskove (Bio-Rad, Marnes-la Coquette, Francuska) i E-testove (E-test, bioMérieux, Marcy I' Etoile, Francuska). Za *Streptococcus pyogenes* određena je antimikrobna aktivnost na eritromicin, klindamicin i penicilin. Za *Streptococcus pneumoniae* određena je osjetljivost na eritromicin, klindamicin, trimetoprim-sulfametoksazol i penicilin. Izolatima *Streptococcus pneumoniae* s zonom inhibicije oko oksacilinskog test diska manjom od 20 mm određen je MIK za penicilin, ampicilin, cefuroksim i ceftriakson. Za *Moraxella catarrhalis* određena je antimikrobna aktivnost na eritromicin, trimetoprim-sulfametoksazol, cefuroksim, ceftriakson, amoksicilin i amoksicilin s klavulanskom kiselinom. Za *Haemophilus influenzae* određena je osjetljivost na trimetoprim-sulfametoksazol, cefuroksim, ceftriakson, ampicilin i amoksicilin s klavulanskom kiselinom. Svi izolati *Moraxella catarrhalis* i *Haemophilus influenzae* testirani su na produkciju β- laktamaze s nitrocefinskim diskom (Cefinase, bioMérieux, Marcy I' Etoile, Francuska). U radu su korišteni bakterijski sojevi *Streptococcus pneumoniae* ATCC 49619 i *Haemophilus influenzae* NCTC 8468, koji su predstavljali kontrolne sojeve u testu osjetljivosti.

Statistička obrada podataka učinjena je s pomoću računalne programske potpore Statistica 12.0.0 (StatSoft Inc., Tulsa, SAD) i programa za obradu podataka MedCalc 12.0.0 (MedCalc Software, MariaKerke, Belgija).

Podatci su prikazani apsolutnim i relativnim frekvencijama, omjerima izgleda i 95% granicama pouzdanosti. Razlika pojave bakterijskih respiratornih patogena i bakterija rezistentnih na antibiotike između djece školske dobi koja su uzimala antibiotike i one koja nisu, prikazana je omjerom izgleda i 95% granicom pouzdanosti. Razlike između frekvencija izračunate su Hi kvadrat testom, korištena je Yatesova korektura i po potrebi su računati Fischerov egzaktni test i test proporcije. Razina značajnosti postavljena je na $p < 0.05$ za sve statističke testove.

### 3.2.2. Rad 2.: Znanje, stavovi i praksa roditelja u svezi uporabe antibiotika - usporedba urbanog i ruralnog dijela Primorsko-goranske županije (Hrvatska)

Istraživanje je provedeno u razdoblju od 15. svibnja do 14. lipnja 2017. godine. U studiju su bile uključene dvije skupine roditelja djece školske dobi od petog do osmog razreda, iz 11 osnovnih škola PGŽ. Prvu skupinu je sačinjavalo 500 roditelja Grada Rijeke (urbano područje). Drugu skupinu je uključivalo 500 roditelja iz Gorskog kotara i Kvarnerskih otoka (Krk, Cres, Mali Lošinj i Rab) (ruralno područje). Roditelji (zakonski zastupnici ili skrbnici) su dobili obavijest o istraživanju i ispunjavanjem upitnika dali svoj informirani pristanak. Strukturirani upitnik o znanju, stavovima i praksi o uporabi antibiotika i rezistenciji bakterija na antibiotike roditelja djece školske dobi PGŽ, (pri čijem su sastavljanju korištene čestice validiranih upitnika iz sličnih istraživanja) je sadržavao 43 pitanja. Ispitanici su imali mogućnost upisivanja podataka, označavanja znakom x u polju ponuđene odgovore, kombiniranja odgovora (zaokružiti ponuđene odgovore i dopisati svoje), skaliranja odgovora, odnosno procjenjivanja slaganja s ponuđenim tvrdnjama na skali Likertova tipa (od -Uopće se ne slažem do -Potpuno se slažem).

Anketni upitnik je sadržavao pet cjelina: 1. podatke o ispitaniku (dob, spol, prebivalište, završena škola, ukupna mjesečna primanja u obitelji, rad u području uključenom u sustav zdravstva, radi li barem jedan član obitelji u području uključenom u sustav zdravstva) te podatke o djetetu (spol, dob i razred), 2. podatke o učestalosti uporabe antibiotika, 3. podatke o znanju o antibioticima, 4. podatke o svjesnosti o otpornosti bakterija na antibiotike i 5. podatke o stavovima i ponašanju u svezi uporabe antibiotika. Prije početka istraživanja upitnik je bio testiran na uzorku od 50 roditelja djece školske dobi od petog do osmog razreda osnovnih škola PGŽ.

Statistička obrada podataka učinjena je s pomoću računalne programske potpore Statistica 13.1 (StatSoft Inc., Tulsa, OK, SAD) i programa za obradu podataka MedCalc 12.1.3 (MedCalc Software, MariaKerke, Belgija).

Kategorijske varijable prikazane su frekvencijama (apsolutnim i relativnim) i razlike među njima su izračunate Hi kvadrat testom. Kontinuirane varijable analizirane su Kolmogorov-Smirnovljevim testom za ispitivanje normalnosti raspodjele brojčanih podataka, s obzirom na to da su odstupale od normalnosti vrijednosti su prikazane medijanom i 5-tom i 95-tom percentilom, dok je dob prikazana medijanom i rasponom vrijednosti (minimalna dob – maksimalna dob). Kako bi se ispitale razlike u stavovima i znanju o uporabi antibiotika između različitih skupina korišten je Mann-Whitney *U* test za nezavisne uzorke i Kruskall-Wallis test s *post hoc* analizom. Sveukupno znanje roditelja o antibioticima grafički je prikazano kutijom s brkovima (box and whisker). Za ispitivanje povezanosti između stavova, znanja i uporabe antibiotika korišten je Spearmanov koeficijent korelacije. Za predviđanje utjecaja kriterijskih varijabli na prediktor, korištena je multivarijatna

regresijska analiza kako bi se identificirali čimbenici povezani sa sveukupnim znanjem o antibioticima. Razina značajnosti postavljena je na $p < 0.05$ za sve statističke testove.

### 3.2.3. Rad 3.: Znanje, stavovi i praksa liječnika dentalne medicine Primorsko-goranske županije o propisivanju antibiotika i otpornosti bakterija na antibiotike (Hrvatska)

Istraživanje je provedeno u razdoblju od 4. lipnja do 5. rujna 2018. godine. U studiju je bilo uključeno 230 liječnika dentalne medicine (opći i specijalisti) PGŽ (privatni i Dom zdravlja PGŽ), 115 grada Rijeke i 115 ostalog dijela PGŽ (okolica Rijeke (manji gradovi i općine), Kvarnerski otoci (Krk, Cres, Mali Lošinj, Rab) i Gorski kotar). Liječnici dentalne medicine su dobili obavijest o istraživanju i ispunjavanjem upitnika dali svoj informirani pristanak. Strukturirani upitnik o znanju, stavovima i praksi o uporabi antibiotika i rezistenciji bakterija na antibiotike liječnika dentalne medicine PGŽ, (pri čijem su sastavljanju korištene čestice validiranih upitnika iz sličnih istraživanja) je sadržavao 24 pitanja. Ispitanici su imali mogućnost upisivanja podataka, označavanja znakom x u polju ponuđene odgovore, kombiniranja odgovora (zaokružiti ponuđene odgovore i dopisati svoje), skaliranja odgovora, odnosno procjenjivanja slaganja s ponuđenim tvrdnjama na skali Likertova tipa (od -Uopće se ne slažem do -Potpuno se slažem).

Anketni upitnik je sadržavao četiri cjeline: 1. podatke o ispitaniku (dob, spol, mjesto/grad ordinacije, tip ordinacije, stupanj obrazovanja), 2. podatke o znanju o antibioticima, 3. podatke o svjesnosti o otpornosti bakterija na antibiotike i 4. podatke o stavovima i ponašanju u svezi uporabe antibiotika. Prije početka istraživanja upitnik je bio testiran na uzorku od 20 liječnika dentalne medicine PGŽ.

Statistička obrada podataka učinjena je s pomoću računalne programske potpore Statistica 13.5.0.17 (TIBCO Software, Inc., Palo Alto, CA, SAD).

Kategorijske varijable prikazane su apsolutnim i relativnim frekvencijama i razlike su izračunate Hi kvadrat testom ili Fischerovim egzaktnim testom. Za izračunavanje trenda korišten je Hi kvadrat test trenda. Za *post-hoc* analizu korišteni su testovi proporcija. Kontinuirane varijable analizirane su Kolmogorov-Smirnovljevim testom za ispitivanje normalnosti raspodjele brojčanih podataka i ovisno o tome prikazane su aritmetičkom sredinom i standardnom devijacijom ili medijanom i interkvartilnim raspršenjem. Kako bi se ispitale razlike u stavovima između skupina korišten je Mann-Whitney *U* test za nezavisne uzorke. Razina značajnosti postavljena je na $p < 0.05$ za sve statističke testove.

## 3.3. PREGLED REZULTATA OBJEDINJENIH RADOVA

### 3.3.1. Rad 1.: Kliconoštvo i osjetljivost na antibiotike najčešćih bakterijskih respiratornih patogena u školske djece

Respiratorni patogeni su bili češće izolirani kod djece školske dobi koja su upotrebljavala antibiotik u prethodnih šest mjeseci (Tablica 1.). Bakterije rezistentne na antibiotike su bile češće kod djece koja su bila izložena antibioticima (Tablica 2.).

Tablica 1. Povezanost između uporabe antibiotika i kliconoštva respiratornih patogena

| Respiratorni patogen | Uzimali antibiotik (Br.=75) | Nisu uzimali antibiotik (Br.=375) | OR | 95% CI | *p* |
|---|---|---|---|---|---|
| *Streptococcus pneumoniae* | 10 | 23 | 2.35 | (1.07-5.18) | 0.048 |
| *Streptococcus pyogenes* | 15 | 33 | 2.59 | (1.33-5.06) | 0.007 |
| *Haemophilus influenzae* | 8 | 12 | 3.61 | (1.42-9.17) | 0.010 |
| *Moraxella catarrhalis* | 5 | 14 | 1.84 | (0.64-5.28) | 0.339 |
| Ukupno | 38 | 82 | 3.67 | (2.19-6.14) | <0.001 |

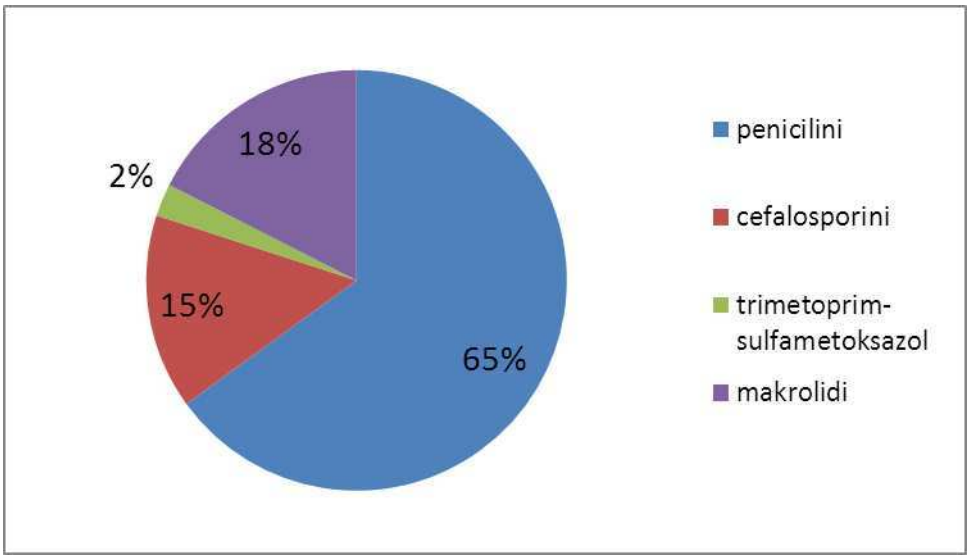
OR=omjer izgleda (engl.odds ratio); 95% CI =95-postotni interval pouzdanosti (engl. 95-percentage confidence interval); *P* vrijednost <0.05 se smatrala statistički značajnom (Fisherov egzaktni test).

Tablica 2. Povezanost između uporabe antibiotika i kliconoštva bakterija rezistentnih na antibiotike

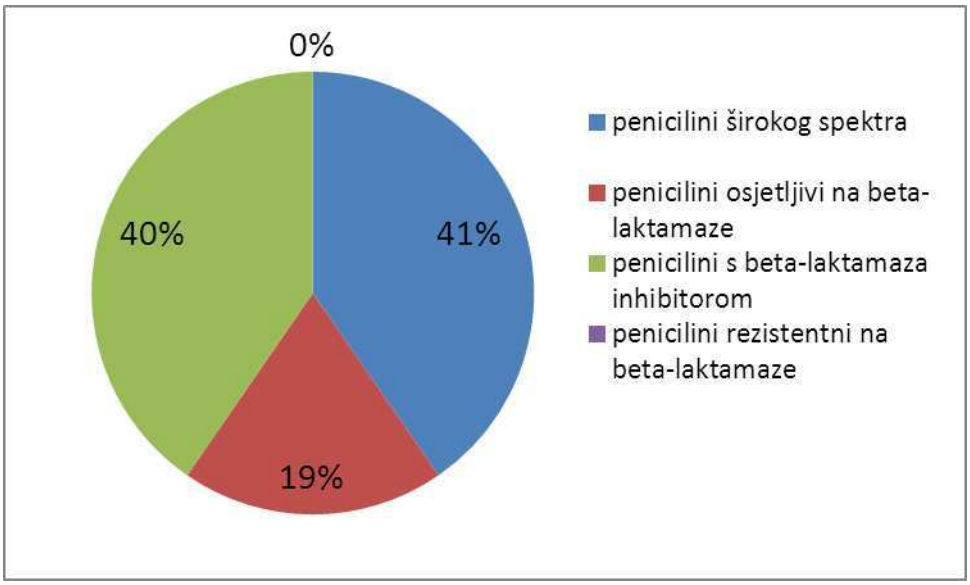
| Respiratorni patogen | Uzimali antibiotik (n=75) | Nisu uzimali antibiotik (n=375) | OR | 95% CI | *p* |
|---|---|---|---|---|---|
| Penicillin NS *Streptococcus pneumoniae* | 4 | 3 | 7.04 | (1.54-32.14) | 0.017 |
| Erythromycin NS *Streptococcus pneumoniae* | 3 | 2 | 7.77 | (1.28-47.34) | 0.035 |
| Erythromycin NS *Streptococcus pyogenes* | 8 | 5 | 8.84 | (2.81-27.83) | <0.001 |
| Amoxicillin R *Haemophilus influenzae* | 1 | 5 | 1.0 | (0.12-8.68) | >0.999 |
| Amoxicillin R *Moraxella catarrhalis* | 5 | 10 | 2.61 | (0.86-7.86) | 0.086 |
| Bilo koji od gore navedenih uzročnika | 21 | 25 | 5.44 | (2.85-10.40) | <0.001 |

NS = neosjetljiv; R = rezistentan; OR =omjer izgleda (engl.odds ratio); 95% CI =95-postotni interval pouzdanosti (engl. 95-percentage confidence interval); *P* vrijednost <0.05 se smatrala statistički značajnom (Fisherov egzaktni test).

Penicilini širokog spektra i kombinacije s inhibitorom su najčešće upotrebljavani antibiotici među djecom školske dobi (Slika 1., Slika 2.).




Slika 1. Uporaba antibiotika u djece školske dobi




Slika 2. Uporaba penicilina u djece školske dobi

### 3.3.2. Rad 2.: Znanje, stavovi i praksa roditelja u svezi uporabe antibiotika - usporedba urbanog i ruralnog dijela Primorsko-goranske županije (Hrvatska)

Sveukupno znanje o antibioticima bilo je veće u roditelja gradske sredine (iako to nije utjecalo na potrošnju antibiotika), dok su roditelji u urbanoj i ruralnoj sredini uglavnom imali slična znanja i stavove o uporabi antibiotika kada su podijeljeni na pojedine izjave (Tablica 3., Tablica 4.).
Roditelji školske djece su imali visoko povjerenje u liječničku odluku o propisivanju antibiotika. Mediji masovnog priopćavanja (televizija, internet, novine) bili su više uključeni u informiranje roditelja o rezistenciji bakterija na antibiotike nego zdravstveni djelatnici.

Tablica 3. Znanje o antibioticima

| Izjava | Odgovor** | Ukupno (Br.=651) Br. % | Urbano (Br.=253) Br. % | Ruralno (Br.=398) Br. % | *p* |
|---|---|---|---|---|---|
| Amoksicilin je antibiotik. | Ne slažem se | 21 (3.2) | 8 (3.2) | 13 (3.3) | 0.876 |
| | Nemam mišljenje/Neutralan | 72 (11.1) | 31 (12.3) | 41 (10.3) | |
| | Slažem se | 558 (85.7) | 214 (84.6) | 344 (86.4) | 0.810 |
| Aspirin je antibiotik. | Ne slažem se | 620 (95.2) | 235 (92.9) | 385 (96.7) | 0.028* |
| | Nemam mišljenje/Neutralan | 20 (3.1) | 11 (4.3) | 9 (2.3) | |
| | Slažem se | 11 (1.7) | 7 (2.8) | 4 (1.0) | 0.115 |
| Paracetamol je antibiotik. | Ne slažem se | 566 (86.9) | 226 (89.3) | 340 (85.4) | 0.180 |
| | Nemam mišljnje /Neutraan | 29 (4.4) | 12 (4.7) | 17 (4.3) | |
| | Slažem se | 56 (8.6) | 15 (5.9) | 41 (10.3) | 0.100 |
| Antibiotici su korisni za liječenje bakterijskih infekcija. | Ne slažem se | 32 (4.9) | 7 (2.8) | 25 (6.3) | 0.068 |
| | Nemam mišljenje/ Neutralan | 37 (5.7) | 15 (5.9) | 22 (5.5) | |
| | Slažem se | 582 (89.4) | 231 (91.3) | 351 (88.1) | 0.284 |
| Antibiotici su korisni za liječenje virusnih infekcija. | Ne slažem se | 477 (73.3) | 184 (72.7) | 293 (74.9) | 0.634 |
| | Nemam mišljenje/ Neutralan | 62 (9.5) | 23 (9.1) | 39 (9.8) | |
| | Slažem se | 112 (17.2) | 46 (18.1) | 66 (16.6) | 0.567 |
| Antibiotici mogu ubiti “dobre bakterije” u našem organizmu. | Ne slažem se | 59 (9.1) | 22 (8.7) | 37 (9.3) | 0.905 |
| | Nemam mišljenje/ Neutralan | 77 (11.8) | 22 (8.7) | 55 (13.8) | |
| | Slažem se | 515 (79.1) | 209 (82.6) | 306 (76.9) | 0.081 |
| Antibiotici služe za skidanje povišene temperature. | Ne slažem se | 567 (87.1) | 221 (87.4) | 346 (86.9) | 0.948 |
| | Nemam mišljenje/ Neutralan | 38 (5.8) | 14 (5.5) | 24 (6.0) | |
| | Slažem se | 46 (7.1) | 18 (7.1) | 28 (7.0) | 0.914 |
| Antibiotici mogu uzrokovati alergijske reakcije. | Ne slažem se | 12 (1.8) | 4 (1.6) | 8 (2.0) | 0.943 |
| | Nemam mišljenje/Neutralan | 35 (5.4) | 12 (4.7) | 23 (5.8) | |
| | Slažem se | 604 (92.8) | 237 (93.7) | 367 (92.2) | 0.572 |

*93% u odnosu prema 97% mogla bi biti statistički značajna razlika, ali u praksi oboje su >90%.
**Odgovor slažem se predstavlja zbroj u postotcima slažem se i potpuno se slažem odgovora. Odgovor ne slažem se predstavlja zbroj u postotcima ne slažem se i uopće se ne slažem odgovora.

Tablica 4. Stavovi o uporabi antibiotika

| Izjava | Odgovor** | Ukupno (Br.=651) Br. % | Urbano (Br.=253) Br. % | Ruralno (Br.=398) Br. % | *p* |
|---|---|---|---|---|---|
| Liječnici u ordinaciji često imaju vremena objasniti kako i zašto treba uzimati antibiotik . | Ne slažem se | 244 (37.5) | 103 (40.7) | 141 (35.4) | 0.547 |
| | Nemam mišljenje/ Neutralan | 97 (14.9) | 37 (14.6) | 60 (15.1) | |
| | Slažem se | 310 (47.6) | 113 (44.7) | 197 (49.5) | |
| Liječnici često propisuju antibiotike, jer pacijenti to očekuju. | Ne slažem se | 290 (44.5) | 107 (42.3) | 183 (46.0) | 0.742 |
| | Nemam mišljenje/ Neutralan | 144 (22.1) | 62 (24.5) | 82 (20.6) | |
| | Slažem se | 217 (33.3) | 84 (33.2) | 133 (33.4) | |
| Liječnici često uzmu vremena da pažljivo razmotre je li antibiotik potreban ili nije. | Ne slažem se | 229 (35.2) | 93 (36.8) | 136 (34.2) | 0.553 |
| | Nemam mišljenje/ Neutralan | 134 (20.6) | 43 (17.0) | 91 (22.9) | 0.080 |
| | Slažem se | 288 (44.3) | 117 (46.2) | 171 (43.0) | 0.470 |
| Ljekarnici Vam često kažu kako treba uzimati antibiotik. | Ne slažem se | 199 (30.5) | 66 (26.1) | 133 (33.4) | 0.060 |
| | Nemam mišljenja/ Neutralan | 45 (6.9) | 16 (6.3) | 29 (7.3) | 0.740 |
| | Slažem se | 407 (62.5) | 171 (67.6) | 236 (59.3) | 0.040* |
| Liječnici često propisuju antibiotik "za svaki slučaj". | Ne slažem se | 364 (55.9) | 141 (55.7) | 223 (56.0) | 0.345 |
| | Nemam mišljenje/ Neutralan | 100 (15.3) | 34 (13.4) | 66 (16.6) | |
| | Slažem se | 187 (28.7) | 78 (30.8) | 109 (27.4) | |

* statistički značajno, **Odgovor slažem se predstavlja zbroj u postotcima slažem se i potpuno se slažem odgovora. Odgovor ne slažem se predstavlja zbroj u postotcima ne slažem se i uopće se ne slažem odgovora.

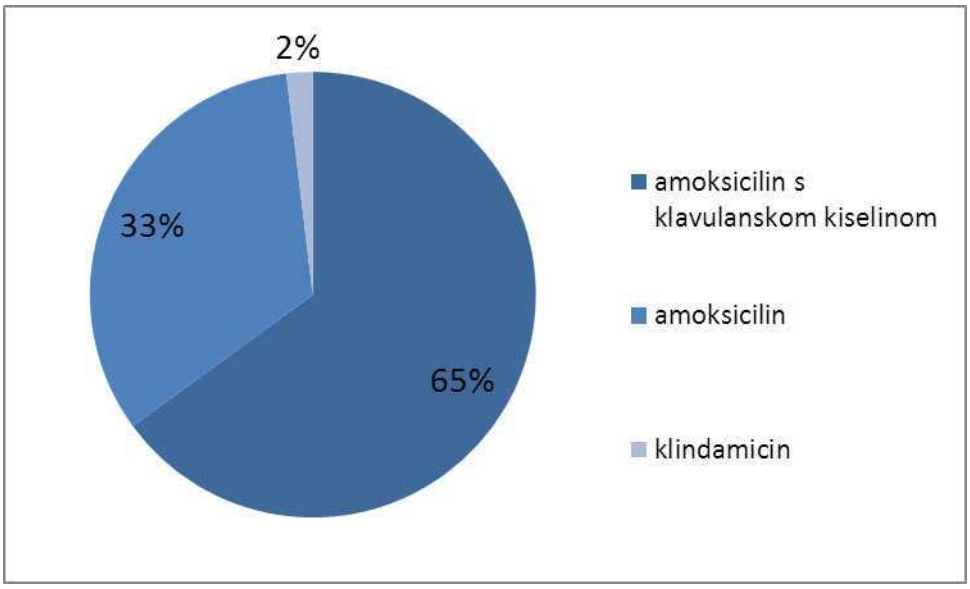
### 3.3.3. Rad 3.: Znanje, stavovi i praksa liječnika dentalne medicine Primorsko-goranske županije o propisivanju antibiotika i otpornosti bakterija na antibiotike (Hrvatska)

Nismo pronašli razliku u stavovima (Tablica 5.), znanju i praksi o uporabi antibiotika i rezistenciji bakterija na antibiotike liječnika dentalne medicine između dvije ispitane sredine u PGŽ. Prema anketi, liječnici dentalne medicine najčešće bi propisivali peniciline (širokog spektra i kombinacije s inhibitorom) unatoč njihovoj visokoj svjesnosti o rezistenciji bakterija na antibiotike. U stomatološkim ordinacijama antibiotici bi se često propisali za stanja gdje je kirurški zahvat prvi izbor (Slika 3., Slika 4.).

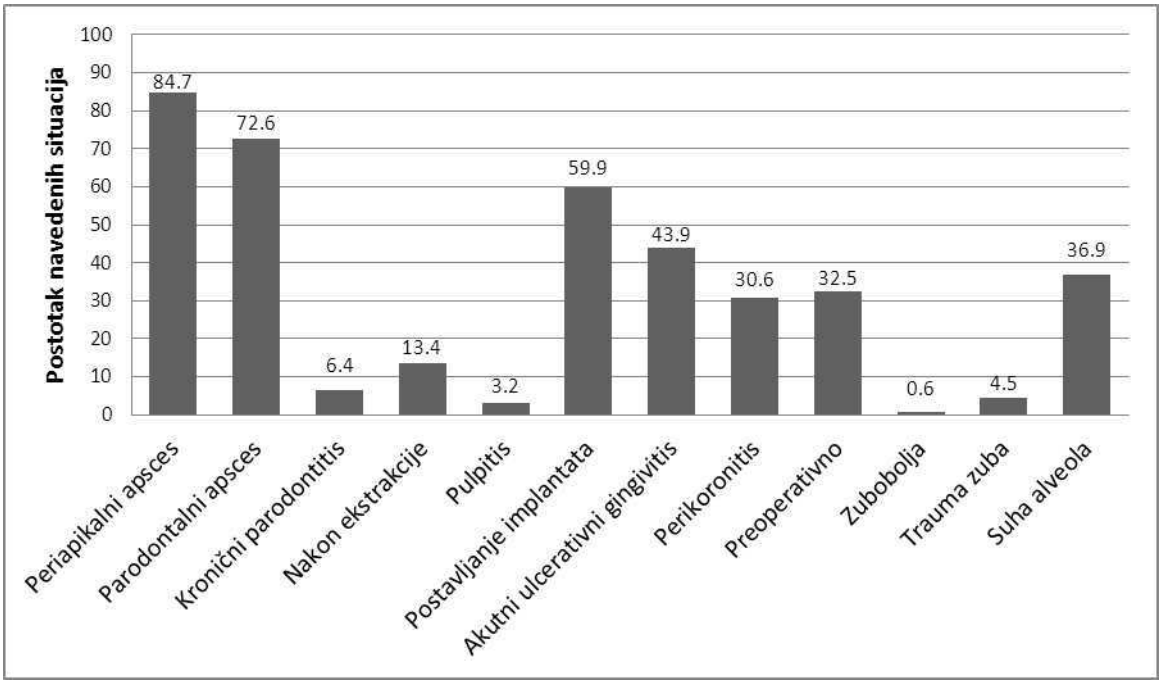
Tablica 5. Stavovi o uporabi antibiotika

| Izjava | Odgovor | Ukupno (Br.=157) Br. % | Grad Rijeka (Br.=83) Br. % | Ostali dio PGŽ (Br.=74) Br. % | *p* |
|---|---|---|---|---|---|
| Liječnici dentalne medicine u ordinaciji često imaju vremena objasniti kako i zašto treba uzimati antibiotik . | Uopće se ne slažem/ Ne slažem se | 15 (9.6) | 6 (7.2) | 9 (12.2) | 0.561 |
| | Nemam mišljenje/ Neutralan | 14 (8.9) | 8 (9.6) | 6 (8.1) | |
| | Potpuno se slažem/Slažem se | 128 (81.5) | 69 (83.1) | 59 (79.7) | |
| Liječnici dentalne medicine često propisuju antibiotike, jer pacijenti to očekuju. | Uopće se ne slažem/ Ne slažem se | 78 (49.7) | 42 (50.6) | 36 (48.7) | 0.858 |
| | Nemam mišljenje/ Neutralan | 25 (15.9) | 14 (16.9) | 11 (14.9) | |
| | Potpuno se slažem/Slažem se | 54 (34.4) | 27 (32.5) | 27 (36.5) | |
| Liječnici dentalne medicine često uzmu vremena da pažljivo razmotre je li antibiotik potreban ili nije. | Uopće se ne slažem/ Ne slažem se | 30 (19.1) | 18 (21.7) | 12 (16.2) | 0.323 |
| | Nemam mišljenje/ Neutralan | 27 (17.2) | 11 (13.3) | 16 (21.6) | |
| | Potpuno se slažem/Slažem se | 100 (63.7) | 54 (65.1) | 46 (62.2) | |
| Ljekarnici pacijentima često kažu kako treba uzimati antibiotik. | Uopće se ne slažem/ Ne slažem se | 23 (14.7) | 13 (15.7) | 10 (13.5) | 0.860 |
| | Nemam mišljenje/ Neutralan | 42 (26.8) | 23 (27.7) | 19 (25.7) | |
| | Potpuno se slažem/Slažem se | 92 (58.6) | 47 (56.6) | 45 (60.8) | |
| Liječnici dentalne medicine često propisuju antibiotik "za svaki slučaj". | Uopće se ne slažem/ Ne slažem se | 67 (42.7) | 35 (42.2) | 32 (43.2) | 0.977 |
| | Nemam mišljenje/ Neutralan | 42 (26.8) | 22 (26.5) | 20 (27.0) | |
| | Potpuno se slažem/Slažem se | 48 (30.6) | 26 (31.3) | 22 (29.7) | |

PGŽ, Primorsko-goranska županija




Slika 3. Uporaba antbiotika u liječnika dentalne medicine




Slika 4. Situacije za koje bi liječnici dentalne medicine propisali antibiotike

## 3.4. RASPRAVA KOJA OBJEDINJUJE RADOVE

Prekomjerna i nepotrebna uporaba antibiotika je jedan od ključnih pokretača za razvoj rezistencije bakterija na antibiotike, koja predstavlja jedan od glavnih problema današnje medicine (3).

Infekcije gornjeg dišnog sustava još uvijek predstavljaju veliki javnozdravstveni problem zbog učestale pojave i propisivanja antibiotika, naročito u dječjoj populaciji. Usprkos činjenici da su najčešće virusne etiologije, pretjerana konzumacija antibiotika dovela je do razvoja rezistencije najvažnijih bakterijskih respiratornih patogena u djece. Najčešći, a ujedno i najvažniji potencijalni patogeni su *Streptococcus pyogenes*, *Streptococcus pneumonia*e, *Moraxella catarrhalis* i *Haemophilus influenza*e u predškolskoj i školskoj dobi. Ukoliko je liječenje antibiotikom zaista neophodno, rezistencija može kompromitirati antibiotsko liječenje, s obzirom da je terapija često empirijska. Zbog ranije navedenog, empirijska terapija uz očekivane uzročnike mora uzeti u obzir i rasprostranjenost rezistencije na antibiotike u lokalnoj sredini. Uz činjenicu da je razvoj bakterijske rezistencije neizbježan i pri medicinski indiciranoj primjeni antibiotika, veliki problem predstavlja učestala i nepotrebna primjena antibiotika kod virusnih infekcija, te kolonizacije ili kliconoštva potencijalnih bakterijskih patogena (1, 19).

Potrošnja antibiotika u dječjoj populaciji značajno doprinosi pojavi rezistencije na antibiotike. Antibiotici se najviše koriste u djece predškolske dobi (19-22), koja su više osjetljiva i izložena infekcijama gornjeg dišnog sustava boraveći u ustanovama poput jaslica i vrtića, nego školska djeca. Ipak, u ovom radu smo dokazali da i djeca školske dobi često konzumiraju antibiotike i predstavljaju važan rezervoar rezistentnih patogena. Antibiotici su dragocjeni i posebni lijekovi, jer njihovom konzumacijom ne utječemo samo na pojedinca, već na cijelu zajednicu (1, 3).

Prijašnje studije su dokazale povezanost između uporabe antibiotika i pojave antimikrobne rezistencije u primarnoj zdravstvenoj zaštiti, koja je jače izražena u zemljama južne i istočne Europe (30-32). Naše istraživanje je potvrdilo češću pojavu bakterijskih respiratornih patogena i rezistentnih sojeva kod školske djece koja su upotrebljavala antibiotik u prethodnih šest mjeseci, te važnost racionalizacije uporabe antibiotika u djece školske dobi.

Iako u Hrvatskoj postoje nacionalne ISKRA smjernice za grlobolju koje kao lijek izbora navode fenoksimetilpenicilin (18), u našem radu u djece školske dobi najčešće su upotrebljavani penicilini širokog spektra i kombinacije s inhibitorom. Sličan obrazac propisivanja antibiotika imaju i mediteranske zemlje u našem okruženju Italija i Španjolska (33, 34). Nasuprot tomu, u Norveškoj i Švedskoj se u izvanbolničkoj populaciji vrlo često propisuje fenoksimetilpenicilin, stavljajući naglasak na očuvanje rezervnih širokospektralnih antibiotika (35-38). Nizozemska već tradicionalno

dugi niz godina ima najnižu stopu antimikrobne rezistencije i ako se liječnici odluče za propisivanje antibiotika u izvanbolničkoj skrbi, vrlo često je lijek izbora fenoksimetilpenicilin (10). Iako je fokus intervencija za racionalizaciju potrošnje antibiotika usmjeren na liječnike primarne zdravstvene zaštite, činjenica je da se od ukupne izvanbolničke potrošnje antibiotika 7-11 % odnosi na uporabu u dentalnoj medicini (16, 17). U Španjolskoj i Italiji liječnici dentalne medicine najčešće propisuju peniciline širokog spektra i kombinacije s inhibitorom (39, 40), kao i u našem radu. I liječnici dentalne medicine u PGŽ bi često propisali antibiotike za stanja gdje je kirurški zahvat prvi izbor te želimo naglasiti da u stomatologiji postoji značajan prostor za unapređenje propisivanja antibiotika, što navode i druge slične studije (24, 40, 41). Posljedično tomu, zemlje s visokom potrošnjom širokospektralnih antibiotika imaju i višu stopu rezistencije za razliku od zemalja koje vrlo često koriste uskospektralne antibiotike kao antimikrobnu terapiju (10, 11, 30).

Ključni izazov za liječnika je osigurati pacijentu pristup antibioticima koji će mu donijeti dobrobit, istovremeno vodeći računa da se antibioticima koriste odgovorno, kako bi se smanjila ili barem usporila antimikrobna rezistencija. Iako su antibiotici dragocjeni lijekovi, imaju i svoju dobru (izlječenje bakterijske infekcije) i lošu stranu (moguće neželjene učinke, tzv. nuspojave). Odluka o propisivanju antibiotika je kompleksan proces, tijekom kojeg je liječnik pod utjecajem različitih čimbenika, kliničkih (klinička slika, podatci utemeljeni na kliničkim dokazima, medicinska literatura, vlastito znanje i iskustvo, i dr.) i nekliničkih (kulturološki, socioekonomski i dr.) u svakodnevnoj komunikaciji s pacijentom (3, 23, 41-43).

Kao važan čimbenik za prekomjerno propisivanje antibiotika u ordinacijama, navodi se nedovoljno znanja i iskustva u praksi od strane liječnika, iz čega proizlazi nesigurnost u postavljanju dijagnoze i odluke o liječenju. U talijanskoj studiji (22), iskusniji liječnici s više godina radnog staža imali su manju vjerojatnost propisivanja antibiotika, sugerirajući problem nesigurne dijagnoze naročito kod mlađih liječnika, što je rezultiralo propisivanjem antibiotika druge linije, tj. rezervnih širokospektralnih antibiotika. U našem istraživanju smo uočili da trend propisivanja amoksicilina pada s godinama starosti liječnika dentalne medicine.

Nedostatak vremena u svakodnevnom radu predstavlja važnu kariku u odlučivanju o propisivanju antibiotika i intenzitetu komunikacije s pacijentom o korištenju antibiotika. Prezaposlenom liječniku u ordinaciji s puno pacijenata možda će biti lakše prepisati antibiotik na zahtjev pacijenta, nego odlučiti uzeti si vremena i objasniti pacijentu zašto antibiotici nisu primjereni za određeno zdravstveno stanje, infekciju koja ne zahtjeva antimikrobnu terapiju (42-45). I liječnici dentalne medicine u našoj studiji smatraju da nedostatak vremena u svakodnevnom radu utječe na češće propisivanje antibiotika.

Nedovoljno znanja, različiti stavovi i iskustvo u praksi roditelja o uporabi antibiotika mogu uvelike doprinijeti odluci liječnika da propiše antibiotik (46, 47). Poznato je da su pritisak i očekivanja pacijenata, naročito roditelja bolesne djece, jedan od glavnih pokretača propisivanja antibiotika u ordinacijama (19, 42-44), što navode i liječnici dentalne medicine u našem istraživanju. U literaturi se navodi da čak 32% pacijenata očekuje antibiotike za akutnu infekciju dišnog sustava (48), što dodatno stvara pritisak na odluku liječnika u svakodnevnom radu. Slično kao u švedskoj studiji (49), i u našem radu se pokazalo da roditelji školske djece u PGŽ imaju visoko povjerenje u liječničku odluku o propisivanju antibiotika i visoku svjesnost o rezistenciji bakterija na antibiotike. Međutim, za racionalnu primjenu antibiotika potrebna je intenzivnija komunikacija zdravstvenih djelatnika s pacijentima o ovom problemu. Već dugi niz godina brojni stručnjaci u Hrvatskoj i svijetu naglašavaju da liječnici propisivači antibiotika imaju važnu ulogu u racionalizaciji uporabe antibiotika i da trebaju prihvatiti činjenicu da su važan čimbenik u kontroli pojave i širenja antimikrobne rezistencije (3, 24, 41, 50, 51).

Kako se navodi i u drugim studijama koje ističu sličnu problematiku (23-25, 39, 41), izradom nacionalnih smjernica o propisivanju antimikrobne terapije u medicini i stomatologiji, i dodatnom edukacijom u sklopu stručnog usavršavanja, trebale bi se postaviti jasne indikacije za antimikrobno liječenje i promijeniti trend visokog propisivanja širokospektralnog amoksicilina s klavulanskom kiselinom. Uz sve spomenuto, liječnici dentalne medicine trebaju povezati visoku svjesnost o rezistenciji bakterija na antibiotike s većom osobnom odgovornošću da ne propisuju antibiotike za stanja gdje je kirurški zahvat prvi izbor, kako bi sačuvali djelotvornost postojećih antibiotika za stanja kada su zaista potrebni. Za racionalnu primjenu antibiotika odgovorni su i oni koji antibiotike propisuju i oni koji ih konzumiraju (1, 3), svi smo dio društvene zajednice prema kojoj imamo odgovornost da sačuvamo antibiotike za liječenje bakterijskih infekcija.

## 3.5. ZNANSTVENI DOPRINOS OBJEDINJENIH RADOVA

1. Ova istraživanja su ukazala da se intenzivna edukacija o racionalizaciji primjene antibiotika treba provoditi i u ciljnim populacijama koje nisu često povezane s problemom rezistencije bakterija na antibiotike (djeca školske dobi, liječnici dentalne medicine).

2. Iako se glavna pažnja posvećuje predškolskoj populaciji, u našem radu smo pokazali da školska djeca predstavljaju važan rezervoar bakterija rezistentnih na antibiotike u zajednici, te roditelje i zdravstvene djelatnike u čijoj su skrbi djeca ove dobne skupine treba uključiti u intenzivno obrazovanje o racionalnoj uporabi antibiotika, s ciljem sprječavanja pojave i širenja rezistentnih bakterija.

3. Naši rezultati su istaknuli potrebu za aktivnijim sudjelovanjem zdravstvenih djelatnika u komunikaciji s pacijentima o problemu uporabe antibiotika (naročito širokospektralnih) i pojavi rezistencije bakterija na antibiotike.

4. Liječnici dentalne medicine trebaju povezati visoku svjesnost o rezistenciji bakterija na antibiotike s većom osobnom odgovornošću, te spoznajom da uz ostale zdravstvene djelatnike predstavljaju važnu kariku u racionalizaciji uporabe antibiotika i očuvanju njihove djelotvornosti, naročito rezervnih širokospektralnih antibiotika.

## 3.6. SAŽETAK

**Uvod:** Neracionalna uporaba antibiotika je zasigurno složen problem kojem doprinosi više čimbenika, ali i jedan od glavnih pokretača za pojavu i širenje rezistencije bakterija na antibiotike.

**Metode:** U prospektivnom istraživanju obrađeni su obrisci ždrijela i nazofarinksa 450 djece školske dobi, 6-15 godina, Grada Rijeke i okolice. Dva presječna istraživanja su provedena pomoću strukturiranih upitnika o znanju, stavovima i praksi o uporabi antibiotika na 1000 roditelja djece osnovnih škola i 230 liječnika dentalne medicine Primorsko-goranske županije, Hrvatska.

**Rezultati:** Izloženost antibioticima u djece školske dobi u prethodnih šest mjeseci je bila povezana s pojavom bakterija rezistentnih na antibiotike. Uporaba uskospektralnih penicilina je bila rjeđa nego uporaba amoksicilina (26% školska djeca, 33.1% liječnici dentalne medicine) i amoksicilina s klavulanskom kiselinom (26% školska djeca, 65% liječnici dentalne medicine). Roditelji i liječnici dentalne medicine su imali visoku svjesnost o rezistenciji bakterija na antibiotike.

**Zaključci:** Uporaba antibiotika je povezana s višom stopom rezistencije u respiratornih patogena. Sociodemografske karakteristike roditelja nisu utjecale na uporabu antibiotika. Iako liječnici dentalne medicine posjeduju visoku svjesnost o rezistenciji bakterija na antibiotike, i dalje postoji prevelika uporaba antibiotika, naročito širokospektralnih te treba povećati osobnu odgovornost za racionalnu uporabu antibiotika.

## 3.7. SUMMARY

Antibiotic use and antimicrobial resistance in school children

**Introduction:** Irrational antibiotic use is certainly complex and multifactorial problem, but also one of the major drivers for the emergence and spread of antimicrobial resistance.

**Methods:** In prospective study throat and nasopharyngeal swabs from 450 school children, 6-15 years of age, from the city of Rijeka and the surrounding area, were processed. Two cross-sectional studies based on a structured questionnaire about knowledge, attitudes and practice regarding antibiotic use, that were given to 1000 parents of children attending elementary schools and 230 dental practitioners in outpatient settings of Primorsko-Goranska County, Croatia.

**Results:** Antibiotic exposure in school children in the previous six months was associated with the carriage of antibiotic-resistant bacteria. The use of narrow spectrum penicillins was less common than the use of amoxicillin (26% school children, 33.1% dental practitioners) and amoxicillin with clavulanic acid (26% school children, 65% dental practitioners). Parents and dental practitioners had a high awareness of antimicrobial resistance.

**Conclusions:** Antibiotic use is linked with higher resistance rates of respiratory tract pathogens. Parents' background did not influence the frequency of antibiotic use. Although there is a high level of antimicrobial resistance awareness among dental practitioners, there is still too much overuse of antibiotics, especially broad spectrum, and personal responsibility for rational antibiotic use should be increased.

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## 3.9. ŽIVOTOPIS

Rođena sam 07. svibnja 1974. g. u Karlovcu. U Rijeci sam završila osnovnu i srednju školu i 1993. g. upisala Medicinski fakultet. Kao stažist radila sam u Kliničkom bolničkom centru u Rijeci. Kao doktor medicine radila sam u Turističkoj ambulanti Cres (pri Domu zdravlja "Dr. Dinko Kozulić" Mali Lošinj), Specijalističkoj internističkoj ordinaciji prim.dr. Jadranko Jelić (Rijeka), Ordinaciji opće medicine dr.med. Alemka Čajkovski (Kostrena) i Ustanovi za hitnu medicinsku pomoć u Rijeci. Od 2004. g. radim na Mikrobiološkom odjelu Nastavnog zavoda za javno zdravstvo Primorsko-goranske županije u Rijeci, najprije kao suradnik u laboratoriju, specijalizant, a sada specijalist medicinske mikrobiologije s parazitologijom.

Na Medicinskom fakultetu u Zagrebu završila sam Specijalistički poslijediplomski studij Medicinska mikrobiologija s parazitologijom. Specijalistički ispit iz medicinske mikrobiologije s parazitologijom položila sam 2009. g. Sada sam koordinator aktivnosti dijagnostike respiratornih i sustavnih infekcija Mikrobiološkog odjela Nastavnog zavoda za javno zdravstvo Primorsko-goranske županije u Rijeci.

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## 4. PRESLIKE OBJEDINJENIH RADOVA

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# Impact of antibiotic consumption on the carriage of antibiotic-resistant bacteria by school children

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**Background:** Antibiotic consumption in the paediatric population is one of the key drivers of the emergence and spread of antimicrobial resistance, which is a serious global threat to public health and clinical medicine. The aims of this study were to investigate systemic antibiotic consumption in school children and to assess the associations among antibiotic consumption, carriage rate and resistance of respiratory pathogens residing in the upper respiratory tract mucosa. **Methods:** In this prospective study, throat and nasopharyngeal swabs from 450 school children, 6–15 years of age (225 healthy children and 225 patients who were ambulatory treated for upper respiratory tract infection), were processed in 2014 in Rijeka, Croatia, and clinical data were obtained via a questionnaire. **Results:** In total, 17% of the children had consumed an antibiotic in the previous 6 months, including 7% of the healthy children and 27% of the acutely ill patients. The most commonly prescribed antibiotics were amoxicillin (26%), amoxicillin with clavulanic acid (26%) and macrolides (18%). Respiratory pathogens were more frequently isolated from children who had consumed an antibiotic in the previous 6 months [odds ratio (OR) 3.67, $P<0.001$]. Antibiotic-resistant bacteria were also more frequent in children who had been exposed to antibiotics (OR 5.44, $P<0.001$). **Conclusions:** Penicillins are the most frequently used antibiotics among school children. The results of this study demonstrate that antibiotic consumption is linked with higher carriage rates and resistance rates of respiratory tract pathogens. Therefore, rational use of antibiotics could prevent the emergence and spread of resistant bacteria.

## Introduction

Antimicrobial resistance is a well-recognized global threat to public health and clinical medicine.[1,2] Antibiotic consumption is one of the key drivers of the emergence and spread of antimicrobial resistance in community. Most antibiotics are prescribed in ambulatory care, and in Croatia, more than 90% of all antibiotics are prescribed in the outpatient setting.[2–4] In Europe, extreme differences in the prescribing of antibiotics and antimicrobial resistance rates have been recorded between northern countries and southern and eastern countries. Croatia belongs to a group of countries with high overall antibiotic consumption and consequently high antimicrobial resistance among bacteria that commonly cause infections in community.[3,5–7] The association between antibiotic consumption and bacterial resistance in primary care has been confirmed at both the individual and population levels.[6,8,9]

Antibiotics are mainly prescribed for upper respiratory tract infections, which are often self-limiting and viral in origin. Broad-spectrum antibiotics are often inappropriately prescribed for these infections, causing significant financial burden and leading to the emergence and spread of bacterial resistance.[4,10–12] Antibiotics are the most commonly prescribed drugs for children, especially among the pre-school population.[10,12,13] School children are not affected as much as children in day-care centres and nurseries, as school children are less susceptible to infections than the children in these facilities.[13–15] However, school children may also serve as important reservoir of antibiotic-resistant bacteria in the community.

The aims of this study were to investigate systemic antibiotic consumption by school children and to evaluate the associations among antibiotic consumption, carriage rate and resistance of respiratory pathogens residing in the upper respiratory tract mucosa. We analyzed the incidence and resistance patterns of the most common respiratory pathogens, namely, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae*.

## Methods

### Study population

All data on children enrolled in this prospective study were processed during the school year, from 29 January 2014 to 16 June 2014 and 22 September 2014 to 04 November 2014. Throat and nasopharyngeal samples were collected from 450 children between 6 and 15 years of age. Two groups of school children were included in the study, 225 healthy children with no signs or symptoms of respiratory tract infection in the previous 2 weeks and

225 patients receiving ambulatory treatment for upper respiratory tract infection. The children attended 31 elementary schools in the city of Rijeka, Croatia and the surrounding area. Parents, legal representatives or guardians of the participating children provided written informed consent and filled out a questionnaire on demographic and socioeconomic characteristics. All children included in the study shared similar socioeconomic statuses. Attending physicians provided data regarding antibiotic consumption and the presence or absence of signs and symptoms of respiratory infection in the previous 6 months. Immunocompromised children were excluded from the study because of the increased sensitivity of these children to infections (especially respiratory tract infections).

### Sample collection

Throat and nasopharyngeal swabs (Venturi Transystem, Copan Italia S.P.A, Brescia, Italy) were obtained from each child. Five paediatricians, two general practitioners, two family physicians (from a private practice and from the Health Care Centre of Primorsko-Goranska County, Rijeka) and a school and university physician (from the Teaching Institute of Public Health of Primorsko-Goranska County, Rijeka) participated in the study. The swabs were transported within 12 h of collection in Amies transport medium with charcoal to the Department of Microbiology of the Teaching Institute of Public Health of Primorsko-Goranska County (Rijeka), where the swabs were processed immediately.

### Bacterial isolation and identification

Each swab was immediately inoculated on Columbia agar containing 5% sheep blood (bioMérieux, Marcy I' Etoile, France) and streaked with *Staphylococcus aureus*. The plates were incubated at 36°C in a 5% CO2-enriched atmosphere and examined for growth after 24–48 h. Bacterial identification of *Streptococcus pyogenes* was carried out by following standard procedures for colony morphology analysis ($\beta$-haemolysis), Gram staining, the catalase test, bacitracin susceptibility testing (BBL, Becton, Dickinson and Company, Sparks, MD, USA) and latex agglutination test (Slidex Strepto Plus, bioMérieux, Marcy I' Etoile, France). *Streptococcus pneumoniae* was identified by colony morphology analysis ($\alpha$-haemolysis), Gram staining, the catalase test, optochin susceptibility testing (BBL, Becton, Dickinson and Company, Sparks, MD, USA) and bile solubility testing. *Moraxella catarrhalis* was identified by colony morphology analysis ($\gamma$-haemolysis), Gram staining, the oxidase test (Bio-Rad, Marnes-la Coquette, France), the catalase test, nitrate reduction testing (nitrate agar, HiMedia Laboratories Pvt. Ltd., Mumbai, India) and the DNAse test (DNAse agar, Oxoid Ltd., Basingstoke, Hampshire, England) and based on the occurrence of a phenomenon called 'hockey puck sign' *Haemophilus influenzae* was identified by colony morphology analysis ($\gamma$-haemolysis), Gram staining, the catalase test and based on satellite formation around *Staphylococcus aureus* and the requirement for X and V factors for growth (Oxoid Ltd., Basingstoke, Hampshire, England). Only one isolate per patient was included in the study.

### Antimicrobial susceptibility testing

Bacterial isolates were tested by the disk diffusion method and minimum inhibitory concentrations (MIC) determination when needed according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST),[16] using Mueller-Hinton Fastidious agar (bioMérieux, Marcy I' Etoile, France) and antibiotic disks (Bio-Rad, Marnes-la Coquette, France). *Streptococcus pyogenes* was tested for susceptibility to erythromycin, clindamycin and penicillin. *Streptococcus pneumoniae* was tested for susceptibility to erythromycin, clindamycin, trimethoprim-sulfamethoxazole and penicillin. For pneumococcal isolates with zones of <20 mm diameters around the oxacillin disks, MICs were determined with penicillin, ampicillin, cefuroxime and ceftriaxone using a gradient strip test (E-test, bioMérieux, Marcy I' Etoile, France). *Moraxella catarrhalis* was tested for susceptibility to erythromycin, trimethoprim-sulfamethoxazole, cefuroxime, ceftriaxone, ampicillin and amoxicillin with clavulanic acid. *Haemophilus influenzae* was tested for susceptibility to trimethoprim-sulfamethoxazole, cefuroxime, ceftriaxone, ampicillin and amoxicillin with clavulanic acid. For all *Moraxella catarrhalis* and *Haemophilus influenzae* isolates, the production of $\beta$-lactamase was tested with the nitrocefin test (Cefinase, bioMérieux, Marcy I' Etoile, France). *Streptococcus pneumoniae* ATCC 49619 and *Haemophilus influenzae* NCTC 8468 were included as quality control strains.

### Statistical analysis

Statistical analysis was performed using the statistical packages Statistica 12.0 (StatSoft Inc., Tulsa, USA) and MedCalc 12.0.0 (MedCalc Software, MariaKerke, Belgium). Data are presented with frequencies (absolute, relative), odds ratios (ORs) and 95% confidence intervals (95% CIs). For categorical variables, chi-square test, Yates correction when needed, Fisher's exact test and proportion test were conducted. *P*-values <0.05 were considered statistically significant.

## Results

The study population included 450 children, of whom 225 were healthy and 225 presented with upper respiratory tract infections, 219 were female and 231 were male. The median age was 12, with ages ranging from 6 to 15 years. From the total of 450 school children, 75 (17%) had used at least one antibiotic in the previous 6 months, including 15 (7%) healthy children and 60 (27%) patients presenting with upper respiratory tract infections. Four children (5%) received more than one antibiotic in the previous 6 months [1 (1%) healthy child and 3 (4%) acutely ill patients]. Overall, boys had higher prescription rates (41, 55%) than did girls (34, 45%) in the study period. Antibiotics were prescribed to 22 male (58%) and 16 female (42%) children in the age group 6–9 years and 19 male (51%) and 18 female (49%) children in the age group 10–15 years. Among the 75 antibiotic consumers, 38 children (51%) were in the age group 6–9 years and 37 children (49%) were 10–15 years old. There were 41 antibiotic treatments recorded in the age group 6–9 years and 39 treatments in the age group 10–15 years.

No difference was observed between the age groups of children in terms of the prescribing of antibiotics, except for the prescribing of second- and third-generation cephalosporins, which were more frequently prescribed to children in the age group 6–9 years than to those in the age group 10–15 years (table 1). Among the antibiotics consumed 6 months prior to the latest visit to the doctor, the most widely prescribed antibiotics were penicillins (65%), which were followed by macrolides (18%) and cephalosporins (15%). Amoxicillin and amoxicillin with clavulanic acid were each used in 21 treatments, and phenoxymethylpenicillin was used in 10 treatments. Azithromycin was used in 13 treatments and clarithromycin in 1 treatment. Cephalexin was used in three treatments, cefuroxime axetil in six treatments and cefixime in three treatments (table 1). Penicillin with an extended spectrum and penicillin in combination with a beta-lactamase inhibitor constituted most of the penicillin consumption. Beta-lactamase resistant penicillins were not used (figure 1).

According to the clinical diagnosis in the 75 children (80 treatments) who received antibiotics, 67% of the antibiotics were prescribed for upper respiratory tract infections, 23% for lower

Table 1 Number of treatments with specific antibiotic agents

| Antibiotic agents | 6–9 years *n* (%) | 10–15 years *n* (%) | Total *n* (%) | *P* |
|---|---|---|---|---|
| Penicillins with extended spectrum | 7 (17) | 14 (36) | 21 (26) | 0.094 |
| Beta-lactamase sensitive penicillins | 7 (17) | 3 (8) | 10 (13) | 0.089 |
| Penicillins + beta-lactamase inhibitor | 10 (24) | 11 (28) | 21 (26) | 0.876 |
| First generation cephalosporins | 3 (7) | 0 (0) | 3 (4) | 0.116 |
| Second and third generation cephalosporins | 8 (20) | 1 (3) | 9 (11) | 0.044 |
| Trimethoprim and sulfamethoxazole | 0 (0) | 2 (5) | 2 (2) | 0.188 |
| Macrolides | 6 (15) | 8 (20) | 14 (18) | 0.769 |
| Total | 41 (100) | 39 (100) | 80 (100) | |

Note: *P*-values <0.05 was considered statistically significant (comparison of proportion).

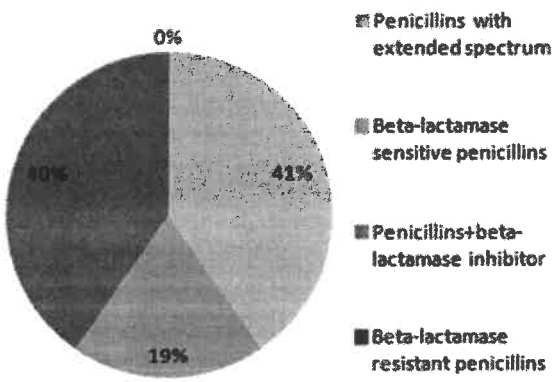


**Figure 1** Penicillin use in school children

respiratory tract infections, 5% for urinary tract infections, 4% for skin infections and 1% for other diagnoses.

In the group of children who had received an antibiotic in the previous 6 months, respiratory pathogens were more frequently isolated than they were in the group of children not exposed to antibiotics (OR 3.67, $P<0.001$; table 2). From the 75 children who had received an antibiotic in the previous 6 months, 21 antibiotic-resistant bacteria were isolated, and 25 antibiotic-resistant bacteria were isolated from the 375 children who had not been exposed to antibiotics, which is a statistically significant difference (OR 5.44, $P<0.001$; table 3).

## Discussion

Croatia is a country with high antibiotic consumption rate that corresponds to the European average (ESAC-Net).[3] School-aged children are not particularly prone to infections and are therefore not considered to be important targets for rationalizing the use of antibiotics. In this study, we showed that 7% of the healthy children had consumed antibiotics in the previous 6 month, and this percentage was even higher for children presenting with upper respiratory tract infection (27%). According to the Special Euro barometer Report for 2016, 36% of all Croatians had been prescribed antibiotics in the previous year.[17]

Wide variations in the prescribing of antibiotics to children have been shown among countries.[18–21] The prevalence of antibiotic use in children aged 0–19 years was higher in Italy and Canada (42–57%) than it was in the Netherlands and the United Kingdom (14–21%).[21] Unlike our study, most of the studies include preschool children, to whom antibiotics are much more commonly prescribed.[13,18–20] Of particular concern is the fact that in many countries, amoxicillin with clavulanic acid is the antibiotic most frequently prescribed to children.[13,22] In countries with more rational antibiotic prescribing, amoxicillin (the Netherlands)[18,19] or phenoxymethylpenicillin (Denmark, Sweden)[18,23] are more frequently used. In our study, amoxicillin and amoxicillin with clavulanic acid were used with equal frequency, and second- and third-generation cephalosporins were used by younger children (6–9 years) with alarming frequency.

Our study demonstrated that 90% of the antibiotics were prescribed for respiratory tract infections, primarily upper respiratory tract infections (67%), similarly as in other studies.[20,23]

Our study confirmed a statistically significant association between antibiotic consumption and antimicrobial resistance of respiratory pathogens isolated from throat and nasopharyngeal swabs from school children. Therefore, antibiotic use in school children is an important driver of antimicrobial resistance in the community. In this study, we also found a statistically significant relationship between antibiotic use and the carriage rate of *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. This result implies that antibiotic consumption may predispose children to colonization by potential respiratory pathogens.

Even in Sweden and the Netherlands, countries with low antibiotic prescription rates, several studies have emphasized the need for increased prudence in outpatient antibiotic use in children.[19,23–25] Mölstad et al. showed that the multi-disciplinary coordinated programme STRAMA (the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance) has greatly contributed to the reduction of total antibiotic use by 15% and outpatient antibiotic use by 20% during the 1995–2004 period in Sweden. This decrease was particularly evident for macrolides (65%). STRAMA recommends phenoxymethylpenicillin as the drug of choice to treat most respiratory tract infections, which is reflected in the high use of narrow-spectrum penicillins in this country.[23,25] Since 2006, the Croatian Intersectoral Coordination Mechanism for the Control of Antimicrobial Resistance (Interdisciplinarna Sekcija za Kontrolu Rezistencije na Antibiotike, ISKRA) has been coordinating all activities related to antibiotic resistance control at the national level. These activities include surveillance of resistance and antibiotic consumption,[4] education of clinicians, patients and pharmacists[7] and development of national guidelines on antibiotic use. Although ISKRA has published national guidelines for antimicrobial therapy for sore throat which promote the use of phenoxymethylpenicillin[26] for this indication the results of our study indicate that much needs yet to be done to improve compliance with the guidelines and that there is a need for developing guidelines for other respiratory tract infections for which antibiotics should generally not be prescribed. Large variations in the prescribing of antibiotics at the community level have been shown to be influenced by many factors, such as socioeconomic and sociocultural factors and patients' and prescribers' attitudes, beliefs and knowledge regarding antibiotic use and resistance.[5,27] André et al.[28] observed that the Swedish public had a high level of trust in the restrictive prescribing of antibiotics by doctors and a high awareness of antibiotic resistance. The Dutch public had the same attitudes, beliefs and knowledge regarding

**Table 2** Association between antibiotic consumption and carriage of respiratory pathogens

| Respiratory pathogen | Antibiotic consumption ($n=75$) | No antibiotic consumption ($n=375$) | OR | 95% CI | P |
|---|---|---|---|---|---|
| *Streptococcus pneumoniae* | 10 | 23 | 2.35 | (1.07–5.18) | 0.048 |
| *Streptococcus pyogenes* | 15 | 33 | 2.59 | (1.33–5.06) | 0.007 |
| *Haemophilus influenzae* | 8 | 12 | 3.61 | (1.42–9.17) | 0.010 |
| *Moraxella catarrhalis* | 5 | 14 | 1.84 | (0.64–5.28) | 0.339 |
| Total | 38 | 82 | 3.67 | (2.19–6.14) | <0.001 |

Notes: *P*-values <0.05 was considered statistically significant (Fisher's exact test).
OR = odds ratio; 95% CI = 95-percentage confidence interval.

**Table 3** Association between antibiotic consumption and carriage of antibiotic-resistant bacteria

| Respiratory pathogen | Antibiotic consumption ($n=75$) | No antibiotic consumption ($n=375$) | OR | 95% CI | P |
|---|---|---|---|---|---|
| Penicillin NS *Streptococcus pneumoniae* | 4 | 3 | 7.04 | (1.54–32.14) | 0.017 |
| Erythromycin NS *Streptococcus pneumoniae* | 3 | 2 | 7.77 | (1.28–47.34) | 0.035 |
| Erythromycin NS *Streptococcus pyogenes* | 8 | 5 | 8.84 | (2.81–27.83) | <0.001 |
| Amoxicillin R *Haemophilus influenzae* | 1 | 5 | 1.0 | (0.12–8.68) | >0.999 |
| Amoxicillin R *Moraxella catarrhalis* | 5 | 10 | 2.61 | (0.86–7.86) | 0.086 |
| Any of the above organisms | 21 | 25 | 5.44 | (2.85–10.40) | <0.001 |

Notes: *P*-values <0.05 was considered statistically significant (Fisher's exact test).
NS = non-susceptible; R = resistant; OR = odds ratio; 95% CI = 95-percentage confidence interval.

antibiotic use and resistance as Swedish citizens. In contrast, Italy and Croatia had poor public knowledge and attitudes regarding antibiotic consumption and resistance.[29,30] Pressure from the pharmaceutical industry, poor quality of physician-patient interaction leading to lack of patients' trust and poor compliance with prescription guidelines play important roles in the prescribing of antibiotics.[27] Our study confirmed the need for increased individual and population level evidence-based studies on antibiotic use and resistance in school children, in order to encourage improvements in the prescribing of antibiotics to this age group.

A limitation of this study is that a small number of respiratory pathogens were obtained from both healthy and ill children, which might have influenced the statistical analysis. Additionally, a relatively small number of patients received antibiotics, so the results of the antibiotic use analysis may not match the results of population-based studies. However, our study has indicated an apparent link between antibiotic consumption, carriage of respiratory pathogens and resistance rates.

## Conclusions

Our findings suggest that school children represent a significant reservoir of antibiotic-resistant bacteria in the community, and this age group should also be considered a target for intensive education on the rational prescribing of antibiotics, at both the patient and health care professional level.

## Ethical approval

The study was approved by the Ethics Committee of the Teaching Institute of Public Health of Primorsko-Goranska County in Rijeka, the Ethics Committee of the Health Care Centre of Primorsko-Goranska County in Rijeka and the Ethics Committee of the University of Rijeka Faculty of Medicine.

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*Conflicts of interest*: None declared.

## Key points

- Penicillins are the most frequently used antibiotics among school children.
- Antibiotic use is linked with higher bacterial carriage and resistance rates.
- Schools represent a notable reservoir of antibiotic-resistant bacteria.
- Rational antibiotic use could prevent the emergence and spread of resistance.

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# Parental Knowledge and Awareness Linked to Antibiotic Use and Resistance: Comparison of Urban and Rural Population in Croatia

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**Abstract**

**Purpose:** To investigate the differences in parental knowledge, attitudes and practice about antibiotic use and resistance among the urban and rural populations in Croatia.

**Materials and Methods:** A cross-sectional study based on a structured questionnaire was distributed to 1000 parents of children attending 11 elementary schools of Primorsko-Goranska County in 2017.

**Results:** The overall response rate was 65.1% (651/1,000) - 50.6% (253/500) in urban and 79.6% (398/500) in rural population. Urban parents had a higher overall knowledge about antibiotics ($p$ <0.001), while urban and rural parents held mostly similar knowledge and attitudes related to antibiotic use when split into individual statements ($p$ >0.05). Age, education, income, work, and family member working in a health-related field were significantly related with the overall knowledge about antibiotics. In the previous year, 28.2% of children and 28.9% of parents reported using an antibiotic. Croatian parents had a high level of trust in doctors' antibiotic-prescribing practices (96.3% reported trusting the doctors' decision not to prescribe antibiotics, 93.5% to prescribe antibiotics) and high awareness of antimicrobial resistance (94.8%). The public's misconception regarding the terms "bacteria" and "virus" was found in 15.5% of parents. The source of information about antimicrobial resistance was television (60.4%), internet (57.1%), newspapers (44.2%), and medical professionals (30.9%).

**Conclusions:** Although the knowledge about antibiotics was higher in urban parents, it was not reflected on the level of antibiotic consumption. There are indications that medical professionals

should be more involved in communicating the problems of antibiotic use and resistance to patients.

**Keywords:** parents, antibiotic prescribing, antimicrobial resistance, self-medication

## Introduction

Antimicrobial resistance is at the top of the list of global threats to public health.[1] During the last several years, there has been a Europe-wide increase in antimicrobial resistance.[2] Extreme differences in attitudes, beliefs, and knowledge concerning antibiotic use and self-medication have been recorded in European countries. The level of misconceptions contributing to inappropriate antibiotic consumption was the highest in southern and eastern countries.[3,4] The irrational antibiotic use is certainly a complex and multifactorial problem, but also one of the major drivers for the emergence and spread of antimicrobial resistance in the community. [5-8]

Since 2006, the Croatian Intersectoral Coordination Mechanism for the Control of Antimicrobial Resistance (Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike [ISKRA]) has coordinated all activities related to antibiotic control on a national level. ISKRA has designed and distributed educational materials to the general public, national guidelines to physicians on antimicrobial therapy for the most frequent indications, but despite all efforts on the local and national levels (educational campaigns, posters, informative flyers, messages broadcasted on television, internet and other mass media, etc.). Croatia still belongs to the group of European countries with a high overall antibiotic use and consequently high antimicrobial resistance in the community.[9-12] Parental pressure and expectations is often cited as one of the key drivers for antibiotic prescribing.[13-16]

The aims of this study were to investigate the differences in parental knowledge, attitudes and practice (KAP) about antibiotic use and resistance among the urban and rural populations and to raise awareness about the need for more prudent antibiotic use in the outpatient setting.

## Materials and Methods

The study was conducted in one county of Croatia, the Primorsko-Goranska County (P-GC), that consists of three well-defined entities: coastal area with hinterland, including the city of Rijeka (about 34% of the area), islands (about 29% of the area), and Gorski kotar (about 37% of the area). According to the Croatian Bureau of Statistics - Census of Population, Households and Dwellings in the Republic of Croatia in 2011 - the total population of P-GC is 296.195 inhabitants.[17] A school-based stratified geographical clustering sampling was used to select a representative sample of children attending the fifth to the eight grade of elementary schools, whose parents (legal representatives or guardians) were asked to fill in a questionnaire after explaining the importance of the topic and their cooperation to the study through a letter. The total number of children attending the fifth to the eight grade of elementary schools in P-GC in 2016 was 9,275, according to the data of the Department of School and University Medicine, Teaching Institute of Public Health of P-GC (Rijeka, Croatia). The sample size was determined using the Raosoft Sample Size Calculator with confidence interval of 95% and a margin of error of 5%. It was estimated that a minimum sample size should include 369 respondents.[18] Assuming a response rate of 50% and anticipating good-quality data, the number of parents enrolled in the study was rounded to 1,000 (500 urban and 500 rural) having children aged between 10 and 16 years. From May 15 to June 14, 2017, a cross-sectional study based on a structured questionnaire was carried out in 11 elementary schools in P-GC. The schools were selected from a number of different venues in P-GC to increase the generalizability of the findings (Fig. 1). A KAP questionnaire regarding the use of antibiotics was developed and distributed (by children) to Croatian parents. Parental participation was voluntary, anonymous, and without compensation. The researchers assured that anonymity would be maintained and ethical principles would be

followed. The returning of the completed questionnaire was considered as consent for participation. All the participating schools were contacted several times (personally, by phone) during the study period.

A 43-point self-administered questionnaire, composed of five parts, was used (Supplementary Data). The questionnaire was developed after a literature review of comparable studies.[1] Most of the questions about antibiotics were copied from other similar questionnaires used in scientific papers (questions 11 - 26, 29 - 31, 34, 35, 38 - 43), [19-21] while the rest of the questions originated from our scientific team (questions 27, 28, 32, 33, 36, 37). To assure clarity, accuracy and consistency of the questions, the questionnaire was pre-tested among a group of 50 parents. The first part of the questionnaire explored sociodemographic characteristics of parents: age, gender, residence, educational level, monthly family income, working in a health-related field, and at least one family member working in a health-related field. Childrens' age, gender, and school grade were also recorded. The questionnaire also investigated the frequency of antibiotic use by parents and children in the last year (according to the one parent – one child principle), parental knowledge about antibiotics, awareness about antimicrobial resistance, and attitudes and behavior regarding antibiotic consumption. The response alternatives were: written answers, dichotomous answers (yes/no), multiple choice, filter questions, and a 5-point Likert scale (strongly disagree, disagree, no opinion/ neutral, agree, strongly agree). The overall median knowledge of the respondents about antibiotics was estimated by the sum of points (min. 8 – max. 40) achieved on a Likert scale. The threshold for the score was fixed according to the range (8-40). A score of 8-13 points was interpreted as insufficient knowledge; between 14 and 20 as sufficient; between 21 and 27 as good; between 28 and 34 as very good; and ≥ 35 - 40 as excellent.

All statistical analyses were performed using the statistical packages Statistica13.1. (StatSoft Inc., Tulsa, OK) and MedCalc12.1.3 (MedCalc Software, MariaKerke, Belgium). Data were presented as frequencies (absolute, relative), median, and percentiles (5th and 95th). Age was presented as a median with minimum and maximum values. For categorical variables, chi-square test was calculated. Kruskall-Wallis test with *post-hoc* analysis was used to analyze the data. To assess the normal distribution of the variables, we used the Kolmogorov-Smirnov test. Mann-Whitney *U* test for independent variables was used to examine the differences between urban and rural participants. Data were presented with box and whisker plots. Correlations between attitudes, knowledge, and antibiotic use were calculated with Spearman correlation coefficient. Multiple regression analysis was used to identify the factors associated with the overall knowledge about antibiotics. *p*- Values <0.05 were considered statistically significant.

**Results**

The response rate in our study was 65.1% (50.6% for urban and 79.6% for rural population). The city of Rijeka, mountainous region of Gorski kotar, and four islands (Krk, Cres, Mali Lošinj and Rab) were, respectively, targeted by 38.9%, (253/651), 23.5% (153/651), and 37.6% (245/651) of respondents (Fig. 1). The study population included 651 parents - 101 (15.5%) males and 550 (84.5%) females. Median age for all responders was 41 (range 29 - 61 years, 44 [min. 31- max. 54] for males and 41 [min. 29 - max. 61] for females). Median age for urban participants was 42 (min. 31- max. 61) and 41 (min. 29 - max. 59) for rural. The rural population had a higher response rate ($\chi^2$= 58.78, $p$ <0.001). The urban population earned a significantly higher salaries compared to the rural population. Also, urban parents were more frequently employed in a health-related field compared with rural parents ($p$ <0.001). Other sociodemographic data of the

participants are presented in Table 1. All the respondents (N= 651) answered all the requested questions.

Of all the respondents, 28.9% claimed to have used antimicrobial drugs in the last year. Of the school children, 28.2% have taken antibiotics in the last year. There was no significant difference between urban and rural populations; neither did age, gender, education, income, participant or family member working in a health-related field, and knowledge about antibiotics show any difference.

The overall median knowledge score about antibiotics was 32, representing very good knowledge. The urban population had statistically significant more overall knowledge about antibiotics compared with the rural (median 33 [min. 24 - max. 39] vs. 32 [min. 18 - max. 39]; $p$ <0.001). The lowest value of knowledge about antibiotics was 18, what was interpreted as sufficient knowledge about antibiotics, while the highest value was 39, representing excellent knowledge about antibiotics (Fig. 2). Multiple regression was made on a sample of 651 respondents; the coefficient of multiple regression was R=0.39 and the coefficient of determination was 15% ($R^2$=0.15, $p$ <0.001). The regression model presented in Table 2 shows age, education, income, working in a health-related field (HCW), and one family member working in health care to be significantly related with the overall knowledge about antibiotics. Younger parents from the urban environment had greater knowledge compared with rural parents, while parental knowledge about antibiotics in the rural area was better among older parents. Urban and rural populations showed a relatively high, similar knowledge level about antibiotic use in individual statements ($p$ >0.05). Of all the respondents, 89.4% knew that "antibiotics are useful for the treatment of bacterial infections", but of these, 15.5% also agreed that "antibiotics are useful for the treatment of viral infections" (Table 3).

Most parents (91.9%) heard about antimicrobial resistance. Of all the respondents, 80% considered that antimicrobial resistance is a global problem, but only 63.9% thought it is a problem on the national level. There was no significant difference between urban and rural respondents, all $p$ >0.05. Television (60.4%) was found to be the main source of information about antimicrobial resistance, followed by internet (57.1%), newspapers (44.2%); only 30.9% of the respondents learned about antimicrobial resistance from a general practitioner, a family medicine practitioner, or a pediatrician (more than one answer was possible). There was no significant difference by area, all $p$ >0.05. Of all the respondents, 9.2% received information about antimicrobial resistance from other sources (friends, family members, neighbours, schooling, professional literature, professional lectures, promotional actions about antibiotics), which was significantly different between the urban and rural parents (urban 13% vs. rural 7%; $p$ <0.015). Of all the respondents, 94.8% were aware that excessive use of antibiotics can lead to increased bacterial resistance to antibiotics, with no significant difference between the urban and rural populations ($p$ >0.05). The overall median knowledge score about excessive use of antibiotics and development of bacterial resistance was 5, representing excellent knowledge (min. 1 - max. 5).

Most parents (96.3%) expressed confidence in doctors deciding not to prescribe antibiotics, while 93.5% expressed confidence in doctors deciding to prescribe antibiotics. The majority of participants (73.1%) have taken the full dose of the antibiotics prescribed, but some claimed to have stopped taking antibiotics due to symptom relief (8.9%) and due to their own wish (18%). There was no significant difference between the urban and rural populations, all $p$ >0.05.

Almost all participants (99.1%) reported they did not use an antibiotic for themselves or their child without physician prescription in the last year. Less than 1% of parents stated they had

acquired an antibiotic without a prescription or used leftover antibiotics from previous treatments. There was no significant difference between the urban and rural respondents ($p$ >0.05). A large majority (97.8%) reported taking antibiotics only when prescribed by a doctor. However, 6.1% of participants wanted to buy antibiotic from a pharmacist without physician prescription. Of all the parents, 9.1% saved leftover antibiotics because these might be useful in the future. There was no significant difference by the area, all $p$ >0.05.

Of all the participants, 82.3 % stated they would never use an antibiotic for themselves without consulting a doctor. The most common indications for intended self-medication were toothache (11.2%), followed by earache (6.9%), sore throat (6.5%), fever (2.9%), and cold (2.2%); more than one answer was possible. Also, 93.7% of all parents would not give an antibiotic to their child without consultation with a doctor. Toothache (2.6%) was the main condition for intended antibiotic use, followed by earache (2.5%), sore throat (2.5%), fever (2.3%); and cold (0.8%); more than one answer was possible. There was no significant difference between the participants, all $p$ >0.05. The urban and rural populations showed similar attitudes related to antibiotic use in most individual statements ($p$ >0.05). A significant difference between urban and rural parents was noted only for the statement "pharmacists often tell you how to take antibiotic" ($p$ = 0.040) (Table 4).

**Discussion**

The results of the present study showed that the frequency of antibiotic use in the previous year in P-GC (28.9% parents and 28.2% children) was lower than the Croatian (36%) and European average (34%), according to the Special Eurobarometer Report in 2016. Our results still indicate

a higher use than in Germany (23%), the Netherlands (20%), and Sweden (18%), but much lower than in Malta (48%), Spain (47%), and Italy (43%). [22] Interestingly, although there was a difference between urban and rural populations in the overall knowledge about antibiotics related to age, education, income, working in a health-related field and one family member working in health care, there was no difference in the frequency of antibiotic use related to these categories. The reasons for lower antibiotic consumption in P-GC compared to the Croatian average are complex but could, at least partially, be due to the enforced national guidelines on antibiotic use and awareness campaign by HCWs. [23,24]

Mothers represented 84.5% of our respondents, which is probably a reflection of their higher involvement in raising family in our society. We obtained a higher response rate from rural areas, which was probably due to the fact that people in these areas spend more time for each other and show more commitment to community wellbeing. Some studies have reported that patients' expectations influence doctors' prescribing practices.[13-16] In our study, the trust in doctors prescribing antibiotics was higher than in two Swedish studies.[21,25] Also in a Greek study has demonstrated that parents do not pressurize physicians to prescribe antibiotics. [26] As suggested by a Swedish study, [21] doctors themselves may be an important target for improving rational antibiotic consumption. Notable in our study, <1% of parents confirmed self-medication with antibiotics in the last year, which is similar to the Swedish restrictive behavior toward self-medication. [21,27] In comparison, self-medication in Denmark (3%) and Greece (44.6%) was higher than in our study. [28,29] Specifically for the pediatric population, Greek authors showed that 10% of parents administrated antibiotics to their children without medical advice.[26] Although the reported rate of self-medication was low, the intended use of antibiotics for themselves (17.7%) or their children (6.3%) was high, but still lower than in the United States (25.4%). In our study

8.9% of participants didn't understand the need to complete the prescribed dose of antibiotics, and 9.1% of respondents saved leftover antibiotics for future consumption, in comparison to 6.1% of Swedish and 14.2% of American citizens. [25] [30] The most common indications for intended use were toothache, earache, and sore throat. Intended self-medication and storage of antibiotics are strong predictors of actual self-medication.[3,] [30] The level of knowledge about antibiotics varies by countries. The proportion of respondents who knew that antibiotics are not meant to kill viruses was highest in Sweden (72%) and the Netherlands (62%) and the lowest in Spain (37%) and Italy (28%), while Croatian findings (44%) were close to the European average (43%). [22] The high rate of positive responses to this question may be due to the public campaigns on antibiotic awareness that are especially active in this region of the country.[10]

Awareness regarding bacterial resistance is generally higher in Scandinavian than in southeastern European countries. [21,25,31] Responders in our study perceived antimicrobial resistance to be more of a global (80%) than a national (63.9%) problem.

In our study, the role of pharmacists in providing information about appropriate antibiotic treatment seems to be higher than in Sweden and Italy, and higher than the Croatian and European average. On the contrary, the role of medical professionals in promoting awareness about bacterial resistance to antibiotics is similar to the European but lower than the Croatian average. [22,31]

There are several limitations in our study. Due to logistical reasons, it was not possible to conduct telephone or internet interviews. As questionnaires were answered at home, there was a possibility that parents searched for answers on the internet or took guidance from other people around them. Also they did not have the opportunity to ask for clarification regarding unclear

questions Another limitation was that parents who agreed to participated were more interested in the subject, thus leading to a potential overestimation of KAP about antibiotic use and resistance. The finding that a higher percentage of urban parents were employed in a health-related field may biased the interpretation of results. Although it is not appropriate to generalize our findings to the whole parental population in Croatia, these results are useful for streamlining the activities of national public health campaigns.

Of all the respondents, 37.5% stated that doctors do not explain how and why an antibiotic should be taken. The main reason for that is the lack of time for communication due to overcrowding in most primary care offices. Public campaign materials and communication tools available at the European Centre for Disease Prevention and Control (ECDC) and World Health Organization (WHO) antibiotic awareness campaign website may be helpful in educating patients. In Croatia, educational posters, flyers, and a picture book promoting care without antibiotics for upper respiratory tract infections are available, but still not widely in use. In conclusion, although the knowledge about antibiotics is higher among urban parents, it is not reflected on the level of antibiotic consumption. According to our study, there are indications that medical professionals should be more involved in communicating the problems of antibiotic use and microbial resistance to patients.

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**Ethical Approval**

The study design and questionnaire were approved by the Ethics Committee of the Teaching Institute of Public Health of Primorsko-Goranska County in Rijeka and the Ethics Committee of the University of Split School of Medicine.

**Disclosure Statement**

No competing financial interests exist.

**Supplementary Material**

Supplementary Data.

**TABLE 1** DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

| Demographic characteristics | Total (N=651) n (%) | Urban (N=253) n (%) | Rural (N=398) n (%) | *p* |
|---|---|---|---|---|
| Responders | 651 (100) | 253 (38.9) | 398 (61.1) | <0.001* |
| Parental gender: | | | | |
| Male | 101 (15.5) | 36 (14.2) | 65 (16.3) | 0.541 |
| Female | 550 (84.5) | 217 (85.8) | 333 (83.7) | |
| Parental educational level | | | | 0.074 |
| Not educated | 2 (0.3) | 0 (0) | 2 (0.5) | |
| Primary school | 10 (1.5) | 3 (1.2) | 7 (1.8) | |
| High school, no degree | 13 (2) | 4 (1.6) | 9 (2.3) | |
| High school, degree | 431 (66.2) | 153 (60.5) | 278 (69.8) | |
| College | 70 (10.8) | 32 (12.6) | 38 (9.5) | |
| University degree | 110 (16.9) | 52 (20.6) | 58 (14.6) | |
| Master or PhD | 15 (2.3) | 9 (3.6) | 6 (1.5) | |
| Monthly family income level**: | | | | 0.001* |
| less than 4 000 HRK | 50 (7.7) | 17 (6.7) | 33 (8.3) | 0.551 |
| from 4 001 to 6 000 HRK | 141 (21.7) | 41 (16.2) | 100 (25.1) | 0.010* |
| from 6 001 to 8 000 HRK | 154 (23.7) | 58 (22.9) | 96 (24.1) | 0.797 |
| from 8 001 to 10 000 HRK | 123 (18.9) | 40 (15.8) | 83 (20.9) | 0.129 |
| from 10 001 to 12 000 HRK | 75 (11.5) | 35 (13.8) | 40 (10.1) | 0.188 |
| more than 12 000 HRK | 108 (16.6) | 62 (24.5) | 46 (11.6) | <0.001* |
| Work in a health-related field | 99 (15.2) | 54 (21.3) | 45 (11.3) | <0.001* |
| At least one family member working in a health-related field | 111 (17.1) | 51 (20.2) | 60 (15.1) | 0.114 |

*statistically significant

**Average salary in March 2017. was 6.022 HRK (=813.7 EUR, 1 EUR= 7.40 HRK; Croatian kuna)

**TABLE 2** FACTORS SIGNIFICANTLY RELATED WITH THE OVERALL KNOWLEDGE ABOUT ANTIBIOTICS

| Factor | Responders | β | $SE_\beta$ | t | *p* |
|---|---|---|---|---|---|
| Age | Total | - | - | - | - |
| | Urban | -0.07 | 0.03 | -2.05 | 0.042 |
| | Rural | 0.08 | 0.03 | 2.84 | 0.005 |
| Education | Total | 0.81 | 0.14 | 5.87 | <0.001 |
| | Urban | 0.57 | 0.20 | 2.86 | 0.005 |
| | Rural | 0.89 | 0.19 | 4.76 | <0.001 |
| Income | Total | 0.41 | 0.08 | 4.83 | <0.001 |
| | Urban | 0.40 | 0.12 | 3.33 | 0.001 |
| | Rural | 0.35 | 0.12 | 2.95 | 0.003 |
| HCW | Total | | | | |
| | Urban | 1.48 | 0.44 | 3.36 | <0.001 |
| | Rural | | | | |
| Family member is an HCW | Total | 0.99 | 0.31 | 3.15 | 0.002 |
| | Urban | | | | |
| | Rural | | | | |

β – coefficient of regression

$SE_\beta$ – standard error of β coefficient

* HCW – health care worker

**TABLE 3** KNOWLEDGE ABOUT ANTIBIOTICS

| Statement | Response** | Total (N=651) n (%) | Urban (N=253) n (%) | Rural (N=398) n (%) | *p* |
|---|---|---|---|---|---|
| Amoxicillin is an antibiotic | Disagree | 21 (3.2) | 8 (3.2) | 13 (3.3) | 0.876 |
| | No opinion/ Neutral | 72 (11.1) | 31 (12.3) | 41 (10.3) | |
| | Agree | 558 (85.7) | 214 (84.6) | 344 (86.4) | 0.810 |
| Aspirin is an antibiotic | Disagree | 620 (95.2) | 235 (92.9) | 385 (96.7) | 0.028* |
| | No opinion/ Neutral | 20 (3.1) | 11 (4.3) | 9 (2.3) | |
| | Agree | 11 (1.7) | 7 (2.8) | 4 (1.0) | 0.115 |
| Paracetamol is an antibiotic | Disagree | 566 (86.9) | 226 (89.3) | 340 (85.4) | 0.180 |
| | No opinion/ Neutral | 29 (4.4) | 12 (4.7) | 17 (4.3) | |
| | Agree | 56 (8.6) | 15 (5.9) | 41 (10.3) | 0.100 |
| Antibiotics are useful for the treatment of bacterial infections | Disagree | 32 (4.9) | 7 (2.8) | 25 (6.3) | 0.068 |
| | No opinion/ Neutral | 37 (5.7) | 15 (5.9) | 22 (5.5) | |
| | Agree | 582 (89.4) | 231 (91.3) | 351 (88.1) | 0.284 |
| Antibiotics are useful for the treatment of viral infections | Disagree | 477 (73.3) | 184 (72.7) | 293 (74.9) | 0.634 |
| | No opinion/ Neutral | 62 (9.5) | 23 (9.1) | 39 (9.8) | |
| | Agree | 112 (17.2) | 46 (18.1) | 66 (16.6) | 0.567 |
| Antibiotics can kill “good bacteria” present in our body | Disagree | 59 (9.1) | 22 (8.7) | 37 (9.3) | 0.905 |
| | No opinion/ Neutral | 77 (11.8) | 22 (8.7) | 55 (13.8) | |
| | Agree | 515 (79.1) | 209 (82.6) | 306 (76.9) | 0.081 |
| Antibiotics are used to relieve fever | Disagree | 567 (87.1) | 221 (87.4) | 346 (86.9) | 0.948 |
| | No opinion/ Neutral | 38 (5.8) | 14 (5.5) | 24 (6.0) | |
| | Agree | 46 (7.1) | 18 (7.1) | 28 (7.0) | 0.914 |
| Antibiotics can cause allergic reactions | Disagree | 12 (1.8) | 4 (1.6) | 8 (2.0) | 0.943 |
| | No opinion/ Neutral | 35 (5.4) | 12 (4.7) | 23 (5.8) | |
| | Agree | 604 (92.8) | 237 (93.7) | 367 (92.2) | 0.572 |

*93% vs 97% might be statistically significantly different but in practice they are both >90%. ** The “agree “ response represent the sum of percentages of “agree” and “strongly agree”. The “disagree” response represent the sum of percentages of “disagree” and “strongly disagree”.

**TABLE 4** ATTITUDES REGARDING CONSUMPTION OF ANTIBIOTICS

| Statement | Response** | Total (N=651) n (%) | Urban (N=253) n (%) | Rural (N=398) n (%) | *p* |
|---|---|---|---|---|---|
| Doctors often explain how and why an antibiotic should be taken | Disagree | 244 (37.5) | 103 (40.7) | 141 (35.4) | 0.547 |
| | No opinion/ Neutral | 97 (14.9) | 37 (14.6) | 60 (15.1) | |
| | Agree | 310 (47.6) | 113 (44.7) | 197 (49.5) | |
| Doctors often prescribe antibiotics as patients expect them to | Disagree | 290 (44.5) | 107 (42.3) | 183 (46.0) | 0.742 |
| | No opinion/ Neutral | 144 (22.1) | 62 (24.5) | 82 (20.6) | |
| | Agree | 217 (33.3) | 84 (33.2) | 133 (33.4) | |
| Doctors often carefully consider whether or not the antibiotic is needed | Disagree | 229 (35.2) | 93 (36.8) | 136 (34.2) | 0.553 |
| | No opinion/ Neutral | 134 (20.6) | 43 (17.0) | 91 (22.9) | 0.080 |
| | Agree | 288 (44.3) | 117 (46.2) | 171 (43.0) | 0.470 |
| Pharmacists often tell you how to take antibiotics | Disagree | 199 (30.5) | 66 (26.1) | 133 (33.4) | 0.060 |
| | No opinion/ Neutral | 45 (6.9) | 16 (6.3) | 29 (7.3) | 0.740 |
| | Agree | 407 (62.5) | 171 (67.6) | 236 (59.3) | 0.040* |
| Doctors often prescribe antibiotics for “just in case” | Disagree | 364 (55.9) | 141 (55.7) | 223 (56.0) | 0.345 |
| | No opinion/ Neutral | 100 (15.3) | 34 (13.4) | 66 (16.6) | |
| | Agree | 187 (28.7) | 78 (30.8) | 109 (27.4) | |

* statistically significant

** The “agree” response represent the sum of percentages of “agree” and “strongly agree”. The “disagree” response represent the sum of percentages of “disagree” and “strongly disagree”.

**FIG. 1** Number of respondents (response rate) per study site

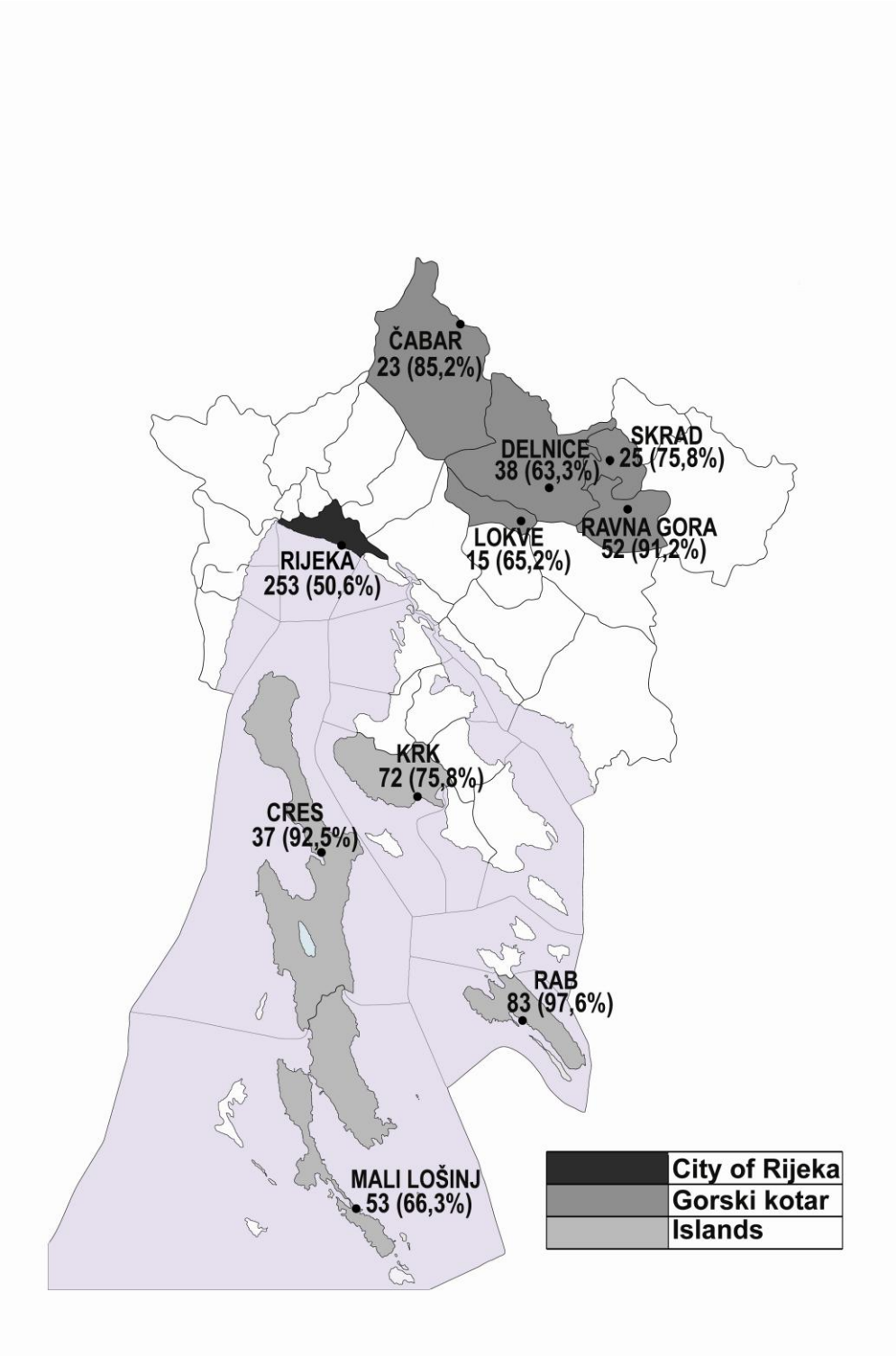
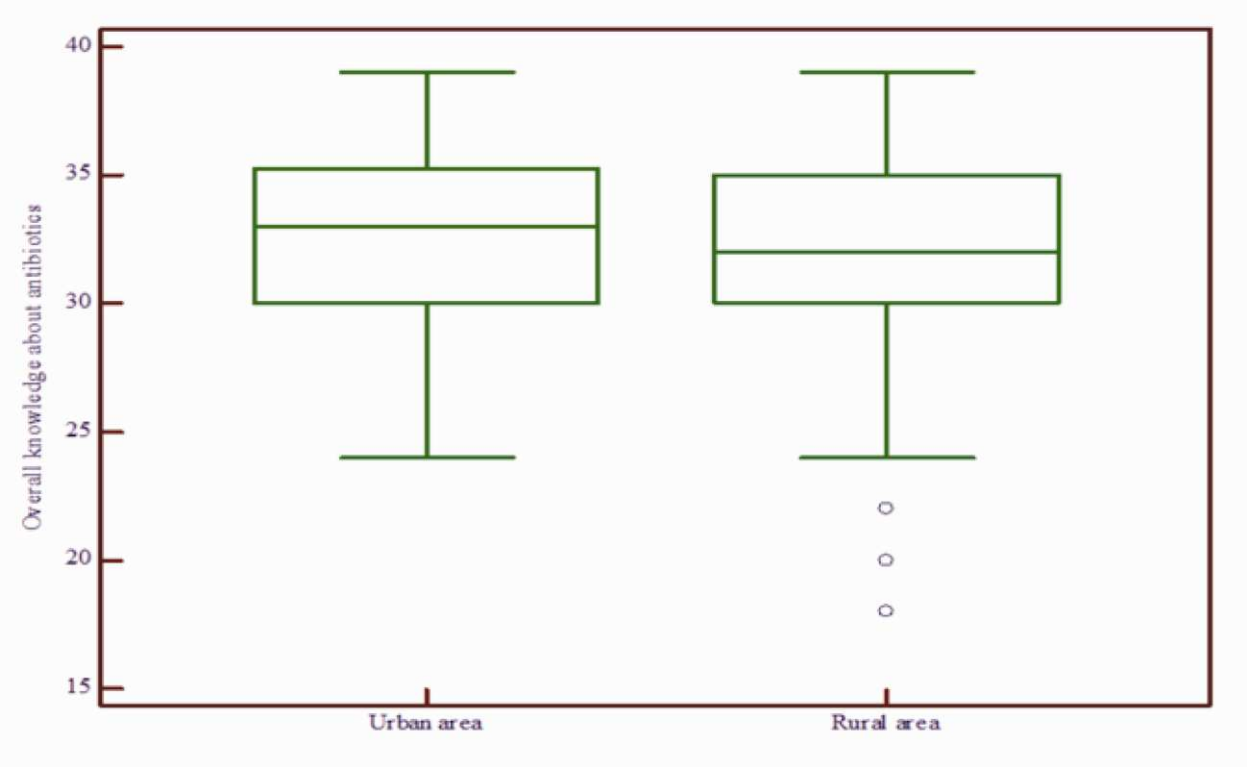


**FIG. 2** Parental overall knowledge about antibiotics (urban vs. rural) represented with median, 25$^{th}$ and 75$^{th}$ percentiles and minimum and maximum



*Priložena autorska prihvaćena inačica, DOI:10.1089/mdr.2020.0478

# Antibiotic Prescribing Habits and Antimicrobial Resistance Awareness of Dental Practitioners in Primorsko-Goranska County, Croatia

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**ABSTRACT**

**Purpose:** The goal of this study was to investigate the differences in dentists' knowledge, attitudes, and practice regarding antibiotic use and resistance among two areas of Primorsko-Goranska County (P-GC), Croatia.

**Materials and Methods:** A cross-sectional study based on a structured questionnaire that was given to 230 dental practitioners in outpatient settings of P-GC in 2018.

**Results:** The overall response rate was 68.3% (157/230), and 72.2% (83/115) in the city of Rijeka and 64.3% (74/115) in the rest of P-GC. Dentists from two areas of P-GC held similar knowledge about prescribing antibiotics and attitudes regarding antibiotic use ($p > 0.05$). Most of the dental practitioners chose penicillins (65.0% amoxicillin with clavulanic acid and 33.1% amoxicillin) as the first-choice antibiotic in patients with no medical allergies. The trend of prescribing amoxicillin decreases with the age of the dentists ($p = 0.046$). Clindamycin (86.6%) was the first choice for patients allergic to penicillin. Postgraduate education changed the attitude towards taking more time to consider whether or not an antibiotic is needed. Croatian dentists had a high awareness of antimicrobial resistance (99.4%). The most common situations for which dentists would prescribe antibiotics were periapical abscess (84.7%), periodontal abscess (72.6%), and implant placement (59.9%). Patient request or expectation (43.4%) and treatment uncertainty (41.5%) were found to be the main factors for prescribing antibiotics with more frequency.

**Conclusions:** Although there is a high level of antimicrobial resistance awareness among dental practitioners, there is still too much overuse of antibiotics and personal responsibility for prudent antibiotic use should be increased. The results of this study indicate that antibiotics are

frequently prescribed for indications where surgical treatment should be the first option and the broad spectrum antibiotic is the preferred treatment option.

**Keywords:** dental practitioners, antibiotic prescribing, antimicrobial resistance, education, national guidelines

## Introduction

Antimicrobial resistance presents a difficult challenge to public health and clinical medicine, with a less than bright future for the patients and antibiotic prescribers.[1,2] Inappropriate antibiotic use is well-recognized as one of the key drivers of the emergence and spread of antimicrobial resistance.[3] Most antibiotics are prescribed in ambulatory care worldwide; likewise in Croatia more than 90% of all antibiotics are prescribed in the outpatient setting.[4-6] Dental practitioners prescribe 7-11% of all antibiotics dispensed in primary care, so they may also serve as an important mediator of antibiotic-resistant bacteria in the community.[7-10] Antibiotics are one of the most commonly prescribed drugs in dentistry despite limited indications for their use and the fact that most dental problems can be resolved by local intervention and oral hygiene measures.[11,12] Broad spectrum antibiotics are often inappropriately prescribed in dentistry, causing significant financial burden and leading to the emergence and spread of bacterial resistance.[13] Dentists' lack of knowledge and experience with antibiotics, as well as pressure from the patients and their expectations, are often cited as the key drivers for prescribing antibiotics.[13-15]

The purpose of this study was to examine dentists' knowledge, attitudes, and practice (KAP) about prescribing antibiotics and their awareness about antimicrobial resistance. We compared the results between the two areas of Primorsko-Goranska County (P-GC).

## Materials and Methods

The study was conducted in one county of Croatia, the Primorsko-Goranska County (P-GC). As stated by the Croatian Bureau of Statistics "Census of Population, Households and Dwellings in the Republic of Croatia in 2011" the total population of P-GC is 296,195 inhabitants.[16]

According to the database of the Teaching Institute of Public Health of P-GC from 2016, 260 dental practitioners were available for the initial contact. The sample size was determined using the Raosoft Sample Size Calculator by taking the following assumptions: 5% margin of error and 95% confidence level. It was estimated that minimum sample size should include 156 respondents. Assuming a response rate of 50% and wanting to obtain a good quality data, the number of dental practitioners enrolled in the study was 230 (115 in the city of Rijeka and 115 in the rest of P-GC).[17]

From June 4th to September 5th, 2018, a cross-sectional study based on a structured questionnaire was carried out in the dental outpatient settings of P-GC (private practice and the Health Care Centre of P-GC). Our study sample included dental practitioners from two areas of P-GC: the city of Rijeka (third largest city in Croatia) and the rest of P-GC (smaller cities and municipalities, mountainous region of Gorski kotar, and the islands of Krk, Cres, Mali Lošinj and Rab). The dentists were selected from a number of different places in P-GC to increase the generalizability of the findings; the participants were consequently divided into two groups based on the site of practice. A KAP questionnaire regarding antibiotic use and resistance was developed and distributed to Croatian dental practitioners by post and personally. Dental practitioners' participation was voluntary, anonymous and without compensation. The researchers assured that anonymity would be maintained and ethical principles would be

followed. The returning of the completed questionnaire was considered as consent for participation.

A 24-point self-administered questionnaire, composed of four parts, was used (Supplementary Data). The questionnaire was developed after a literature review of comparable studies. The questions about antibiotics were taken over or customized from other similar questionnaires used in published scientific articles.[18-23] To assure the clarity, accuracy, and consistency of the questions the questionnaire was pre-tested among 20 dental practitioners. The first part of the questionnaire explored sociodemographic characteristics of dental practitioners: age, gender, area, type of dental practice, and level of education. The questionnaire investigated dental practitioners' knowledge about antibiotics and individual antibiotic prescribing habits, awareness of antimicrobial resistance, attitudes and behavior regarding consumption of antibiotics, and postgraduate education on antibiotics in the last 2 years. The response alternatives were: written answers, dichotomous answers (yes/no), multiple choice, filter questions, and a 5-point Likert scale (strongly disagree, disagree, no opinion/ neutral, agree, strongly agree).

Dentists were divided into different age groups depending on the research needs. To explore the differences between younger and elderly dentists, they were divided by the median age of 45 years. Dentists aged 45 years or less were in the younger group; dentists older than 45 were in the elderly group. To explore the trend in antibiotic prescription dentists were divided in 4 age groups by median (45) and quartile range as follows: 24 – 36 years; 37 – 45; 46 – 56 and 57 – 65 years.

All statistical analyses were performed using the statistical package Statistica 13.5.0.17 (TIBCO Software Inc., Palo Alto, CA). Categorical variables are presented with frequencies and

percentages; numerical variables are presented with arithmetic mean and standard deviation or median and interquartile range. Age is presented with median, minimum and maximum. The normality of distribution is tested with Kolmogorov-Smirnov test. Differences between groups were calculated with chi-square test or Fischer's exact test. To test for trend when there are more than two levels we calculate chi-square test for trend. *Post hoc* analyses were performed with t test for proportion. Differences between groups in attitudes are tested with Mann-Whitney *U* test. All $p$-values < 0.05 were considered statistically significant.

**Results**

The response rate in our study was 68.3% (72.2% in the city of Rijeka and 64.3% in the rest of P-GC). The study population included 157 dental practitioners, 55 (35%) males and 102 (65%) females. Median age for all respondents was 45 (range 24 - 65 years, 44 [minimum 25 - maximum 65] for males and 45 [minimum 24 - maximum 64] for females). Median age for participants in the city of Rijeka was 45 (minimum 25 - maximum 65) and 45 (minimum 24 - maximum 64) in the rest of P-GC. There was a significant difference in the prevalence of dental practices, depending on the type; private practices are quantitative prevalent ($p$ = 0.033) regardless of location. Other sociodemographic data of the participants are presented in Table 1. All respondents (n= 157) completed the questionnaire in its entirety.

Of all participants, 65.0% chose amoxicillin with clavulanic acid as the first-choice antibiotic in patients with no medical allergies, followed by amoxicillin (33.1%) and clindamycin (1.9%). The majority of the respondents (86.6%) selected clindamycin for penicillin allergic patients, 8.3%

azithromycin, 0.6% metronidazole, and 4.5% other (erythromycin, midecamycin, doxycycline, cefuroxime). There was no significant difference by area, all *p*-values > 0.05.

Compared to amoxicillin, amoxicillin with clavulanic acid was prescribed significantly more often for patients without medical allergies by all dental practitioners, regardless of age, gender, type of dental practice, area, level of education, or antibiotic training within the last 2 years (all *p*-values < 0.05) There was no difference between dental practitioners in antibiotic prescribing with respect to age, gender, type of dental practice, area, level of education, or antibiotic training within the last 2 years (all *p*-values > 0.05) (Table 2). We noticed that the trend of prescribing amoxicillin decreases with the age of the dentists ($p = 0.046$), whereas no trend was observed for amoxicillin with clavulanic acid and clindamycin ($p > 0.05$).

Respondents' attitudes on antibiotic use did not differ depending on whether they would more frequently prescribe amoxicillin or amoxicillin with clavulanic acid in patients without medical allergies. In addition, these attitudes did not differ with respect to age, gender, type of dental practice, area, level of education, or antibiotic training within the last two years, all *p*-values > 0.05.

A significant difference between dental practitioners was noted only for the following statement: “dental practitioners often take the time to carefully consider whether or not an antibiotic is needed”. Dental practitioners who were additionally educated on antibiotics within the last 2 years agreed more with above statement ($p = 0.043$) than those who had not been educated.

The most common situations for which dentists would prescribe antibiotics were periapical abscess (84.7%), periodontal abscess (72.6%), and implant placement (59.9%) (more than one

answer was possible)**.** There was no significant difference between the participants, all *p*-values > 0.05 (Fig. 1).

All dental practitioners (100.0%) heard about antimicrobial resistance. Of all respondents, 89.8% considered that antimicrobial resistance is a global problem, but only 76.4% considered that it is a problem on the national level. Of respondents, 72.0% stated that they take the resistance rate of the bacteria in the local setting into account when prescribing antibiotics. There was no significant difference between the respondents, all *p*-values > 0.05. Professional literature (70.7%) was found to be the main source of information regarding antimicrobial resistance, followed by professional meetings (symposia, conferences) (68.8%), professional courses (47.1%), internet (42.0%), television (34.4%), and newspapers (29.3%). Of all respondents, 5.7% received information about antimicrobial resistance from other sources, such as schooling, family members, experience, and colleagues (more than one answer was possible). There was no significant difference by area, all *p*-values > 0.05. Of all respondents, 99.4% were aware that excessive use of antibiotics can lead to increased bacterial resistance to antibiotics, with no significant difference between the city of Rijeka and the rest of P-GC ($p > 0.05$).

Of all participants, 33.8% of them stated that they are influenced by external factors to prescribe antibiotics with more frequency. Patient request or expectation (43.4%) and treatment uncertainty (41.5%) were found to be the main factors for prescribing antibiotics more frequently (more than one answer was possible). Of all respondents, 32.1% reported other influencing factors for more frequent antibiotic prescribing and these included the following: patients who are seafarers, patients who visit their dentist away from their place of living, patients who are planning to travel, worsening of the patients' condition, prevention of complications and postoperative infections, immunocompromised patients, bad oral hygiene, and emergency

conditions with questionable prognosis. There was no significant difference between the participants, all *p*-values > 0.05 (Fig. 2).

Of the participants, 23.6% had received postgraduate education on antibiotics (seminars, lectures, courses, and similar) in the last 2 years, 91.9% 1-2 times and 8.1% more than two times. Of all dental practitioners, 86.6% reported the need for more education. There was no significant difference by area, all *p*-values > 0.05.

All respondents showed similar attitudes related to antibiotic use in all individual statements ($p > 0.05$). (Table 3).

**Discussion**

Our study shows data regarding antibiotic prescribing behaviour and awareness about antimicrobial resistance in outpatient practice of dental practitioners in one county in Croatia, P-GC. The distance from the Clinical Hospital Centre in the city of Rijeka, which offers the possibility of obtaining professional dental advice or surgical (emergency) intervention, did not statistically significantly affect the differences in knowledge, attitudes, and habits about antibiotic use and antimicrobial resistance between the respondents.

Most of the dental practitioners in this study chose amoxicillin with clavulanic acid (65.0%) as the first-choice antibiotic in patients with no allergies to medication, which is higher compared to a few European studies: in Croatia (Zagreb), Italy, and Spain.[24-26] In comparison, British, Swedish and Norwegian dentists would most frequently prescribe amoxicillin and phenoxymethylpenicillin.[8,27,28] Phenoxymethylpenicillin and amoxicillin are recommended as the antibiotic of choice for the treatment of endodontic infections. Amoxicillin with clavulanic acid with its wide spectrum of action should be reserved for immunocompromised patients or those

whose infections have not responded to first-line antibiotics when provided in conjunction with surgical treatment. In addition, it's important to be aware that it has a greater potential for the emergence of antibiotic-resistant bacteria.[11,12,29-31] In case of a confirmed penicillin allergy, the recommended antibiotic of choice is lincosamide clindamycin, because of its high oral absorption, significant antibiotic level in tissues, especially in bone, and low emergence of bacterial resistance.[32,33] According to our statistics, clindamycin (86.6%) was the first choice for patients allergic to penicillin, which is a higher percentage compared to Croatian (Zagreb) and Spanish dentists.[24,26]

Different approaches to antibiotic use between medical professionals have resulted in a substantial difference in the appearance of antimicrobial resistance. Croatia, Italy and Spain still belong to a group of countries with high overall antibiotic use, especially broad spectrum antibiotics, and high antimicrobial resistance among bacteria that commonly cause infections in the community, compared to the United Kingdom, Sweden, and Norway.[4-6] Antibiotic prescribing in dentistry is a complex multifactorial process. The lack of clear national guidelines for the antibiotic treatment may impede the selection of the most effective antimicrobial therapy. In dental practice, antibiotic prescription is empirical and is based on clinical and bacteriological epidemiological factors in addition to factors such as the education and experience of antibiotic prescribers, patients' expectations and economic benefit.[15,29,30]

There are no uniform criteria regarding the use of antibiotics in practice among dentists worldwide. Clinical situations that require antibiotic therapy are limited, and include oral infections with evidence of spreading infection (cellulitis, lymph node involvement, swelling) or systemic involvement (fever, malaise). Antibiotics are also appropriate in cases of necrotizing ulcerative gingivitis or pericoronitis.[11,12,34,35] Large differences in antibiotic prescribing practices

were found in European studies in the United Kingdom, Spain, and Croatia,[24,26,28] and similar findings regarding the inappropriate use of antibiotic for endodontic infections and conditions have been found in our study as well. Our results show that implant placement (59.9%) was the third most common situation for which dentists would prescribe antibiotics. Two large systematic reviews and a meta-analysis suggest that the administration of preoperative antibiotics (single-dose oral amoxicillin given 1 hour preoperatively) significantly reduces early failure of dental implants but no statistically significant effect was observed on the occurrence of postoperative infections.[36,37] However, a wide range of different antibiotic prescribing habits was reported, with some countries (Italy, Spain) demonstrating unnecessarily long post-operative courses of antibiotics.[38] Despite a high level of awareness about antimicrobial resistance among Croatian dentists in our study, there are obvious knowledge gaps about basic indications for the effective use of antibiotics. The lack of clear national guidelines for the antibiotic treatment and continuing medical education on antibiotic use for prescribers could account for this finding. All dental prescribers need to be aware that antibiotics should be used for support when treating dental infections and not as a replacement for conventional surgical methods.

Some European dental practitioners (Croatia, United Kingdom) tend to prescribe antibiotics for non-clinical factors,[24,28] as shown in our study that patients' expectations for antibiotics lead to overprescribing. Some of the possible explanations for this difference in antibiotic prescribing among dental practitioners include dentists' training environment, professional tradition and cultural expectations.[15,39] However, only half of the participants in our study disagree that dentists often prescribe antibiotics because of patients' expectations.

Only 23.6% of all respondents had received postgraduate education about antibiotics in the last 2 years, which is less than in the study done in Zagreb (Croatia).[24] In both studies participants with

additional education showed similar gaps in knowledge regarding indications about frequent antibiotic prescribing. A high percentage of our participants (86.6%) reported the need for more education about antibiotics. We noticed that postgraduate education changed the attitude towards taking more time to consider whether or not an antibiotic is needed. Our findings support the need for the urgent publication of clear national guidelines for the antibiotic treatment and continuing medical education on antibiotic use for dentists.

Dentists are more likely to prescribe antibiotics inappropriately, probably because of their "softening" to patients' demands for antibiotics or high-volume practices. In addition, inappropriate antibiotic prescribing could be the result of the wish to avoid time-consuming education of patients, their practice experience, and a lack of dentists' knowledge about clinical criteria for prescribing antibiotics.[39] Dentists, same as other medical professionals, have a significant role in restricting inappropriate antibiotic prescribing with the goal of preventing and minimizing the threat of antimicrobial resistance. The results of our study need to be considered by taking some limitations into account. Dental practitioners who agreed to participate were more interested in the topic thus leading to a potential overestimation of KAP about antibiotic use and resistance. Another limitation is that the study population is not representative of the whole Croatian dental population, but our results are useful for improving the activities of national public health campaigns.

In conclusion, there is a high level of antimicrobial resistance awareness in both areas of P-GC, but at the same time the results of this study indicate a high rate of broad spectrum antibiotic prescribing, even for conditions in which antibiotic therapy is not the first option. Personal responsibility for rational antibiotic use should be increased among dental practitioners.

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**Ethical Approval**

The study design and questionnaire were approved by the Ethics Committee of the Teaching Institute of Public Health of Primorsko-Goranska County in Rijeka, the Ethics Committee of the Health Care Centre of Primorsko-Goranska County in Rijeka and the Ethics Committee of the University of Split School of Medicine.

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**Supplementary Material**

Supplementary Data

**TABLE 1** DEMOGRAPHIC CHARACTERISTICS OF DENTAL PRACTITIONERS

| Demographic characteristics | Total (N= 157) n (%) | Rijeka (N= 83) n (%) | Rest of PG-C (N= 74) n (%) | *p* |
|---|---|---|---|---|
| Participants | 157 (100) | 83 (52.9) | 74 (47.1) | |
| Gender | | | | 0.490 |
| Male | 55 (35.0) | 27 (32.5) | 28 (37.8) | |
| Female | 102 (65.0) | 56 (67.5) | 46 (62.2) | |
| Dental practice | | | | 0.033* |
| Private practice | 142 (90.4) | 79 (95.2) | 63 (85.1) | |
| Health Care Centre of P-GC | 15 (9.6) | 4 (4.8) | 11 (14.9) | |
| Level of education | | | | 0.075 |
| General dental practitioner | 150 (95.5) | 77 (92.8) | 73 (98.6) | |
| Specialist | 7 (4.5) | 6 (7.2) | 1 (1.4) | |

*statistically significant

P-GC, Primorsko-Goranska County

**TABLE 2** FACTORS CONNECTED TO PRESCRIBING AMOXICILLIN WITH CLAVULANIC ACID COMPARED WITH AMOXICILLIN

| Factor | AMX n (%) | AMC n (%) | Total n | *p*-value AMX/AMC |
|---|---|---|---|---|
| Gender | | | | |
| Male | 16 (30) | 38 (70) | 54 | <0.001* |
| Female | 36 (36) | 64 (64) | 100 | <0.001* |
| *p*-value | | | 0.427 | |
| Dental practice | | | | |
| Private practice | 48 (35) | 91 (65) | 139 | <0.001* |
| Health Care Centre of P-GC | 4 (27) | 11 (73) | 15 | <0.001* |
| *p*-value | | | 0.542 | |
| Level of education | | | | |
| General dental practitioner | 50 (34) | 97 (66) | 147 | <0.001* |
| Specialist | 2 (29) | 5 (71) | 7 | 0.014* |
| *p*-value | | | 0.767 | |
| Area | | | | |
| Rijeka | 33 (40) | 50 (60) | 83 | <0.001* |
| Rest of PG-C | 19 (27) | 52 (73) | 71 | <0.001* |
| *p*-value | | | 0.090 | |
| Age | | | | |
| ≤45 | 30 (38) | 48 (62) | 78 | <0.001* |
| >45 | 22 (29) | 54 (71) | 76 | <0.001* |
| *p*-value | | | 0.213 | |
| Education on antibiotics 2 y. | | | | |
| No | 40 (34) | 78 (66) | 118 | <0.001 |
| Yes | 12 (33) | 24 (67) | 36 | <0.001* |
| *p*-value | | | 0.950 | |

*statistically significant

AMX, Amoxicilin; AMC, Amoxicilin with clav. acid; P-GC, Primorsko-Goranska County

TABLE 3 ATTITUDES REGARDING CONSUMPTION OF ANTIBIOTICS

| Statement | Response | Total (N= 157) n % | Rijeka (N= 83) n % | Rest of PG-C (N= 74) n % | *p* |
|---|---|---|---|---|---|
| Dental practitioners often have time to explain how and why an antibiotic should be taken. | Disagree/Strongly disagree | 15 (9.6) | 6 (7.2) | 9 (12.2) | 0.561 |
| | No opinion/ Neutral | 14 (8.9) | 8 (9.6) | 6 (8.1) | |
| | Agree/Strongly agree | 128 (81.5) | 69 (83.1) | 59 (79.7) | |
| Dental practitioners often prescribe antibiotics as patients expect them to. | Disagree/Strongly disagree | 78 (49.7) | 42 (50.6) | 36 (48.7) | 0.858 |
| | No opinion/ Neutral | 25 (15.9) | 14 (16.9) | 11 (14.9) | |
| | Agree/Strongly agree | 54 (34.4) | 27 (32.5) | 27 (36.5) | |
| Dental practitioners often take the time to carefully consider whether or not the antibiotic is needed. | Disagree/Strongly disagree | 30 (19.1) | 18 (21.7) | 12 (16.2) | 0.323 |
| | No opinion/ Neutral | 27 (17.2) | 11 (13.3) | 16 (21.6) | |
| | Agree/Strongly agree | 100 (63.7) | 54 (65.1) | 46 (62.2) | |
| Pharmacists often tell patients how to take an antibiotic. | Disagree/Strongly disagree | 23 (14.7) | 13 (15.7) | 10 (13.5) | 0.860 |
| | No opinion/ Neutral | 42 (26.8) | 23 (27.7) | 19 (25.7) | |
| | Agree/Strongly agree | 92 (58.6) | 47 (56.6) | 45 (60.8) | |
| Dental practitioners often prescribe an antibiotic for “just in case”. | Disagree/Strongly disagree | 67 (42.7) | 35 (42.2) | 32 (43.2) | 0.977 |
| | No opinion/ Neutral | 42 (26.8) | 22 (26.5) | 20 (27.0) | |
| | Agree/Strongly agree | 48 (30.6) | 26 (31.3) | 22 (29.7) | |

**FIG.1**. Reported situations for which dentists would prescribe antibiotics

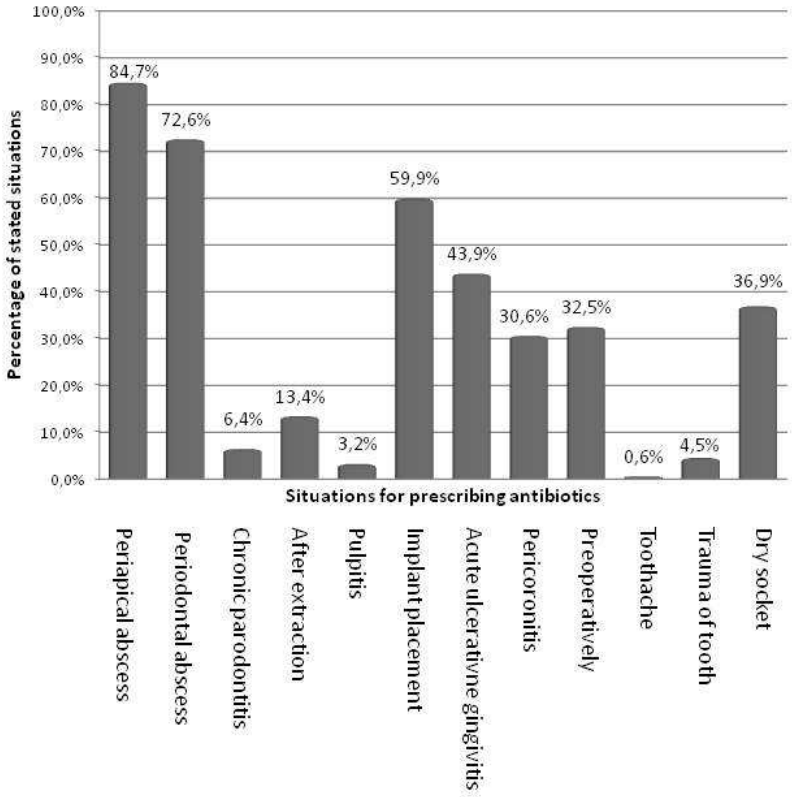

**FIG 2.** Factors connected with dentists more frequent antibiotic prescribing