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ORIGINAL ARTICLE

Outpatient Utilization of Systemic Antibiotics in the Republic of Srpska

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ABSTRACT

Introduction. Information on antibiotic utilization in the Republic of Srpska is limited. The aim of this study was to analyze antibiotic utilization in the community from 2007 to 2011 and to compare this data with antibiotic use in other European countries.

Materials and Methods. We did a population-based study to analyze systemic antibiotic utilization by an outpatient population using Anatomical Therapeutic Chemical/Defined Daily Dose methodology. The results were expressed as the defined daily dose (DDD) per 1000 inhabitants per day. The data were obtained from the annual reports of the Agency for Drugs and Medical Devices of the Republic of Srpska and Public Health Institute.

Results. Outpatient use of systemic antibiotics ranged between 21.51 DDD in the year with the highest use (2010) and 17.01 DDD in the year with the lowest use (2011). Penicillins were the most frequently prescribed antibiotic group, and amoxicillin was the most frequently prescribed drug. Cefalexin was the most frequently prescribed cephalosporin. Increased use of a second-generation cephalosporin, cefuroxime constituted almost a third of cefalexin consumption in 2011. Second-generation quinolones, mostly ciprofloxacine, accounted for about 70% of total quinolones consumption, with rising third-generation drugs also in proportion to the increasing use. Erythromycine was the most frequently used macrolide, followed by long-acting azithomycin.

Conclusion. Outpatient use of systemic antibiotics in the Republic of Srpska, at about 19 DDD, does not exceed that in Europe. As in other European countries, a shift between generations of drugs was noted for antibiotic use. Additional studies, including monitoring of seasonal variation impact on antibiotic use, are needed.

KEY WORDS
Antibiotics, drug utilization, outpatient care, pharmacoepidemiology.

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The overuse of antibiotics is the main force driving increased bacterial resistance, which poses a major threat to public health.[1,2] The vast majority of human antibiotic utilization occurs within the community,[3,4] where as much as 20 to 50% of antibiotic use may be questionable.[5] Although antibiotics are prescription-only medicines, their use may also include self-medication.[6,7] In addition to higher rates of antimicrobial resistance, the consequences of antibiotic overuse and misuse include the risk of adverse side effects and higher costs.[8,9] Cost-effectiveness studies on antibiotic therapy now consider the influence of bacterial resistance.[10] In order to assess the extent of the problem, it is necessary to collect and analyze data on antimicrobial prescribing in different clinical settings.

The number of antibiotic prescriptions has remained fairly stable in recent years,[11] but prescribing practices and outpatient antibiotic utilization vary widely across Europe.[12,13] Data on the prevalence of resistance in human pathogens show geographic differences in resistance to various classes of antibiotics in Europe. For example, resistance remains low in northern European countries.[3,14] Countries with the highest per capita antibiotic utilization have the highest resistance.[15]

Southern and Eastern European countries are recognized as high antibiotic-consuming countries with increasing use by outpatients.[3,11,16] Taking these findings into consideration along with its geographical location in Southeastern Europe, we assumed that the Republic of Srpska might have a high rate of antibiotic utilization compared with other European countries. However, information on outpatient antibiotic utilization in the Republic of Srpska is limited.[17,7]

The aim of this study is to measure and analyze the utilization of systemic antibiotics in the Republic of Srpska from 2007 to 2011 and to compare these data with those from other European countries.

Materials and Methods

A retrospective, observational, population-based study analyzed antibiotic utilization in the Republic of Srpska during the 5-year period from 2007 through 2011. The analysis covered antibacterials for systemic use (class J01, according to Anatomical Therapeutic Chemical (ATC) classification), excluding antifungals, antibacterials for tuberculosis, antitumoral and topical antibiotics. By legislation, antibiotics for systemic use are prescription-only medicines prescribed by a physician and dispensed by a pharmacist; they are only available in pharmacies.

The data were collected from the annual reports of the Agency for Drugs and Medical Devices of the Republic of Srpska (Agency) for 2007-2008 and Public Health Institute (Institute) for 2009-2011 period. Although the Agency ceased to exist in 2009, data collection procedures were transferred to the Institute. Because of the mandatory annual reporting required of health institutions on drug utilization, the collected data constitute the overall outpatient utilization of antibiotics for systemic use from 2007-2011.

Drug utilization was analyzed using Anatomic Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology, and the results were expressed as the defined daily dose (DDD) per 1000 inhabitants per day (DDD/TID). The ATC system classifies the drugs according to the organ or system on which they act and by their chemical, pharmacological and therapeutic properties. All drugs were classified into ATC groups by their international nonproprietary names (INN). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD/TID is a useful indicator for national and international comparisons, especially when areas to be compared have different numbers of inhabitants. Hereafter, for the purposes of this study, the acronym DDD will indicate DDD/TID. The DDD was calculated according to new DDD values.[18] Although DDDs do not take into account different doses for children and might not adequately address differences in dosage and length of treatment for specific classess of antibiotic between countries,[3] it was confirmed that DDD/TID is an acceptable measurement unit to express and compare outpatient antimicrobial use among countries.[19] Statistics on total population number were taken from Republic of Srpska Institute of Statistics.[20]

Results

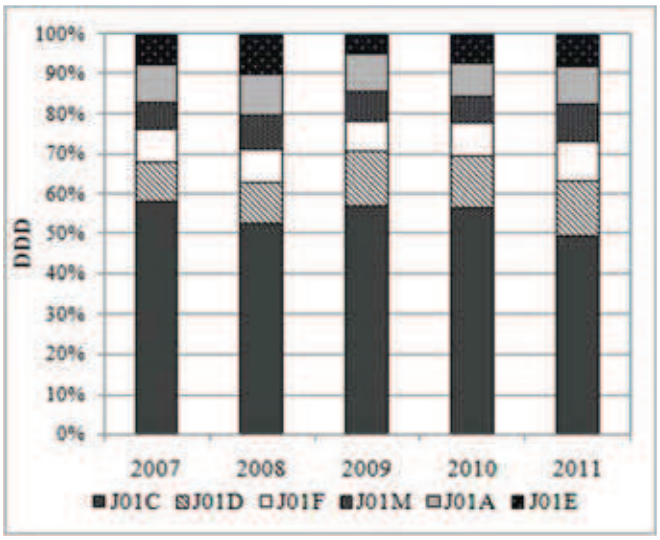
Outpatient antibiotic use varied from 21.51 DDD in the year with a highest use (2010) to 17.01 DDD in the year with the lowest use (2011). Penicillins were the most frequently pre-

Table 1. Yearly outpatient antibiotic use expressed in DDD

INN		2007	2008	2009	2010	2011
J01A	tetracyclines	1,89	1,79	1,85	1,75	1,55
J01C	penicillins	11,58	9,29	10,98	12,12	8,41
J01CA	extended-spectrum	8,56	7,49	9,20	10,15	6,10
J01CE	beta-lactamase-sensitive	2,35	1,38	1,40	1,57	0,98
J01CR	combination of penicillins*	0,64	0,42	0,37	0,39	1,33
J01D	cephalosporins	1,96	1,82	2,64	2,86	2,30
J01DB	first generation	1,51	1,57	2,04	2,16	1,58
J01DC	second generation	0,45	0,24	0,57	0,66	0,68
J01DD	third generation	na	0,01	0,03	0,041	0,040
J01EE	sufonamides & trimethoprim	1,55	1,77	0,92	1,55	1,40
J01F	macrolides and lincosamides	1,67	1,46	1,44	1,72	1,70
J01FA	macrolides	1,67	1,46	1,43	1,71	1,68
J01FF	lincosamides	na	na	0,006	0,007	0,013
J01M	quinolones	1,33	1,57	1,46	1,51	1,64
J01	total	19,98	17,70	19,29	21,51	17,01

INN = International Nonproprietary Name;*combination with β-lactamase inhibitors;
N/A = not applicable, i.e. not on the market

Figure 1. Outpatient use of J01 subgroups, expressed as % of total J01 consumption in DDD



J01C = Penicillins; J01D = Cephalosporins; J01F = Macrolides and lincosamines;
J01M = Quinolones; J01A = Tetracyclines; J01E = Sulfonamides and trimethoprim
DDD = Defined Daily Dose

scribed antibiotics in all years, ranging between 59% (2007) and 49,4% (2011), followed by cephalosporins, which ranged from 13,5% (2011) to 9,8% (2007) for total outpatient antibiotic use. The proportion of macrolides within the total antibiotic use ranged from 10,0% (2011) to 7,5% (2009); quinolones ranged from 9,6% (2011) to 6,7% (2007, and tetracyclines ranged from 10,1% (2008) to 8,1% (2010). Sulfonamides and trimethoprim were solely represented by sulfomethoxazole with trimethoprim, and their use varied from 8,2% (2011) to 4,8% (2009) (Table 1, Figure 1).

Narrow-spectrum penicillins (NSP, J01CE) represented 14,5% of total antibiotic use, broad-spectrum penicillins (BSP, J01CA) 78,9% and combinations of penicillins with β-lactamase inhibitor (COP, J01CR) made up 6,6% of total outpatient penicillin use (Table 1). Benzathine phenoxymethylpenicillin was the most used NSP with 11,2% of the total penicillin utilization by 2011 (1.4 DDD 2007; 1.0 DDD 2010; 0.2 DDD 2011), followed by phenoxymethylpenicillin, where we noted considerable fluctuations in use (Table 2). Amoxicillin was the most used BSP (Table 2). The proportion of amoxicillin in total penicillin use was the form given with an enzyme-inhibitor (co-amoxicillin); this figure increased from 3,2% (2010) to 15,8% (2011) (Table 2). First-generation cephalosporins, namely cefalexin, represented 77% of the total use of that drug class. Second-generation cephalosporins contributed 22,1%, and third-generation drugs contributed 0,9% (Table 1). Cefuroxime was the most prescribed second-generation cephalosporin (Table 2), followed by cefaclor (0.2 DDD 2007; 0.1 DDD 2011).

Second-generation quinolones accounted for 67,8% of the total drugs in that class, and first-generation quinolones contributed 32,2%, with the rising third generation contributing only a small proportion (0,3% 2009; 1,0% 2011). Utilization of a first-generation quinolone, pipemidic acid, declined continuously from 0.24 DDD in 2007 to 0.17 DDD in 2011, while norfloxacin utilization was approximately 0.3 DDD. Ciprofloxacine was the most prescribed second-generation quinolone with increased consumption over time (Table 2) while ofloxacin use decreased (0.07 DDD 2007; 0.003 DDD 2011). Doxycycline accounted for 93,4% of total outpatient tetracycline use; oxytetracycline and tetracycline use was minor and decreased over time. A short-acting macrolide, erythromycin, was the most prescribed drug of this class, followed by the long-acting azithomycin (Table 2) and an intermediate-acting macrolide clarithromycin (0.2 DDD 2007; 0.4 DDD 2011). Table 2 shows the ten most commonly prescribed antibiotics during the period observed in this study.

Discussion

Total outpatient antibiotic utilization was not as high as expected, based upon reported antibiotic use in Southern and Eastern Europe.[3,12,14] Indeed, our average consumption of 19.1 DDD over the five year period of 2007-2011 is comparable to that in European countries, where an average of 19.9 DDD was reported in 2009.[21] The total outpatient antibiotic utilization in the Republic of Srpska in 2009 was similar to that in countries in our near surroundings, such as Croatia (21.2 DDD) or Bulgaria (18.6 DDD). The moderate use of systemic antibiotics in our country is comparable to that in countries with a long history of low antibiotic utilization, such as the Nordic countries.[22]

In contrast, there were large differences between neighboring Northern European countries. Outpatient antibiotic use in Europe in 2009 differed widely, varying by a factor of 3.5 between the country with the highest (38.6 DDD in Greece) and the lowest (11.1 DDD in Estonia).[21] Unlike the increase noted in most European countries,[16,21] our outpatient antibiotic use remained stable over the five year period of observation. Differences in antibiotic use between countries might be explained by a number of factors, such as variations in incidence of community-acquired infections, culture, education, differences in drug regulation and in the structure of the national pharmaceutical market.[3] Some differences in total outpatient antibiotic use in the European countries were likely influenced by fluctuations in availability of certain antibiotics, e.g., mostly narrow-spectrum penicillins, and the seasonality of outpatient antibiotic use.[3,16,21] Fluctuations in antibiotic availability also occurred in our market, but due to the lack of relevant data, we were unable to evaluate the influence of seasons. Further investigation of such variations may help to identify sources of inefficiency in antibiotic therapy.[12]

Penicillins were the most frequently prescribed antibiotics in the Republic of Srpska and showed an increasing use, similar to other countries. Proportional use of NSP in total penicillin

Table 2. Ten most prescribed antibiotics for systemic use (DDD)

ATC	INN	2007	2008	2009	2010	2011
J01CA04	amoxicillin	7.82	6.64	8.41	9.62	5.72
J01DB01	cefalexin	1.51	1.57	2.04	2.16	1.58
J01AA02	doxycycline	1.66	1.66	1.75	1.67	1.48
J01EE01	sulfamethoxazole and trimethoprim	1.55	1.77	0.92	1.55	1.41
J01CR02	amoxicilline and enyzme inhibitor	0.64	0.42	0.37	0.39	1.33
J01MA02	ciprofloxacin	0.77	1.03	0.94	1.00	1.13
J01CE02	phenoxymethylpenicillin	0.92	0.33	0.37	0.15	0.81
J01FA01	erythromycin	0.99	0.75	0.88	1.10	0.71
J01FA10	azythromycin	0.49	0.45	0.30	0.32	0.59
J01DC02	cefuroxime	0.24	0.06	0.44	0.50	0.56

ATC = Anatomic Therapeutic Chemical; INN = International Nonproprietary Name;
DDD = Defined Daily Dose

utilization was considerably less than that in Nordic countries (50%) but much higher than in France, Greece, Spain and Belgium (<5%).[16,23] We prescribed benzatin phenoxymethylpenicillin more often than phenoxymethylpenicillin, as did Austria, Croatia and the Czech Republic but not the Nordic countries.[23] Both of these NSP were reimbursed. Amoxicillin was the most prescribed of all penicillins, accounting for about 70% of total outpatient penicillin utilization. It was used far more than ampicillin, which is almost entirely superseded by amoxicillin in most European coutries.[23] Continuous decline in ampicillin use was also noted in our study. Amoxicillin utilization declined by 40% in 2011 followed with a 3.5 times increase in the use of co-amoxiclav (Table 2). Versporten et al. reported that BSP (mainly amoxicillin) use decreased in favor of COP in most countries participating in the European Surveillance of Antimicrobial Consumption (ESAC) project, where co-amoxiclav use reached 7 to 10 DDD in the high-consuming countries.[23] This finding raises concern regarding the appropriate prescribing of co-amoxiclav for respiratory tract infections, which are one of the main reasons that antibiotics are prescribed in outpatients.[24] Our co-amoxiclav utilization is still comparable to that of the low-consuming countries (Denmark, Finland),[25,26] but close monitoring of COP utilization is needed especially because one more amoxicillin combination (with sulbactam) became available in 2011.

Cefalexin was the most prescribed cephalosporin, mostly because it has been the only reimbursable cephaloporin for years. Predominant prescribing of a first-generation cephalosporin was reported as well in Finland, Sweden and Iceland, but since 1997, cefalexin use decreased while most countries recorded proportionate increases in second- and third-generation cephalosporins, mostly cefuroxime.[27] Increased utilization of oral cefuroxime (second-generation) and cefixime (third-generation) was also noted in our study. Cephalosporin treatment of uncomplicated respiratory infections with a presumed etiology has increased, despite the lack of clinical indication.[27,28] The appropriateness of cephalosporin use in such circumstances should be questioned and closely monitored in compliance with existing guidelines for treatment of respiratory tract infections.

We noted a shift from the quinolones that were predominantly used to treat urinary tract infections (pipemidic acid, norfloxacin) to those used systematically (ofloxacin, ciprofloxacin, levofloxacin). In addition, the use of quinolones in treatment of respiratory infections (third generation moxifloxacin) has increased over time, similar to the ESAC study findings on outpatient quinolone use in Europe.[29] Ciprofloxacin was the most prescribed quinolone with a continous increase in utilization (Table 2). Our rising quinolones utilization should be closely monitored in the view of seasonal variations, because other studies indicate a substantial increase in use of respiratory quinolones as well as an increase in use of so-called urinary tract quinolones, e.g. ciprofloxacin, in the winter months.[28] This inappropriate use of both older and respiratory quinolones will inevitably lead to emergence of resistant pneumococci, *Escherichia coli* and also of resistant Gram-negative bacteria.[29,30] Removal of subsidisation in Denmark of both tetracyclines and fluoroquinolones resulted in a rapid drop in utilization of these antibiotics.[3] Norfloxacine is now the only reimbursed quinolone. Tetracycline use with high seasonal variations declined significantly in the European countries. This may reflect the fact that prescription of antibiotics for respiratory tract infection is limited.[31] Doxycyclin was the third most prescribed antibiotic over the five year period of observation, but its use has diminished. Because of problems with resistance, doxycylin is no longer among the antibiotics recommended in the Netherlands for lower respiratory tract infections.[31,32]

Like in most European countries, we also noted that the newer antibiotics in almost all classes displaced older drugs, although narrow-spectrum and first-generation penicillins are still widely prescribed for treatment of community-acquired infections in certain northern European countries.[3] Pharma-

ceutical marketing can make doctors less sensitive to the costs and quality of prescribing drugs, and influence their choice of competing drugs, as observed in the Netherlands.[3] This could account for the growing use of newer antibiotics, [3] although most physicians eventually switch to newer antibiotics.[12]

Diagnostic labelling of respiratory tract infections as commom cold or bronchitis can affect antibiotic use as well, along with the propinsity of some physicians (high prescribers) to diagnose more bacterial infections than others (low prescribers).[33] Under the capitation payment scheme, our doctors have less incentive to prescribe antibiotics, and the quality of treatment is not directly related to the quantity of antibiotics prescribed. Instead, it may be improved by our doctors' ability to solicit patient compliance and reduce inappropriate antibiotic use. Educated individuals may refrain from using antibiotics because they are concerned about contributing to increased bacterial resistance.[12] A combination of educational and restrictive interventions seems to be more efficient than any single intervention for reduction of antibiotic utilization.[15]

Thus far, data on the extent of antibiotic resistance and utilization are limited in the Republic of Srpska, although several studies[2,3] indicate a correlation between antibiotic resistance and outpatient antibiotic use. However, a steady decline in utilization of some antimicrobial drug classes does not reflect concomitant decline of resistance in pathogens under selective pressure. Mathematical models, as well empirical data, suggest that after reduction in prescribing, resistance will take longer to decline than it took to rise.[34] For example, no decline in resistance against co-trimoxazole was observed in the United Kingdom even 10 years after it was no longer precribed.[35] Besides legislative regulating of prescribing and dispensing of anibiotics, our policy interventions to improve antibiotics use included standard treatment guidelines, reimbursment prescribing policy restricted to first-generation antibiotics and infection prevention (infection control and immunization). Unfortunately, comprehensive and systematic data on interventions designed to control outpatient antibiotic utilization are limited.

In conclusion, outpatient use of systemic antibiotics in the Republic of Srpska does not exceed that in Europe. The trends in time and the shift between generations in our antibiotic use need further examination, including monitoring of seasonal variation and antibiotic resistance impact on antibiotic use. Better and continuous surveillance of antibiotic use and resistance rates, optimization of antibiotic use with diagnostic tests, strict compliance to the guidelines, and education of professionals and public could all improve antibiotic therapy in our community and others.

Authorship statement
All authors contributed equally.

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Vanbolnička upotreba antibiotika za sistemsku primjenu u Republici Srpskoj

APSTRAKT

Uvod. Još uvijek nema dovoljno objavljenih podataka o upotrebi antibiotika u Republici Srpskoj. Cilj ove studije je analizirati vanbolničku upotrebu antibiotika od 2007. do 2011. godine, i podatke uporediti sa podacima drugih Evropskih zemalja.

Materijal i metode. Da bi se analizirala vanbolnička upotreba antibiotika za sistemsku primjenu provedena je retrospektivna studija upotrebe lijekova, uz primjenu metodologije anatomsko-hemijsko-terapijske klasifikacije lijekova i definisane dnevne doze. Rezultati su izraženi u definisanim dnevnim dozama (DDD) na 1000 stanovnika na dan. Podaci su preuzeti iz godišnjih izvještaja Agencije za lijekove i medicinska sredstva Republike Srpske i Instituta za javno zdravstvo.

Rezultati. Vanbolnička upotreba antibiotika za sistemsku primjenu kretala se između 21,51 DDD u godini sa najvećom upotrebom (2010.) i 17,01 DDD u godini sa najnižom upotrebom (2011.). Penicilini su bili najčešće propisivana grupa antibiotika, a amoksicilin najpropisivaniji antibiotik. Cefaleksin je bio najčešće propisivan cefalosporinski antibiotik. Primijećen je porast upotrebe cefalosporina druge gerenacije cefuroksima, čija je upotreba 2011. godine činila trećinu upotrebe cefaleksina. Upotreba druge generacije hinolonskih antibiotika, uglavnom ciprofloksacina, činila je oko 70% ukupne upotrebe hinolonskih antibiotika, uz porast treće generacije hinolona. Eritromicin je bio najčešće propisivan makrolidni antibiotik, a slijedi dugodjelujući makrolidni antibiotik azitromicin.

Zaključak. Vanbolnička upotreba antibiotika za sistemski primjenu u Republici Srpskoj nije iznad evropskog prosjeka, i kreće se oko 19 DDD. Slično drugim evropskim zemljama, i kod nas je primijećen prelazak na propisivanje novijih generacija antibiotika. Potrebno je provesti daljnja istraživanja upotrebe antibiotika, uključujući i uticaj sezonskih varijacija na upotrebu.

KLJUČNE REČI

Antibiotici, upotreba lijekova, vanbolnička zdravstvena zaštita, farmakoepidemiologija.