



ORIGINAL ARTICLE

doi:10.18575/msrs.sm.e.16.08
UDC: 615.33(497.6 Republika Srpska) "2009/2014"
COBISS.RS-ID: 5703704

Outpatient antibiotic consumption in the Republic of Srpska during the period from 2009 to 2014

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ABSTRACT

Introduction. Antimicrobial resistance is a very serious public health threat worldwide. The main cause of antimicrobial resistance is irrational use of antimicrobial drugs.

The goal of the article is to analyze data on outpatient antibiotic consumption in the Republic of Srpska during the period from 2009 to 2014, to present outpatient consumption of the first six antibiotics (the fifth level of the ATC classification), and, finally, to compare the antibiotic use in Republic of Srpska in relation to the antibiotic use in European Union countries.

Materials and Methods. Collection and analysis of data on drug consumption is done using ATC/DDD methodology, established by the WHO. Data are taken from the report on drug consumption and distribution in the Republic of Srpska during the period from 2009 to 2014, which are based on submitted data from pharmacies registered in the Republic of Srpska.

Results. Results on outpatient antibiotic consumption in the Republic of Srpska, during the period from 2009 to 2014, indicate a total decrease by 3.41 DDDs/1000 inhabitants/day, with the exception of 2010 and 2013, when the antibiotic consumption was increased. In 2014, total outpatient antibiotic consumption in the Republic of Srpska was 31.2% lower than the average consumption in the European Union. During the period from 2010 to 2014, the European Union had a significant increase in antibiotic consumption, while antibiotic consumption in the Republic of Srpska had a tendency of falling.

Conclusion. Presented results show a quantitative analysis of antibiotic consumption and provide insight into the outpatient use of antibiotics in the Republic of Srpska, and can be used for further pharmacoepidemiological analysis of antibiotic consumption, which would give a better insight into the therapeutic practice, with the aim of improving the rational pharmacotherapy in the Republic of Srpska.

Keywords: antibiotics, outpatient consumption, DDD/1000 inhabitants/day

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(*Ser Med* 2016;47:47-52)

Submitted: January 28th, 2016
Accepted: Februar 8th, 2016

Introduction

The discovery of antibiotics is one of the greatest discoveries in the history of pharmacotherapy. In fact, thanks to that discovery, the effective control of infectious diseases, which was the leading cause of morbidity and mortality in human history, was enabled. However, the discovery of antibiotics was very soon followed by the occurrence of resistance of some bacteria strains. Unfortunately, due to the genetic mutations of bacteria and resistant genes transfers, the emergence and spread of antibiotic resistance is rising even today.¹⁻³ Antimicrobial resistance today is a very serious global public health threat to effective treatment of infectious diseases, as well as conducting numerous of a modern medical procedures, and it requires a multi-disciplinary action in order to suppress occurrence and spread worldwide.⁴ According to data from 2009, it is estimated that about 25 000 people die each year in the EU as a result of infections caused by resistant bacteria strains, which leads to the direct and indirect costs of about 1.5 million annually, including the cost of decreased productivity and increased healthcare costs.^{3,5}

The main cause of emergence and spread of antibiotic resistance is irrational antibiotic use. If we take into consideration that very few new antibiotics are developed by pharmaceutical industry today, and even when we have a new antibiotic, bacteria eventually have the capability to develop resistance, therefore, we can conclude that the situation we are facing with is very serious, and it will be even more serious if we do not rationally use existing antibiotics in the future.² It is estimated that by 2050, unless we have effective antibiotics, the world population will be reduced by 11 to 444 million people.^{6,7}

According to the World Health Organization, rational use of drugs means that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" (WHO, 1985).⁸

Objectives:

1. To analyze the data on outpatient consumption of anti-infectives for systemic use (J group) and antibiotics (J01 group) in the Republic of Srpska during the period from 2009 to 2014;
2. To show outpatient consumption of the first six antibiotics at the fifth ATC level (INN) per year;
3. To compare outpatient antibiotic consumption in the Republic of Srpska in relation to consumption in the European Union.

Materials and Methods

Collection and analysis of data on drug consumption is done using ATC/DDD methodology established by the WHO Collaborating Centre for Drug Statistical Methodology in Oslo. The WHO guidelines are used to implement the ATC drug classification (Anatomical Therapeutic Chemical Classification) and DDDs (Defined Daily Doses), and to monitor the annual drug consumption.^{9,10} Monitoring of annual consumption in the Republic of Srpska is regulated by national legislation.¹¹⁻¹³

ATC/DDD system includes the Anatomical Therapeutic Chemical (ATC) Classification of drugs and defined daily doses (DDDs) as the unit for monitoring the use of medicines in a given population or health institution.

ATC includes classification of active substances in different groups, depending on the organs or systems of organs to which they are effective on, and according to their therapeutical, pharmacological and chemical properties.

DDD is defined as a statistical unit of agreed and determined amount of the drug that is most commonly used for the most common indication for measuring exposure of given population to certain drugs or groups of drugs. DDD is mostly expressed as weight units (g, mg, µg), and if this is not possible due to various reasons (for example, the combined preparations, variably dosage, etc.), the unit dose (UD) of a given pharmaceutical dosage unit (tablet, capsule, ampoule) is used. DDD methodology is independent of price and number of inhabitants, so it is suitable for describing and comparing drug use over time, comparison of prescribing between different geographical areas and different health facilities. Therefore, this method is suitable for monitoring pharmacotherapy and rationalization of therapy.

Drug consumption is expressed as the number of DDDs per 1000 inhabitants prescribed for one day (DDD/1000 inhabitants/day), and in hospital settings as the number of defined daily doses per 100 patient-days (DDD/100 patient-days).⁹

Results

The analysis on drug consumption is based on data submitted from 93.7% of pharmacies registered in the Republic of Srpska. The data shown in tables are obtained from annual reports on drug consumption and distribution in the Republic of Srpska during the period 2009-2014.¹⁴

Table 1. presents data on the total outpatient consumption of antiinfectives for systemic use (group J), total consumption of antibiotics (J01 group), and consumption of beta-lactam antibiotics, penicillins, as the most used antibiotics in the Republic of Srpska during the period from 2009 to 2014.¹⁴

Table 1. Total outpatient consumption of antiinfectives for systemic use, antibacterial drugs and beta-lactam antibacterials, during the period from 2009 to 2014

ATC level	ATC	Anatomic group/subgroup	DDDs/1000 inhabitants/day					
			2009.	2010.	2011.	2012.	2013.	2014.
I level	J	Antiinfectives for systemic use	18.74	21.30	17.10	15.17	17.33	14.95
II level	J01	Antibacterials for systemic use (antibiotics)	18.27	20.87	16.78	15.03	17.21	14.86
III level	J01C	Beta-laktam antibacterials, penicillins	10.25	11.43	8.03	7.68	9.43	7.49

Outpatient consumption of the first ten groups of antibiotics at the fourth ATC level in the Republic of Srpska during the period from 2009 to 2014 is shown in Table 2.

Table 2. Outpatient consumption of the first ten groups of antibiotics (the fourth ATC level) during the period from 2009 to 2014

ATC	Anatomic subgroup	DDDs/1000 inhabitants/day					
		2010.	2011.	2012.	2013.	2014	
J01CA	Penicillins with extended spectrum	8.31	9.37	5.81	5.61	7.09	5.10
J01DB	First-generation cephalosporins	1.84	2.00	1.51	1.25	1.81	1.37
J01CE	Beta-lactamase sensitive penicillins	1.60	1.69	0.95	0.89	0.96	0.82
J01AA	Tetracyclines	1.68	1.62	1.48	1.27	1.23	1.20
J01FA	Macrolides	1.34	1.58	1.65	1.37	1.55	1.41
J01EE	Combinations of sulfonamides and trimethoprim, incl. derivatives	0.79	1.43	1.34	1.01	0.99	0.97
J01MA	Fluoroquinolones	1.13	1.24	1.40	1.26	1.29	1.38
J01DC	Second-generation cephalosporins	0.52	0.61	0.65	0.56	0.55	0.50
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors	0.33	0.36	1.26	1.18	1.38	1.57
J01XD	Imidazole derivatives	0.24	0.23	0.23	0.22	0.16	0.19

Figure 1. shows the outpatient antibiotic use (the fourth level), which was among the top five groups of antibiotics used during the mentioned period, while Figure 2. shows

the consumption of the first six antibiotics at the fifth level of the ATC classification (INN), by year.¹⁴

Figure 1. Outpatient antibiotic consumption (the fourth ATC level), which were one of the top five groups of antibiotics by consumption, expressed as DDDs/1000 inhabitants/day

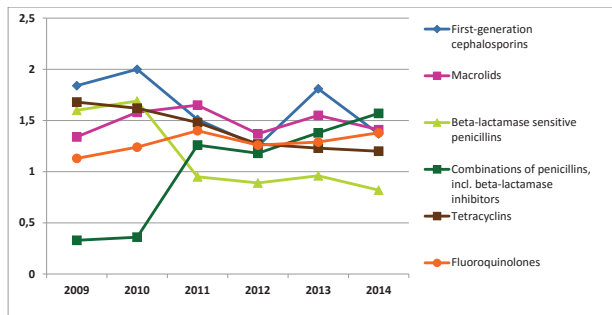
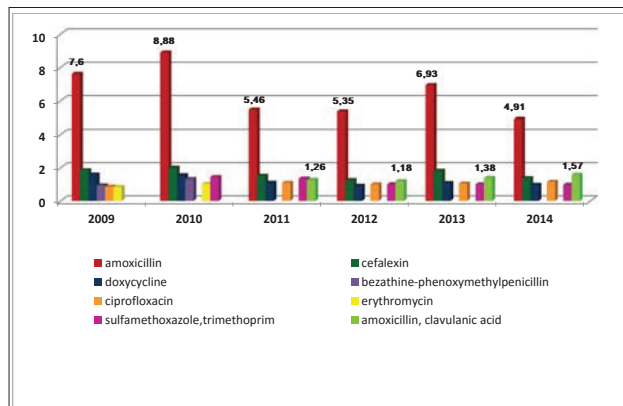


Figure 2. Outpatient consumption of the first six antibiotics at the fifth ATC level by year (DDD/1000 inhabitants/day)



Data were expressed as defined daily doses per 1000 inhabitants per day (DDD/1000 inhabitants/day).

Discussion

Irrational antibiotic use is the main reason of occurrence and spreading of antimicrobial resistance. Studies have shown that over 80% of antibiotics are prescribed for respiratory tract infections, which have very often viral etiology.^{15,16} Because of these reasons, it is important to continuously monitor antibiotic consumption, and based on the obtained, as well as other relevant data (antimicrobial resistance, indications, age, morbidity, mortality, cost, etc.), to create adequate national evidence-based therapeutic guidelines for hospital and outpatient antibiotic use, that are specific for particular population.

Antibiotics (J01 group) are the most used anti-infective drugs (J group) in the Republic of Srpska during the reported period, participating on the average with 98.6% of total consumption (Table 1.).

The average outpatient antibiotic consumption in the Republic of Srpska during the period from 2009 to 2014 amounted 17.17 DDDs/1000 inhabitants/day. In this six-

year period, the antibiotic consumption is generally reduced by 3.41 DDDs/1000 inhabitants/day, or 18.7%, with the increasing trend in 2010 and 2013. The highest consumption was in 2010 with 20.87 DDDs/1000 inhabitants/day, and the lowest was in 2014 with 14.86 DDDs/1000 inhabitants/day (Table 1.).

During this period, the highest antibiotic consumption was of beta-lactam antibiotics, penicillins (J01C), with an average consumption of 9.05 DDDs/1000 inhabitants/day. The most frequent by consumption were the broad spectrum penicillins (J01CA) during all six years, making an average of 6.88 DDDs/1000 inhabitants/day, or 75.3% of the total consumption of penicillins, or 39.6% of the total consumption of antibiotics (Table 1. and Table 2.). Consumption of penicillins decreased by 26.9% during the mentioned period, and it showed a larger trend of decline compared to the overall decline in total consumption of antibiotics (Table 1.).

The second place in consumption took the first-generation cephalosporins (2009, 2010 and 2013), followed by macrolides (2011 and 2012), and combinations of penicillin, including combination with beta-lactamase inhibitors (2014) (Table 2.).

Other groups of antibiotics had significantly lower consumption (≤ 2.0 DDDs/1000 inhabitants/day). Beside a broad spectrum penicillins, among the top five groups of antibiotics were the first generation cephalosporins (J01DB), macrolides (J01FA), tetracyclins (J01A), beta lactamase sensitive penicillins (J01C), penicillin combinations, including combinations with beta-lactamase inhibitors (J01CR), and fluoroquinolones (J01M), wherein the order of the first five groups of antibiotics was changing during this period (Table 2.).

The average outpatient consumption of antibiotics for systemic use (J01) in the EU/EEA in 2014 amounted 21.6 DDDs/1000 inhabitants/day, while in the Republic of Srpska it was 14.86 DDDs/1000 inhabitants/day (Table 1.), which is by 31.2% less than in the EU. Furthermore, the EU recorded a significant increase trend of the consumption of systemic antibiotics during the period from 2010 to 2014, while the Republic of Srpska had a declining trend in consumption of systemic antibiotics during the same period. The lowest antibiotic consumption among EU countries in 2014 had the Netherlands (10.6 DDDs/1000 inhabitants/day), while Greece had the highest with 34.1 DDDs/1000 inhabitants/day. Antibiotic consumption in the Republic of Srpska is higher by 40% compared to the Netherlands in 2014, and 56% lower compared to Greece.¹⁷

The first place by consumption in relation to the total outpatient antibiotic consumption in 2014, and in the past,

occupy penicillins (J01C) in all countries in EU, with the share of consumption from 32% in Germany to 67% in Slovakia.⁷Total consumption of penicillins in 2014 in the Republic of Srpska took 50.4% of the total consumption of antibiotics (Table 1.).

If we observe the fourth level of ATC classification, the consumption of the first-generation cephalosporins is reduced during this period in the Republic of Srpska, with a certain upward trend in consumption in 2010 and 2013. Furthermore, there is a significant increase in consumption of combinations of penicillins, incl. beta-lactamase inhibitors, as a broader spectrum antibiotics, which in this period climbed from second place (1.57 DDDs/1000 inhabitant/day) to ninth place (0.33 DDDs/1000 inhabitants/day) by consumption. At the same time, there was a decrease in consumption of beta-lactamase sensitive penicillins by 51.2%. The largest drop in consumption of beta-lactamase sensitive penicillins was in 2011, with simultaneously the largest increase in consumption of combinations with inhibitors. Also, there is a visible increase in consumption of fluoroquinolones, decrease in consumption of tetracyclines, while the macrolides had variable trend of consumption, with alternating highs and lows (Table 2., Figure 1.).

Figure 2. shows the consumption of the first six antibiotics at the fifth ATC level, by years. The first place by consumption belonged to amoxicillin (J01CA04) with an average consumption of 6.52 DDD/1000 inhabitants/day and the highest consumption recorded in 2010 and 2013. At the second place was cefalexin during the period from 2009 to 2013, while in 2014 the second place was occupied by amoxicillin in combination with clavulanic acid, and cefalexin was at the third place, which corresponds to consumption at the fourth ATC level.

Conclusion

Analyzing the data on antibiotic consumption in the Republic of Srpska during the period from 2009 to 2014, it is found that the antibiotic consumption in the Republic of Srpska is decreased, opposed to the consumption in the European Union, where there was a significant increase during the mentioned period. Furthermore, the largest consumption was of the group of beta-lactam antibiotics or penicillins (J01C), both, in the Republic of Srpska and EU. During this period, amoxicillin was the most frequently used medicine in the Republic of Srpska, followed by cefalexin or, in 2014, amoxicillin in combination with clavulanic acid.

These data provide a quantitative analysis of outpatient antibiotic consumption in the Republic of Srpska, and can serve as a basis for further pharmacoepidemiological analysis, which would be even better insight into the drug

consumption, bound for indications and other characteristics (gender, age, comorbidities, antibiotic resistance), and the impact of socio-economic and other factors to their use. It would give a clearer insight into therapeutic practice and allow the revision of the existing guidelines for antibiotic use for specific indications, with the aim of improving the rational pharmacotherapy in the Republic of Srpska.

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Vanbolnička potrošnja antibiotika u Republici Srpskoj u periodu od 2009. do 2014. godine

SAŽETAK

Uvod. Antimikrobna rezistencija predstavlja veoma ozbiljnu javnozdravstvenu prijetnju širom svijeta. Glavni uzrok nastanka antimikrobne rezistencije je neracionalna upotreba antimikrobnih lijekova.

Cilj rada. Ciljevi rada su sljedeći: analizirati podatke o vanbolničkoj potrošnji antibiotika u Republici Srpskoj, u periodu od 2009. do 2014. godine, zatim prikazati vanbolničku potrošnju prvih šest antibiotika na petom nivou ATC klasifikacije te uporediti potrošnju antibiotika u Republici Srpskoj u odnosu na potrošnju antibiotika u zemljama Evropske unije.

Materijal i metode. Prikupljanje i analiza podataka o potrošnji lijekova se vrši ATC/DDD metodologijom koja je ustanovljena od strane SZO. Podaci su preuzeti iz Izvještaja o potrošnji i prometu gotovih lijekova u Republici Srpskoj, u periodu od 2009. do 2014. godine, koji se temelje na podacima dostavljenim iz apoteka otvorenog tipa registrovanih na području Republike Srpske.

Rezultati. Rezultati o vanbolničkoj potrošnji antibiotika u Republici Srpskoj, u periodu od 2009. do 2014. godine, ukazuju na ukupno smanjenje potrošnje antibiotika za 3,41 DDD/1000 stanovnika/dan, sa izuzetkom u 2010. i 2013. godini, kada se bilježi porast potrošnje antibiotika. U 2014. godini, ukupna vanbolnička potrošnja antibiotika u Republici Srpskoj je bila za 31,2% niža u odnosu na prosječnu potrošnju u zemljama Evropske unije. U periodu od 2010. do 2014. godine u Evropskoj uniji je zabilježen značajan porast potrošnje antibiotika, dok u Republici Srpskoj potrošnja antibiotika ima tendenciju pada.

Zaključak. Dobijeni podaci predstavljaju kvantitativnu analizu potrošnje antibiotika i daju uvid u vanbolničku potrošnju antibiotika u Republici Srpskoj, a mogu poslužiti kao osnov za dodatne farmakoepidemiološke analize, koje bi dale jasniji uvid u terapijsku praksu, sa ciljem unapređenja racionalne farmakoterapije u Republici Srpskoj.

Ključne riječi: antibiotici, vanbolnička potrošnja, DDD/1000 stanovnika/dan