# Relationship between outpatient antibiotic use and the prevalence of bacterial infections in Montenegro

## Odnos vanbolničke upotrebe antibakterijskih lekova i prevalencije bakterijskih infekcija u Crnoj Gori

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**Abstract**

**Background/Aim.** The overuse of antibiotics unnecessarily exposes patients to risk of side effects, encourages reconsultation for similar problems and enhances antimicrobial resistance. The use of antibiotics in the year 2011 in Montenegro was high (39.05 Defined Daily Dose – DDD/1,000 inhabitants/day), but it was not considered in relation to the frequency of bacterial diseases. The aim of our study was to determine the degree of conformance between the amount of outpatient antibiotic consumption and the reported prevalence of outpatient bacterial infections in the Republic of Montenegro. **Methods.** Data on the use of antibacterial drugs was obtained from the Agency for Medicines and Medical Devices of Montenegro for the year 2012. The amount of antibiotics was calculated using the Anatomic Therapeutic Chemical (ATC) DDD methodology. Data on the prevalence of outpatient infective disease was obtained from the Health Statistical Yearbook 2012 of Montenegro and it was expressed *per* 1,000 inhabitants. **Results.** A total of 30.34 DDD/1,000 inhabitants/day of antibiotics in outpatients were prescribed in Montenegro in 2012, with penicillins being most frequently prescribed. Amoxicillin and amoxicillin with clavulanic acid were the most frequently used antibiotics. The prevalence of outpatient bacterial infections was 6,745 cases or 10.87/1,000. The most frequent infections were respiratory tract infections. Less than 50% of the prescribed amount of antibiotics were prescribed in accordance with national guidelines on treatment of bacterial infections. **Conclusion.** Use of antibiotics in Montenegro in 2012 was more than double than necessary according to prevalence of bacterial infections and average duration of treatment. The structure of antibiotics was not in full compliance with the national good practice guidelines, but it was in accordance with data on bacterial antibiotic resistance in outpatient practice. It is necessary to initiate measures to rationalize the use of antibiotics both in terms of quantity and in terms of the structure of the most used antibiotics.

**Key words:**
bacterial infection; anti-bacterial agents; outpatients; prevalence; montenegro.

**Apstrakt**

**Uvod/Cilj.** Prekomerna upotreba antibiotika izlaže bolesnike riziku od pojave neželjenih dejstava, uzrokuje ponovne posete lekaru i dovodi do pojave rezistencije bakterija na antibiotike. Upotreba antibiotika u Crnoj Gori u 2011. godini bila je visoka [39,05 definisanih dnevnih doza (DDD)/1 000 stanovnika/dan)], ali nije razmatrana u odnosu na učestalost vanbolničkih bakterijakih infekcija. Cilj ovog rada bio je da se ispita usklađenost upotrebe antibiotika i učestalosti vanbolničkih bakterijskih infekcija u Crnoj Gori. **Metode.** Podaci o upotrebi antibiotika dobijeni su od Agencije za lekove i medicinska sredstva Crne Gore. Upotreba je izračunata pomoću *Anatomic Therapeutic Chemical* (ATC)/DDD metodologije. Podaci o učestalosti vanbolničkih bakterijskih infekcija dobijeni su iz Zdravstvenog statističkog godišnjaka Crne Gore, a učestalost je izražena brojem slučajeva na 1 000 stanovnika. **Rezultati.** Vanbolnička upotreba antibiotika u Crnoj gori u 2012. godini iznosila je 30,34 DDD/1000 stanovnika/dan, a najčešće korišćeni bili su penicilini. Amoksicilin sam i u kombinaciji sa klavulanskom kiselinom bili su najčešće korišćeni antibiotici. Bakterijske infekcije bile su registrovane kod 6 745 bolesnika, odnosno kod 10,87 bolesnika/1 000 stanovnika. Najčešće zabeležene bile su respiratorne infekcije. Manje od 50% od upotrebljene količine antibiotika korišćeno je u skladu sa nacionalnim preporukama za lečenje bakterijskih in-

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fekcija. **Zaključak.** Vanbolnička upotreba antibiotika u Crnoj Gori u 2012. godini bila je više nego dvostruko veća od potrebne, ukoliko se u obzir uzme učestalost vanbolničkih bakterijskih infekcija i prosečna dužina lečenja. Struktura upotrebljenih antibiotika nije bila u potpunosti u skladu sa nacionalnim preporukama dobre kliničke prakse, ali je bila u skladu sa podacima o bakterijskoj rezistanciji u vanbolničkim us-

lovima. Potrebno je sprovesti mere sa ciljem racionalizacije upotrebe antibiotika u Crnoj Gori, kako u pogledu količine, tako i u pogledu izbora najčešće korišćenih antibiotika.

## Introduction

According to current pharmacotherapeutic guidelines, antibiotics should be used for treatment of bacterial infections when clinical signs clearly indicate bacterial infection, or based on susceptibility testing. However, it often happens that antibiotics are used for treatment of viral infections, particularly in outpatient institutions which are less able to obtain antibiogram, and when self-medication is present in the community [1, 2].

Overuse, which is most common deviation in antibiotic use, unnecessarily exposes patients to risk of side effects, encourages reconsultation for similar problems and enhances antimicrobial resistance [3–5]. High use can significantly overload health care budget.

Agency for Medicines and Medical Devices of Montenegro cooperates with European Center for Disease Prevention Network (ESAC –NET). Data on antibiotic use in the year 2011 in Montenegro was published in The Lancet, where consumption of antibiotics in Montenegro of 39.05 Defined Daily Dose (DDD)/1,000 inhabitants/day occupied second place among 42 countries involved [6]. Although the authors concluded that the use was unjustifiably high, the consumption of antibiotics was not considered to the frequency of bacterial diseases, which could confirm or deny this statement.

The aim of our study was to determine the degree of conformance between the amount of outpatient consumption of antibiotics and the reported prevalence of outpatient bacterial infections in the Republic of Montenegro, and, based on this, to estimate if the consumption of antibiotics is in agreement with the prevalence of infective diseases in Montenegro.

## Methods

The study was performed in Montenegro, a country with 620,029 inhabitants, for the year 2012.

Data on the use of antibacterial drugs was obtained from the Agency for Medicines and Medical Devices of Montenegro for the year 2012. They referred to total consumption of antibiotics – those obtained by prescription and those purchased in retail pharmacies. The amount of antibiotics was calculated using the Anatomic Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology [7].

Data on the prevalence of outpatient infective disease was obtained from the Health Statistical Yearbook 2012 of Montenegro [8]. The prevalence was expressed *per* 1,000 inhabitants. Data on the use of antibiotics and the prevalence of reported outpatient bacterial diseases in Montenegro was compared in order to get conformance between the number of bacterial infections and the amount of prescribed antibiotics.

## Results

A total of 30.34 DDD/1,000 inhabitants/day of antibiotics in outpatients were prescribed in Montenegro in 2012, with penicillins being most frequently prescribed. Macrolides occupied the second place, with cephalosporins holding the third position (Table 1).

Amoxicillin and amoxicillin with clavulanic acid were the most frequently used antibiotics, followed by azithromycin, ciprofloxacine and cefalexin. Pipemidic acid was also among the top 10 antibiotics (Table 2).

The prevalence of outpatient infective diseases reported to the Institut of Public Health for the year 2012 was 8,679 cases, or 13.99 cases/1,000 inhabitans (1.4%) (Table 3). The most frequent infections were respiratory tract infections, intestinal infections and urinary tract infections.

When total amount of outpatient use of antibacterial drugs was considered in relation to the prevalence of outpatient bacterial infections in Montenegro in 2012, it becomes obvious that less than 50% of the prescribed amount of antibiotics was prescribed in accordance with national guidelines on treatment of bacterial infections (13.86 out of 30.34 DDD/1,000 inhabitants/day).

## Disscusion

The use of antibiotics is now in the spotlight for several reasons: it has been significantly increased during recent decades, they were often administered for the treatment of a viral infection, and unclear cases of fever [1, 9]. This resulted in an increase in pathogen resistance, with consequent narrowing of choice of antibiotics and often the lack of therapeutic success [10, 11]. That is why an international network such as ESAC was created, which aimed to monitor and compare the use of antibiotics among the countries, and to start with educational or administrative measures in case of excessive use of antibiotics [12–14]. Another option to assess the appropriateness of antibiotic prescribing is a comparison with morbidity statistics.

Data on the prevalence of outpatient bacterial infections published by the Institute of Public Health of Montenegro indicate that bacterial infections occurred in 722 persons *per* 1,000 inhabitants *per* year, or 1.98 persons *per* 1,000 inhabitants *per* day [8]. Assuming that all bacterial infections were treated with antibiotics, and that the therapy lasted 7 days, the amount of antibiotics used should be 13.86 DDD/1,000 inhabitants/day. The use of antibiotics in our study was 30.34 DDD/1,000 inhabitants *per* day, which means that the amount of antibiotics used was more than two times higher than it is optimal. Although the number of bacterial infections in

Table 1

**Total amount of antibacterial drugs for systemic use Anatomic Therapeutic Chemical (ATC) group J01 at ATC level 3 and/or 4 in Montenegro in 2012 expressed as Daily Defined Dose (DDD) 1,000 inhabitants/day**

| ATC code | Antibiotics | DDD/1,000 inhab/day |
|---|---|---|
| J01A | Tetracyclines | 1.13 |
| J01C | Beta lactam antibiotics – penicillins | 15.08 |
| J01CA | Broad-spectrum penicillins | 9.49 |
| J01CE | Narrow-spectrum penicillins | 1.47 |
| J01CR | Combination of penicillins and enzyme inhibitors | 4.12 |
| J01D | Other beta-lactam antibacterials | 3.60 |
| J01DB | First-generation cephalosporins | 1.93 |
| J01DC | Second-generation cephalosporins | 0.19 |
| J01DD | Third-generation cephalosporins | 1.48 |
| J01E | Sulfonamides and trimethoprim | 1.02 |
| J01F | Macrolides, lincosamides, and streptogramins | 4.62 |
| J01FA | Macrolides | 4.60 |
| J01G | Aminoglycosides | 0.66 |
| J01GB | Other aminoglycosides | 0.66 |
| J01M | Quinolones | 3.66 |
| J01MA | Fluorinated quinolones | 2.38 |
| J01MB | Other quinolone derivatives | 1.28 |
| J01X | Imidazole derivatives | 0.58 |
| Total | | 30.34 |

Table 2

**The 10 most often used antibiotics in Montenegro in 2012**

| ATC code | Antibiotic | DDD/1,000 inhab/day |
|---|---|---|
| J01CA04 | Amoxicillin | 8.75 |
| J01CR02 | Amoxicillin and clavulanic acid | 4.12 |
| J01FA10 | Azithromycin | 2.76 |
| J01MA | Ciprofloxacine | 2.29 |
| J01DB01 | Cephalexin | 1.93 |
| J01FA01 | Erythromycin | 1.82 |
| J01DD08 | Cefixime | 1.32 |
| J01MB04 | Pipemidic acid | 1.28 |
| J01EE01 | Cotrimoxazole | 1.02 |
| J01A | Doxycycline | 0.94 |

**ATC – Anatomic Therapeutic Chemical; DDD – defined daily dose.**

Table 3

**Prevalence of outpatient bacterial infections in Montenegro in 2012**

| Diagnosis | No | No of cases / 1,000 inhabitants / year |
|---|---|---|
| Respiratory infectious diseases | 6,381 | 10.29 |
| Intestinal infectious diseases | 1,170 | 1.89 |
| Parasitic infectious diseases | 942 | 1.52 |
| Anthropozoonic infectious diseases | 33 | 0.05 |
| Sexually transmitted infectious diseases | 35 | 0.06 |
| Transmissive infectious diseases | 14 | 0.02 |
| Other infectious diseases | 74 | 0.12 |
| Carriers | 28 | 0.05 |
| Total number of bacterial infections | 6,745 | 10.87 |
| Total | 8,679 | 13.99 |
| No/1,000 inhabitants/day | | 1.98 |

**No – number.**

Montenegro population was probably higher than reported, as not all of the patients visited doctors for the treatment, the obtained ratio of antibiotic use/prevalence of infection shows a disproportion between the amount of antibiotics and the number of people with bacterial infections. Even more, according to national pharmacotheraputic guidelines, many bacterial infections should not be routinely treated with antibiotics, which makes the results even worse [15]. This practice of high use of antibiotic was common in the former Yugoslavia, which has traditionally been at the top among the European countries according to the use of antibiotics [16]. Data from Serbia show that the use of antibiotics remains

high [6]. Available studies from southern regions of Serbia report an increase in outpatient use of antibiotics and a pretty high amount of antibiotics used (22.83 DDD/1,000 inhabitants/day in 2005 to 25.96 DDD/1,000 inhabitants/day in 2007) [17]. Only in certain cases, where the administrative measures were taken, their use in some parts of Serbia was significantly reduced [2, 18]. According to some sources consumption of antibiotic even higher than in Montenegro was detected in Croatia with 33.28 DDD/1,000 inhabitants/day in 2012. However consumption in Croatia shows decreasing trend (37.38 DDD/1,000 inhabitants/day in 2008) [19]. To the contrary some papers report consumption of antibiotics in Croatia of approximately 24 DDD/1,000 inhabitants/day in 2011, and approximately 20 DDD/1,000 inhabitants/day in Bosnia and Herzegovina [6].

Besides the tradition, one of the reasons for high consumption of these drugs is the possibility to obtain antibiotics without a prescription, as it is the case in Greece or Turkey, and, until a few years ago, in Serbia [9, 20]. In Montenegro during 2012 there was also a possibility to buy antibiotics without a prescription. Studies carried out in Montenegro and in Serbia have showed that more than a half of the total antibiotics used in outpatient practice was bought without a prescription [2, 10]. Restriction of the free sale of antibiotics through administrative measures is one of the most effective measures for the reduction of antibacterial drugs use.

The most commonly used antibiotics in outpatient practice in Montenegro in 2012 were amoxicillin and amoxicillin with clavulanic acid. Similar results are available from studies in Croatia as well [19]. According to the national guidelines of good clinical practice, issued by Ministry of Health of Montenegro, semisynthetic penicillins and/or macrolides are the drugs of first choice in the treatment of respiratory infections, which were most frequently reported [15]. When resistance to amoxicillin is high, amoxicillin/clavulanic acid is recommended instead. According to studies performed in Montenegro in 2009, the most frequent isolate from the throat of outpatients (beta haemolitic streptococcus) was sensitive to amoxicillin. The second isolate, *Staphylococcus aureus* was completely resistant to amoxicllin. The most frequent isolate from urinary tract infections, *Escherichia coli*, was resistant to amoxicillin, and sensitive to amoxicilin clavulanic acid [10]. This fact could explain the empirically more frequent use of amoxicillin clavulanic acid, despite the current national recommendations [21, 22].

## Conclusion

This study estimated an association of the prevalence of outpatient bacterial infections among the population of Montenegro with the use of antibiotics in outpatients. We found that the use of antibiotics is more than twice as needed when taking into account the number of people with bacterial infections and the average duration of treatment of 7 days. The structure of antibiotics is not in full compliance with the national good practice guidelines, but it is in accordance with the situation of antibiotic resistance in outpatient practice. It is necessary to initiate measures to rationalize the use of antibiotics both in terms of quantity and in terms of the structure of the most used antibiotics.

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## Conflict of interest

The authors of this manuscript have no conflicts of interest to declare.

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