Specificity of Antimicrobial Consumption in Bosnia and Herzegovina

Tijana Spasojević-Došen[[1]](#footnote-1),2

Corresponding author: Tijana Spasojević-Došen, e-mail: tijana.spasojevic-dosen.treciciklus@student.med.unibl.org

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Presentation of continuous monitoring of antimicrobial drug consumption is very important, since consumption is associated with antimicrobial resistance. Data are collected and processed to be valid, representative and comparable to data on antimicrobial drug consumption in other countries. Valid 2014-2021 total antimicrobial use data of Bosnia and Herzegovina were analysed according to the WHO Anatomical Therapeutic Chemical (ATC)/Defined Daily Doses (DDD) methodology and expressed in DDD /1000 inhabitants /day (DID). Consumption was also analyzed using the WHO AwaRe (*Access, Watch, Reserve)* classification. Total antibacterial consumption has increased during observatinal period. The top 3 antibacterials (ATC level 5) in 2021 were: amoxicillin and enzyme inhibitor, azithromycin and amoxicillin. Until 2019 Bosnia and Herzegovina had met the WHO target of at least 60% of total consumption being Access agents. During the Covid-19 pandemic, there was an increase in the consumption of antibiotics from the *Watch* group.

Key words

antimicrobial consumption, Bosnia and Herzegovina, azithromycin, amoxicillin and enzyme inhibitor

**Introduction**

The discovery of antibiotics is one of the greatest discoveries in the 20th century. However, excessive use of antibiotics causes antimicrobial resistance. That is the resistance of microorganisms to a previously effective drug. In addition, a small number of new antibiotics are in development.1 Therefore, mass and self-initiated access to antibiotics is one of the most pressing problems in the field of healthcare throughout the world. Irrational use of antibiotics includes the prescribing and dispensing of antibiotics for upper respiratory tract infections caused by viruses. Inappropriate prescribing, as well as dispensing without a prescription, are caused by patient pressure and sub-optimal knowledge about antibiotics and viral infections among patient, pharmacists and physicians. Among physicians and pharmacists are fears that if they do not prescribe or dispense an antibiotic, patients will go elsewhere.1

Many low- and middle-income cuuntries, including Bosnia and Herzegovina, try to issue antibiotics only by prescription.2 In Bosnia and Herzegovina over-the counter (OTC) sales of antibiotics is prohibited by low, but that does not mean that antibiotics are not sold OTC.

The aforementioned reasons point to the fact that it is necessary to continuously monitor the consumption of antimicrobial drugs with the aim of determining whether the consumption of antibiotics increases during the follow-up period and which are the most commonly used antibiotics.

**Methods**

This was a retrospective observational study on total antibiotic consumption in Bosnia and Hercegovina from 2014 to 2021., based on data obtained from wholesalers of drugs (data on realized importation of drugs from foreign manufacturers) and domestic manufacturers (data on drugs which are produced and put on trade in Bosnia and Herzegovina).3 Consequently, data types are sales data. These data cover total consumption without separate data for community and hospital sector.

Drug consumption analysis data was undertaken using ATC (Anatomical Therapeutic Chemical classification)/DDD (Defined Daily Dose) methodology (WHO, 2021) which is the internationally accepted methodology for measuring medicin consumption within and across population. DDDs are defined as the amount of drug most commonly used in adults for the most common indication. Data on antibiotic consumption are expressed in DDD/1,000 inhibitans/day (DID) for comparative purposes. Statistical analysis was performed using Microsoft Excel.

The World Health Organisation (WHO) Expert Committee on the Selection and Use of Essential Medicines, in April 2017, categorized antibiotics into *Access, Watch* and *Reserve* groups. This classification of antibiotics aims to be a tool for monitoring the consumption of antibiotics as well as a tool for managing the consumption of antibiotics.

To the group of *Access* agents belong antibiotics that have activity against a wide range of commonly pathogens which also showing lower resistance potential than antibiotics in the other groups.

In *Watch* group are agents that are among the most important for human medicine as well as antibiotics that have a relatively high risk of developing antibacterial resistance.

In *Reserve* group are agents that should be reserved for treatment of confirmed or suspected infections caused by multidrug-resistant organisms. These antibiotics should be available, but their use should be limited to patients when all alternatives have failed or are not suitable.

In 2021 WHO revised these categorisation and also created a list of antibiotics that are not recommended. Antibiotics that are not recommended are fixed-dose combinations of multiple broad-spectrum antibiotics. These antibiotics have no evidence-based indications for use. 4,5

Data used in analyses and included in this report

* Total consumption of J01 antibacterials by pharmacological subgroup (ATC3):

- tetracyclines (J01A)

- amphenicols (J01B)

- beta-lactam antibacterials, penicillins (J01C)

- other beta-lactams (includes cephalosporins) (J01D)

- sulfonamides and trimethoprim (J01E)

- macrolides, lincosamides and streptogramins (J01F)

- quinolone antibacterials (J01M)

- other J01 antibacterials (J01G, J01R, J01X)

* The ten most consumed agents – oral and parenteral formulation in 2021.
* Relative consumption of J01 antibacterials by pharmacological subgroup expressed in percent.
* Consumption of *Access*, *Watch* and *Reserve* group agents.

**Results**

Total consumption of antibiotic for systematic use (J01 group) was 17,5 DID in 2014, 19,0 DID in 2015, 20,8 DID in 2016, 20,3 DID in 2017, 19,3 DID in 2018, 17,4 DID in 2019, 19,2 DID in 2020. and 19,0 DID in 2021. By applying DDD values ​​valid from January 2019. for the period 2014-2017. year, consumption of antibiotic for systematic use was 15,3 DID in 2014, 16,2 DID in 2015, 17,9 DID in 2016 and 17,4 DID in 2017. From 2018. the total consumption of antibiotic for systematic use is calculated using the DDD valid from January 2019.6

Consumption by subgroups of antibacterial drugs (at the third level of ATC classification) in 2021. were: penicillins, ATC group J01C, 5.8 DID, (30,7% total consumption antibiotic for systematic use); macrolides, lincosamides and streptogramins, J01F 3.6 DID (19.1%); other beta-lactams (includes cephalosporins) J01D 2.8 DID (15 %); quinolone J01M 2.5 DID (13.4 %); tetracyclines J01A 2.2 DID (11.5 %), sulfonamides and trimethoprim J01E 1.3 DID (6.0%) and other J01 antibacterials (J01G, J01R, J01X) 0.8 DID (4.3%)

The first nine antibacterial drugs by consumption (at the fifth level of the ATC-classification) in 2021 were oral formulations: amoxicillin and enzyme inhibitor (2.86 DID), azithromycin (2.47 DID), amoxicillin (2.26 DID), doxycycline (2.19 DID), ciprofloxacin (1.74 DID), sulfamethoxazole and trimethoprim (1.14 DID), clarithromycin (0.91 DID), cefixime (0.77 DID) and cefalexin (0.75 DID). (Tabele 1, Figure 1)

 Among the top ten antibacterial drugs oral formulation by consumption in 2021, there are four of them from the *Watch* group: azithromycin, ciprofloxacin, clarithromycin and cefixime. When it comes to parenteral formulations, they were among the top ten drugs by consumption in 2021: ceftriaxone (0.77 DID), cefazolin (0.17 DID), gentamicin (0.15 DID), amikacin (0.1 DID), metronidazole (0.08 DID), ciprofloxacin (0.06 DID), meropenem (0.06 DID), vancomycin (0.05 DID), amoxicillin and enzyme inhibitor (0.04 DID) and imipenem and enzyme inhibitor (0.03 DID). Among the top ten antibacterial drugs by consumption in 2021. when it comes to parenteral formulations, there are even five from the Watch group: ceftriaxone, ciprofloxacin, meropenem, vancomycin and imipenem and enzyme inhibitor.

During consumption monitoring using the *AwaRe* classification in the period 2014-2019. year, the relative consumption of antibiotics from the *Access* group according to *AwaRe* is over 60%. In 2020 and 2021, the consumption of antibiotics from the *Watch* group increases, so the consumption of antibiotics from the *Access* group is less than 60%. (Table 2, Figure 2)

The increase in the consumption of antibiotics from the *Watch* group was mostly contributed by the increase in the consumption of azithromycin, ciprofloxacin and ceftriaxone, which were among the top ten antibiotics by consumption in 2020. and 2021.

The consumption of azithromycin in 2019. was 1,13 DID, in 2020. 3,39 DID, and in 2021. 2,47 DID. The consumption of ciprofloxacin in 2019. was 1,79 DID, in 2020. 1,85 DID, and in 2021. 1,79 DID. The consumption of ceftriaxone in 2019. was 0,21 DID, in 2020 0,36 DID, and in 2021 0,63 DID. The consumption of clarithromycin was in 2019. 0,81 DID, in 2020. 0,76 DID, and in 2021. 0,91 DID. The consumption of cefixim was in 2019. 0,42 DID, in 2020. 0,69 DID, and in 2021. 0,77 DID.

**Discussion**

Consumption of antibiotics for systematic use (J01 group) varied between 15,3 and 19,3 DIDs during the observed period. The increase in consumption is best observed when the consumption for the entire observation period is expressed in DDD valid from January 2019.

The penicillins (J01C) were the most consumed antibiotics comparasing 38% of total antibiotic utilization on average followed by other beta-lactam antibiotics (J01D) – 15%. Only in 2020. and 2021.consumption of macrolides, lincosamides and streptogramins (J01F) was 23% and 19%, respectively and was higher then consumption of J01D group.

During 2020. and 2021. it also changes the relationship between the *Access* and *Watch* groups according to *AwaRe,* in such a way that the consumption of antimicrobial drugs from the *Watch* group increases, and the consumption of antimicrobial drugs from the *Access* group decreases. The Covid-19 pandemic during 2020. and 2021. certainly contributed to this facts. During the COVID-19 health crisis, pharmacists in public pharmacies had an increased role in supporting health systems that were overburdened with the care of seriously ill patients. Patintes have visited pharmacies first, seeking professional advice on the management of their symptoms and treatments for other acute and chronic medical conditions. 7

**Conclusion**

Total consumption of antibacterial drugs for systemic use in Bosnia and Herzegovina has increased. During 2020. and 2021. Bosnia and Herzegovina no longer satisfied the WHO requirement that at least 60% of the total consumption of antibacterial drugs is from the *Access* group. This points to the fact that it is necessary to take measures aimed at more rational use of antimicrobial drugs. Additional research is also necessary at the level of public pharmacies, but also at the level of hospitals, which will provide clearer guidelines for further activities in terms of reducing the consumption of antibacterial drugs for systemic use.

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Table 1. Total consumption 2014-2021 of antibiotic for systemic use (J01) at ATC3 level expressed in DID (upper number) and % of total (lower number)\*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Class of antibacterial agents** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** | **2020** | **2021** |
| Tetracyclines (J01A) | 1.28 | 1.37.7 | 1.910.7 | 1.48.1 | 1.26.3 | 0.63.6 | 1.36.6 | 2.211.5 |
| Beta-lactams (J01C) | 5.838.2 | 6.841.5 | 7.340.5 | 7.141 | 7.639.4 | 7.341.7 | 5.830.4 | 5.830.7 |
| Other beta-lactams (includes cephalosporins) (J01D) | 2.214.3 | 2.112.9 | 2.413.1 | 2.414 | 315.4 | 2.715.8 | 3.216.6 | 2.815 |
| Sulfonamides and trimethoprim (J01E) | 1.59.6 | 1.58.9 | 1.58.4 | 1.58.7 | 1.89.5 | 0.95.3 | 1.36.7 | 1.16 |
| Macrolides, lincosamides and streptogramins (J01F) | 1.610.6 | 2.112.6 | 1.810 | 211.6 | 2.412.2 | 2.413.8 | 4.523.2 | 3.619.1 |
| Quinolone antibacterials (J01M) | 2.113.9 | 212.2 | 2.413.6 | 2.313.2 | 2.513.1 | 2.413.5 | 2.512.9 | 2.513.4 |
| Other J01 antibacterials (J01G, J01R, J01X) | 0.85.4 | 0.74 | 0.73.7 | 0.63.4 | 0.84 | 1.16.3 | 0.73.6 | 0.84.3 |
| **Total**\*Total % not always 100% due to rounding   | **15.3** | **16.3** | **18.0** | **17.4** | **19.3** | **17.4** | **19.2** | **19.0** |

Table 2. Consumption according to WHO AWaRe grouping expressed in DID (upper number) and as proportion of total J01consumption (% ) (upper number)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **AWaRe classification** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** | **2020** | **2021** |
| ***Access*** | 10.769 | 11.5 69 | 12.970 | 12.168 | 12.9 66 | 11.1 63 | 10.3 53 | 11.2 58 |
| ***Watch group*** | 4.8 31 | 5.131 | 5.429 | 5.732 | 6.7 34 | 6.6 37 | 9.1 47 | 8.2 42 |
| ***Reserve*** | 00 | 00 | 0 0 | 00 | 00 | 00 | 00 | 00 |

1. Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina, Banjaluka, Bosnia and Herzegovina

²Department of Pharmacy, Faculty of Medicine University of Banja Luka, Banja Luka, Bosnia and Herzegovina [↑](#footnote-ref-1)