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SHORT COMMUNICATION

Outpatient Antibiotic Consumption Fluctuations in a View of Unreasonable Antibacterial Therapy

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Abstract

Unreasonable antibacterial therapy is suspected to be the main reason of emergence of multi-resistant bacteria. The connection between seasonal variability of antibiotic use and reasonable antibacterial therapy has been described. We examined the issue basing on the data obtained from the primary care system in Szczecin (Poland) in order to verify the situation in this region of Central Europe. Increase in antibiotic consumption in a viral infection season was proved to be statistically significant. Statistically significant differences in various drug forms dispensation were also observed. Increased consumption of antibiotics in seasons of influenza-like illnesses might be connected with a lack of proper diagnostics or numerous cases of bacterial co-infections.

K e y w o r d s: antibacterial agents, drug resistance, drug usage fluctuations, outpatient infection treatment, unreasonable antibacterial therapy

The attitude to antibacterial therapy needs to be fundamentally changed. After the period of indisputable efficient outcomes of treatment (Aminov, 2010) and intensive search for new substances with a wide spectrum activity and better pharmacological characteristics, a crisis in antibiotic therapy has emerged (Davies, 2014). This situation results from the underestimated plasticity of bacterial genomes and ability to accumulate features, which allow bacteria to endure environment which is hostile and rich in antibacterial substances. A vital example of this kind of environment is an organism of a person treated with antibiotics (Ambur *et al.*, 2009). Increasing frequency of multi-drug resistance hinders the ability to treat patients in life-threatening conditions. Unreasonable antibacterial therapy is suspected to be the main reason of the problem.

The most common causes of the community acquired respiratory infections in children over 3 years old and adults are viruses (respectively up to 85% and 95%): respiratory syncytial virus (RSV), influenza and parainfluenza viruses, adenoviruses and even rhinoviruses (Korppi *et al.*, 2004; Macfarlane *et al.*, 2001). According to Jennings *et al.* (2008), bacterial pathogens isolated from adults were *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Staphylococcus aureus*.

Large national, European and worldwide programs have been started in order to improve the situation (WHO, 2014a; National Institute of Allergy and Infectious Diseases, 2014; National Medicines Institute, 2014; ECDC, 2014). In the presented study the relevance between the number of doses of different antibiotic types prescribed for patients and autumn-winter season with the increased number of viral infections was examined.

Data on the number of systemic-use antibiotics prescribed between July 2009 and June 2014 was obtained from a leading twenty-four-hour pharmacy located in the city center of Szczecin, Poland, and was grouped according to the drug's active substance. Due to its location and local conditions, for most of the analyzed period, the pharmacy, aside from its regular activity, was the only one to serve patients at night and on public holidays. Data obtained from an internal pharmacy system have been converted into the consumed DDDs (defined daily doses) according to WHO guidelines and ATC/DDD Index 2014 (WHO, 2014b) and divided according to a month of prescription. Months from October to March were classified as viral infections "season", which correlates with autumn/winter period in the Polish climate zone. Months from April to September were classified as "out of season", which

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is characterized by a significant decrease in viral infections in Europe (Bollaerts *et al.*, 2013). Data has also been divided according to antibiotic classes and drug form type. Afterwards, data was converted into DDDs per 1000 inhabitants. As a part of those calculations, a number of all prescriptions in the analyzed pharmacy was used, as well as a number of all prescriptions in all pharmacies in Szczecin over the respective periods of time. Data on prescriptions dispensed in the entire city has been obtained from the records of the Polish National Health Fund (NFZ). The population of Szczecin, according to the Central Statistical Office Report (2013) (Central Statistical Office, 2013) was calculated as 408 502 people. In order to determine the age structure of patients for whom antibiotics in 2012/2013 season and 2013 out-of-season periods were prescribed, prescriptions were divided by patients' age. Differences between numbers of DDDs consumed in season and out of season, noticed in the analyzed data, were statistically tested using Statsoft STATISTICA 10 software. Statistical tests were chosen according to Statsoft guidelines based on Cobb (1998) publication, depending on results' distribution in the analyzed groups: *t*-test or Mann-Whitney *U* test.

Conducted research comprised information on prescriptions for 42 997 drug packages with antibiotics for systemic use, which relates to 369 909 DDDs of active substances, dispensed in a four-year period. Averages of DDDs consumption per 1000 inhabitants in different seasons and out of season period are shown in Table I. The number of prescribed penicillins, cephalosporins and macrolides (which are the most frequently prescribed antibiotic classes) in season always surpassed the quantity in "out of season" periods. As far as lincosamides are concerned, the trend was exactly opposite. For tetracyclines, quinolones, and sulphonamides the results are divergent in different years. As far as different drug forms were analyzed, the increase in season was noticed in both tablets and suspensions.

Overall fluctuations in the number of the prescribed antibiotics are shown in Fig. 1.

Fluctuations were significantly different for various classes of antibiotics, as shown in Table I. The largest differences were noticed for cephalosporins (*e.g.* 60.71 DDDs/1000 inhabitants in season 2012/2013 in comparison to 26.96 DDDs/1000 inhabitants in out-of-season 2012), macrolides (*e.g.* 79.69 DDDs/1000 inhabitants in season 2012/2013 in comparison to 36.27 DDDs/1000 inhabitants in out-of-season 2012), penicillins (*e.g.* 145.90 DDDs/1000 inhabitants in season 2009/2010 in comparison to 74.09 DDDs/1000 inhabitants in out-of-season 2009), sulphonamides (*e.g.* 11.17 DDDs/1000 inhabitants in season 2012/2013 in comparison to 5.59 DDDs/1000 inhabitants in out-of-season 2012) and tetracyclines (*e.g.* 40.52 DDDs/1000 inhabitants in season 2012/2013 in comparison to 29.23 DDDs/1000 inhabitants in out-of-season 2012).

The scale of the observed differences depended also on the type of a drug form. The term "Tablets" also refers to capsules. The term "Suspensions" also refers to syrups and solid dry forms intended for dissolution in water and oral administration as a suspension. Taking into account pharmaceutical practice, suspensions are predominantly prescribed in treatment of children. Larger differences were observed for suspensions (*e.g.* 34.74 DDDs/1000 inhabitants in season 2009/2010 in comparison to 11.95 DDDs/1000 inhabitants in out-of-season 2009) than for much more often prescribed tablets (*e.g.* 384.06 DDDs/1000 inhabitants in season 2012/2013 in comparison to 220.63 DDDs/1000 inhabitants in out-of-season 2012). Statistical analysis results are shown in Table II.

For the age groups 0–10, 21–30 and over 70 years old there were prescribed the highest number of anti-

Table I
Averages of systemic-use antibiotic consumption (DDDs per 1000 inhabitants) in viral infections seasons (Oct-Mar) and out of seasons (Apr-Nov).

DDDs per 1000 inhabitants	out of season 2014	season 2013/ 2014	out of season 2013	season 2012/ 2013	out of season 2012	season 2011/ 2012	out of season 2011	season 2010/ 2011	out of season 2010	season 2009/ 2010	out of season 2009
TOTAL	370.08	428.24	329.82	443.72	245.30	263.40	228.54	361.69	282.62	316.67	186.46
Penicillins	164.57	189.71	147.95	197.75	110.14	117.95	98.39	173.37	131.43	145.90	74.09
Cephalosporins	48.60	59.08	39.12	60.71	26.96	30.72	23.13	35.73	26.47	28.27	12.75
Macrolides	45.97	65.00	42.55	79.69	36.27	44.25	33.62	60.90	45.15	53.07	31.15
Lincosamides	23.82	20.89	20.96	19.60	14.18	13.59	15.36	14.12	12.79	11.38	9.11
Tetracyclines	48.15	47.61	39.79	40.52	29.23	31.12	33.07	46.85	39.18	42.73	31.65
Quinolones	23.84	30.38	27.02	29.60	20.29	15.96	14.07	16.08	18.11	21.16	17.53
Sulphonamides	9.66	8.59	7.60	11.17	5.59	6.86	6.02	10.68	6.09	9.70	6.43
Suspensions	37.09	47.15	31.62	59.47	24.48	27.59	19.55	63.72	24.27	34.74	11.95
Tablets	332.46	380.85	297.97	384.06	220.63	235.64	208.61	297.57	258.05	281.56	174.04

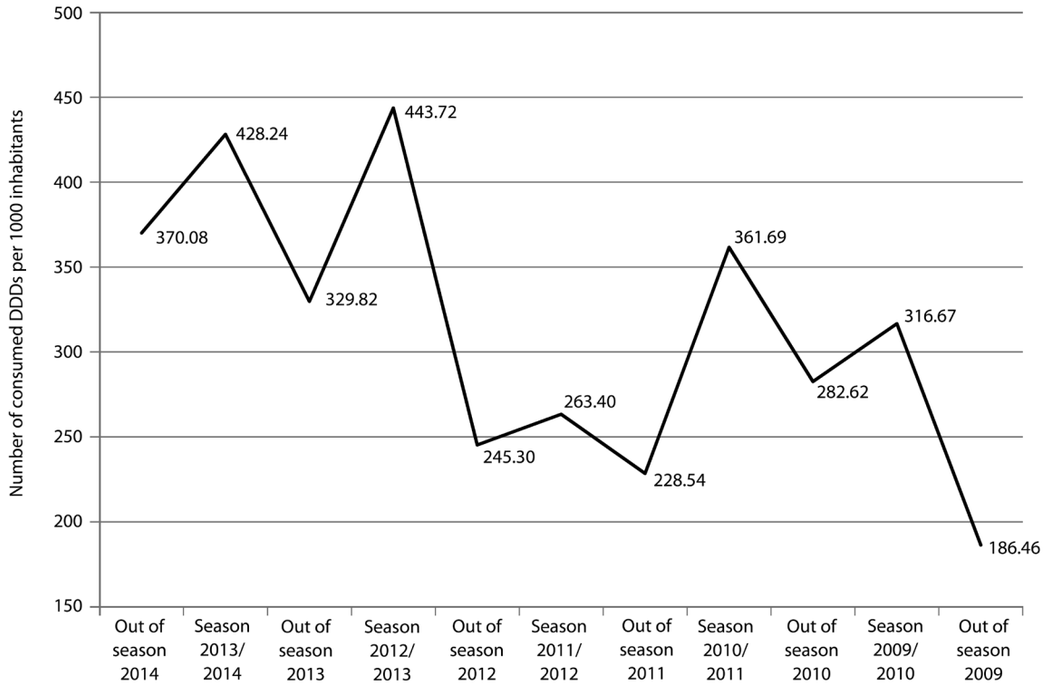

Fig. 1. Overall fluctuations in the number of the prescribed antibiotics (DDD per 1000 inhabitants).

biotics, based on the number of prescriptions in season 2012/2013 and out of season period in 2013. The largest increase in the number of prescriptions in the abovementioned season in comparison with out-of-season period was observed in age groups 41–60 and 71 and older.

According to the data collected by the European Centre for Disease Prevention and Control (ECDC, 2013a) consumption of antibacterial agents for systemic use (primary care sector, no hospital use) as well as antibiotic distribution systems vary significantly in European countries. In Scandinavian countries, *e.g.* in Sweden antibiotic consumption is at the lowest level in Europe (*e.g.* in 2012 – 14.1 DDDs per 1000 inhabitants per day) (ECDC, 2013b), which can be directly linked with prescription-only distribution system, high awareness among specialists, patients and also efficient national efforts to reduce the problem of bacterial resistance (Malmvall *et al.*, 2007). The opposite situation is in France, where the consumption of antibiotics is at

Table II
Averages of antibiotic consumption in division by antibiotic group and drug form with statistical analysis results.

	Overall antibiotic consumption (DDDs per 1000 inhabitants)				
	Season average	Out of season average	Increase in season [%]	Statistical significance	p value
	362.75	270.29	34.21%	significant	0.000066
Classification by antibiotic group					
Cephalosporins	42.90	28.76	49.18%	significant	0.001201
Quinolones	22.64	19.94	13.49%	insignificant	–
Lincosamides	15.92	15.74	1.11%	insignificant	–
Macrolides	60.58	39.02	55.28%	significant	0.000004
Penicillins	164.94	120.16	37.27%	significant	0.000239
Sulphonamides	9.40	6.62	41.93%	significant	0.002510
Tetracyclines	41.77	36.00	16.03%	significant	0.033546
Classification by drug form					
Suspensions	46.53	24.53	89.72%	significant	0.000003
Tablets	315.94	245.44	28.72%	significant	0.001265

the highest level in Europe (in 2012–29.7 DDDs per 1000 inhabitants per day) (ECDC, 2013b), which might be connected with the wide availability of antibiotics and frequent prescribing by primary care practitioners (Humphreys, 2011; Grimaldi-Bensouda *et al.*, 2014). In Polish healthcare system, antibiotics for systemic use are prescription-only drugs, nonetheless the awareness of the problem of unreasonable antibacterial therapy seems to be quite low (Panasiuk *et al.*, 2010; Godycki-Cwirko *et al.*, 2014). Therefore Poland is placed in the middle of the ECDC list (in year 2012 –22.6 DDDs per 1000 inhabitants per day) (ECDC, 2013b).

The connection between seasonal variability of outpatient antibiotic use in European countries and reasonable antibacterial therapy has already been described by Goossens *et al.* (2005) in *Lancet*. In countries where antibiotic consumption has been highest (with France as a leading country), fluctuations have been most significant. On the contrary, in countries with low consumption of antibiotics and restricted policy for antibiotics usage, seasonal fluctuations have been very low. Comparing the data from the aforementioned article and ECDC data, the situation in Poland over 10 years (2002–2012) has not changed substantially. The seasonal variability was significant and antibiotics consumption in year 2002 was estimated at around 21.4 DDDs per 1000 inhabitants per day (ECDC, 2013b), so at even a slightly lower level than in 2012.

According to the treatment recommendations presented by the National Medicines Institute (2010) 90–95% of cases of acute pharyngitis and tonsillitis in adults are caused by viruses (*e.g.* rhinoviruses, coronaviruses, adenoviruses, Epstein-Barr Virus, Coxackie, *Herpes simplex*, influenza and parainfluenza viruses). From five to ten percent of these cases are caused by streptococcal infections (*e.g. Streptococcus pyogenes*). According to the abovementioned document, only about 0.5–2% of cases of rhinitis and sinusitis are caused by bacterial infections (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*). The aforementioned bacterial infections and a small percent of viral diseases followed by bacterial infections can justify a slight increase in antibiotics consumption during season in all analyzed countries. Unreasonable prescribing of antibacterial substances for likely viral infections might cause a more significant increase in antibiotic intake in the viral infections season.

Worldwide medical recommendations, in the USA as well as in Poland and other European countries (National Medicines Institute, 2010; L'Agence Nationale de Sécurité du Médicament et des Produits de Santé, 2003; CDC, 2014) require differentiation between viral and bacterial etiology. According to these recommendations, it is based on medical history and analysis of symptoms but also on rapid infection tests like RS virus test (Slinger *et al.*, 2004), influenza A/B tests (Ko *et al.*, 2013) and streptococcal antigen tests (Lean *et al.*, 2014). Despite well-defined recommendations, this kind of rapid diagnostic tests is restricted in the primary care system in Poland. The decision on the course of treatment is usually empirical and not preceded by comprehensive diagnostics. Because of the lack of rational antibiotic prescriptions in the light of microbial diagnostics, the most frequently used antibacterial agents are wide-spectrum penicillins and cephalosporins. The high prevalence of macrolides (especially azithromycin) might result from a simple dosing scheme and shortage of information about potential penicillin hypersensitivity in patients. Particularly high fluctuations in the consumption of oral suspensions might indicate that children are the largest group of patients subjected to unjustified antimicrobial therapy.

Obtained results show that unreasonable antibiotic treatment still poses a serious problem in Szczecin area. Despite the introduction of the Polish National Antimicrobial Surveillance Program in 2004, which propagates rational antibacterial therapy (Hryniewicz, 2011; Mazińska and Hryniewicz, 2010; National Medicines Institute, 2014), further actions need to be taken. Unfortunately, in the Polish primary care system, antimicrobial agents are still too frequently and unreasonably prescribed for the treatment of cold-like infections, especially in children (0–10 years old), young adults (21–30 years old) and elderly people (over 70 years old). Furthermore, rapid diagnostics tests are not common in Polish primary care system. It is essential to enhance the knowledge about different causes of infections and methods of differentiating them among physicians and pharmacists.

Presented study shows that changes in attitude to rational antibacterial therapy proceed too slowly and need permanent monitoring. According to ECDC data, the situation in various European countries hasn't changed significantly over past decade. In the era of globalization and common travelling of people between countries and continents, the problem of multi-resistant bacteria has become international and might be escalating in the following years.

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