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Antimicrobial Use and Indication-based Prescribing Among General Practitioners in Eastern Croatia: Comparison with Data from the European Surveillance of Antimicrobial Consumption Project

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Aim To investigate antibiotic consumption in a sample of physicians from Osijek-Baranja county in Eastern Croatia and to determine the volume of prescribed antimicrobials and assess the appropriateness of prescribing practices.

Methods Analysis of routine prescribing data was carried out in 30 primary care practices in both urban and rural communities of eastern Croatia, corresponding to a total population of 48 000 patients. Prescribing practices were studied over a period of 3 years, from 2003 to 2005. Both the quantity of antimicrobials and differences and similarities between individual practitioners were analyzed.

Results Urban and rural practices did not significantly differ in regard to the volume of antimicrobials prescribed. However, significant differences were found between individual physicians. Total consumption was 17.73 defined daily doses per 1000 inhabitants per day or 6456.85 defined daily doses per 1000 inhabitants per year. The 10 most frequently used antimicrobials (93.70% of the total quantity) were amoxicillin, co-amoxiclav, co-trimoxazole, cephalexin, norfloxacin, penicillin V, azithromycin, cefuroxime, doxycycline, and nitrofurantoin. Sore throat was the most frequent reason for prescribing antibiotics.

Conclusion Prescription of medicines in Osijek-Baranja county was characterized by high consumption of broad-spectrum penicillins, combined penicillins, combined sulfonamides and long-acting macrolides (azithromycin), together with disproportionately low use of doxycycline and erythromycin. The use of combined sulfonamides and azithromycin in this part of Croatia was among the highest in Europe. Great differences between prescribers in regard to indication-based prescribing have been found, and future studies should examine the factors behind these heterogeneous practices.

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The importance of analyzing prescribing practices goes beyond the mere necessity of statistical systematization or financial savings. The ultimate goal should be an effort to reduce overconsumption and consequently diminish the development of antimicrobial resistance. Antibiotic overconsumption is the single most important factor directly correlated with the initiation and spread of resistance (1-3). The link between antibiotic use and bacterial resistance has been demonstrated at the level of individuals (emergence of resistance after a course of antimicrobial therapy) and of populations (rise of resistance with large volumes of antimicrobial consumption) (4,5).

In most countries, antibiotics are prescribed exclusively by general practitioners (family physicians). The quantitative and qualitative aspect of their prescribing practice is, therefore, one of the most significant points of reference of health consumption in general. The European Surveillance of Antimicrobial Consumption (ESAC) is a European project on the use of antibiotics, coordinated by the University of Antwerp, Belgium, with 34 participating countries including all 27 members of the EU (6,7). According to ESAC antimicrobial consumption data, Croatia ranks among countries with a large total volume of outpatient consumption in 2005, with 23.40 defined daily doses per 1000 inhabitants per day (DID) (6). The prevalence of low/intermediate resistant *S. pneumoniae* in 2007 was 27%, while that of the high-resistant type was 3%. Macrolide-resistance of *S. pneumoniae* did not exceed 30% in 2005 and 2006, while in 2007 it increased to 34% (8). At the end of 2007, the Croatian Interdisciplinary Group for Monitoring of Antimicrobial Consumption and Resistance (ISKRA) published national guidelines for antimicrobial therapy of sore throat, urinary tract infections, methicillin-resistant ***S. aureus*** infections, and surgical prophylaxis, as part of a concerted action toward prevention of the development of resistance (9). As there are no previous data on antimicrobial use in the region, in this study we attempted not only to assess the quantity of consumption (expressed as DID rates) and compare it with the data from other sources, but to measure the consumption of individual drugs in relation to diagnoses, as well as the consumption in individual general practitioners (GP) offices. In addition, we examined whether urban GPs, because of their easier access to microbiological laboratories, prescribed less than rural GPs. Finally, we aimed to assess the appropriateness of prescribing practices by physicians in eastern Croatia.

METHODS

Indication-based antibiotic prescribing was investigated on a random sample of 30 general practitioners in Osijek-Baranja county (eastern Croatia). Primary care pediatricians, gynecologists, and dentists, all of whom also prescribe antimicrobials, were excluded from the study.

According to the 2001 census, the county had 330 506 inhabitants. Thirty primary care teams were selected arbitrarily from the 169 registered in the database of the Croatian Institute for Health Insurance (CIHI), which manages the national health care system. Approximately 48 000 people, or 15% of the population in the County, are registered with CIHI. The study group was divided into two subgroups: 15 GPs with urban practices based in the city of Osijek (with 114 000 inhabitants according to the 2001 census) and 15 with practices in the neighboring communities, which are referred to in this study as "rural," irrespective of their location in a village or a small city. Individual GPs were identified with anonymous descriptors (D1, D2, D3...).

Data on both antibiotic consumption and indication-based prescribing were extracted from the CIHI database, which collects monthly reports from all retail pharmacies in the national health system. Pharmacies send electronically recorded information on dispensed drugs to the central CIHI office on a monthly basis. There, the data are not processed statistically or otherwise, but only stored in the form of large Excel tables. Because monthly reports contain raw data pooled from many thousands of prescription forms, it was possible to extract different types of data using Microsoft Access tools (queries), such as antibiotic name, dose, number of tablets/capsules per package, number of packages prescribed (but not in terms of defined daily dose [DDD]), diagnoses (expressed as ICD-10 codes) (10), and age and sex of patients. DDD per 1000 inhabitants per day (referred to as "DID") and DDD per 1000 inhabitants per year were computed (11) from the number of packages in the case of most antibiotic oral formulations for systemic use (tablets, suspensions), with the exception of drugs that have no standardized DIDs, such as eye drops, ointments, and dermatologic formulations. Another exception was parenteral antibiotics, which are not dispensed through prescriptions. A total of 21 systemic antimicrobials were selected for measurement of utilization (Table 1). The period of data collection was 3 years, from January 1, 2003 through December 31, 2005.

Consumption rates from the county were compared with those from Croatia as a whole and those from several European countries that are members of the ESAC project. Of 25 members of the ESAC I project (2001-2004), 8 were selected for comparisons: Slovenia and Hun-

TABLE 1. Total consumption of antimicrobials among general practitioners in Osijek Baranja County, 2003-2005*

	Defined daily doses								
	total			per 1000 inhabitants per year			per 1000 inhabitants per day		
Antibiotic	urban GPs	rural GPs	total	urban GPs	rural GPs	total	urban GPs	rural GPs	total
Doxycycline	12 710	22 507	35 217	88.26	156.3	244.56	0.24	0.43	0.67
Oxytetracyc	308	328	636	2.14	2.28	4.42	0.01	0.01	0.02
Amoxicillin	89 205	121 018	210 223	619.48	840.4	1459.88	1.70	2.30	4.00
Coamoxiclav	79 986	114 132	194 118	555.46	792.58	1348.04	1.52	2.17	3.69
Penicilline V	21 349	43 819	65 168	148.25	304.3	452.55	0.41	0.83	1.24
Cloxacilline	109	665	774	0.76	4.62	5.38		0.01	0.01
Cephalexine	37 536	39 391	76 927	260.66	273.55	534.21	0.71	0.75	1.46
Cephadroxil	1616	2968	4584	11.22	20.61	31.83	0.03	0.05	0.09
Cefuroxime	21 112	32 217	53 329	146.61	223.73	370.34	0.40	0.61	1.01
Cefprozil	13	225	238	0.09	1.56	1.65			
Ceftibuten	8218	12 648	20 866	57.07	87.83	144.9	0.16	0.24	0.40
Cefixime	9	176	185	0.06	1.22	1.28			
Cotrimoxazole	41 560	48 126	89 686	288.61	334.21	622.82	0.80	0.92	1.72
Azithromycine	20 861	33 865	54 726	144.87	235.17	380.04	0.40	0.64	1.04
Erythromycin	2608	1926	4534	18.11	13.37	31.49	0.05	0.04	0.09
Clarithromycin	6110	3551	9661	42.43	24.66	67.09	0.12	0.07	0.20
Clindamycin	2700	3570	6270	18.75	24.79	43.55	0.05	0.07	0.12
Ciprofloxac	4393	3871	8264	30.51	26.88	57.39	0.08	0.08	0.16
Moxifloxac	782	1767	2549	5.43	12.27	17.7	0.02	0.03	0.05
Norfloxacine	38 112	28 231	66 343	264.66	196.05	460.71	0.73	0.54	1.27
Nitrofurant	16 544	8947	25 491	114.89	62.13	177.02	0.31	0.17	0.48

*GP – general practitioner.

gary as the neighboring countries; Italy and France as the countries with high consumption volume; the UK and the Netherlands as the countries with low consumption volume; and Czech Republic and Austria as the countries with an intermediate volume of prescribed antibiotics. The DID rates for the abovementioned EU states and Croatia were extracted from the ESAC results (6), while for the Osijek-Baranja county they were independently calculated from the CIHI data, using the number of inhabitants from the sample (48,000) as a denominator. As the total consumption volume remained balanced (with variations of just 2%-4% over the 3 years), the annual average (total consumption in DDDs divided by 3) was used for calculating the DID rates.

A two-sample, independent group *t*-test (provided by OpenOffice Calc) was chosen to test the differences between the two groups, both regarding the frequency of diagnoses and total volume of prescribed antibiotics. Calculations with this test were carried out using OpenOffice Calc (OpenOffice 2.0, www.openoffice.org). For an in-depth analysis of indication-based prescribing and comparisons between individual physicians, total DDDs for all 3 years were used. The DID rate, although convenient for investigating the use of large quantities of drugs, on a state level or higher, gave very low and impractical numbers for comparisons between individual prescribers. For example, for acute sinusitis, physician "1" prescribed 0.002 DID compared with 131 total DDD, physician "2" prescribed 0.017 DID (per day) and 938 DDD, and physician "3" prescribed 0.002 DID (per day) compared with 135 DDD.

RESULTS

The average yearly consumption of systemic antibiotics, comprising 21 drugs, was 17.73 DID or 6456.85 DDD/1000 inhabitants/y (Table 1). No significant difference was found between urban and rural GPs in the total volume of prescribed antibiotics in DIDs (calculated *t*-score, 0.50, $P = 0.05$). Penicillins were used at a rate of 8.93 DID in Osijek Baranja County, 12.36 DID in Croatia, and 5.14 DID in Austria and 14 DID in France (Table 2). The use of narrow-spectrum penicillins in Austria and Hungary was similar to that of Croatia as a whole and Osijek-Baranja county (1.30 DID approximately), while in Slovenia and Czech Republic these rates were nearly double (2.61 and 2.24 DID). Amoxicillin use in Croatia and Osijek-Baranja county was in the high-

TABLE 2. Comparison of antimicrobial consumption (defined daily doses/1000 inhabitants/day) in Osijek-Baranja county, as well as from Croatia and some European countries*

	Osijek Baranja county	Croatia	Hungary	Slovenia	Czech Republic	Austria	Italy	France	Netherlands	UK
Classes of antibiotics	1	2	3	4	5	6	7	8	9	10
Total outpatient use	17.57	23.50	19.63	17.10	16.65	12.49	25.63	28.97	9.78	14.90
Penicillins total	8.93	12.36	9.33	10.14	6.89	5.14	12.35	14.00	3.86	6.88
Narrow spectrum	1.24	1.60	1.34	2.61	2.24	1.15	0.01	0.16	0.44	0.66
Broad spectrum	4.00	4.84	3.31	3.23	2.59	1.07	6.54	7.92	1.77	4.47
Penicillins combined	3.69	5.86	4.67	4.14	1.96	2.91	5.78	5.46	1.39	0.89
Cephalosporins total	2.87	3.89	2.32	0.71	0.99	1.63	3.37	3.34	0.06	0.76
Cephalosporins 1st generation†	1.46	2.08	0.14	0.09	0.24	0.31	0.17	0.38	0.01	0.56
Cephalosporins 2nd generation‡	1.01	1.36	1.73	0.54	0.75	0.46	1.23	1.31	0.03	0.19
Cephalosporins 3rd generation§	0.40	0.44	0.45	0.09	0.00	0.86	1.94	1.65	0.01	0.01
Macrolides, linkosamin	1.13	2.10	3.14	3.18	2.49	2.89	5.01	4.85	1.33	2.31
Short acting	0.09	0.13	0.20	0.30	0.16	0.07	0.56	0.11	0.10	1.81
Intermediate acting	0.18	0.26	1.96	1.41	1.73	2.14	3.18	1.28	0.84	0.44
Long acting	1.04	1.50	0.34	1.29	0.50	0.46	1.19	0.79	0.33	0.04
Tetracyclines total‖	0.68	1.89	1.99	0.72	2.85	1.08	0.50	3.35	2.23	3.23
Sulfonamides¶	1.72	1.71	1.27	1.16	1.18	0.40	0.70	0.45	0.67	1.05

*Data from ESAC project, 2003 (6).
†In Osijek-Baranja county, only cephalexin, because of minimal use of cefadroxil.
‡In Osijek-Baranja county, only cefuroxime.
§In Osijek-Baranja county, only ceftibuten.
‖In Osijek-Baranja county, only doxycycline.
¶All, including combination with trimethoprime. In Osijek-Baranja county, sulfamethoxazole-trimethoprime.

er range (4.00 and 4.84 DID), together with Italy, France, and the UK (6.54, 7.92, and 4.47 DID, respectively), whereas in other countries it did not exceed 3.30 DID. The consumption of co-amoxiclav was 3.70 DID in Osijek-Baranja county and 5.86 DID in Croatia, compared with mere 0.89 DID in the UK or 1.39 in the Netherlands. In contrast with the UK, where the use of co-amoxiclav was lowest in Europe, the consumption in Osijek-Baranja county was 4.15 times greater, and in Croatia 6.6 times. Thus, like Croatia as a whole, Osijek-Baranja county was a "leading consumer" of combined penicillins in Europe (5.86 DID), even after taking into consideration its pre-school children population. This level of consumption was greater than that in Italy and France (5.78 and 5.46 DID).

Consumption rates for cephalosporins in Osijek-Baranja county and in Croatia were, again, in the higher category (2.87 and 3.89 DIDs), comparable with other "big spenders," such as Italy (3.37 DIDs) and France (3.34). The lowest rates were in the Netherlands (just 0.06 DID), Slovenia (0.71), and the UK (0.76 DID) (Table 2).

The leading macrolide-class drug was clarithromycin in most of the EU countries, but it was prescribed on a smaller scale in Croatia (0.26 DID) and Osijek-Baranja county (0.18 DID). The most frequently used was azithromycin in both Croatia (1.50 DID) and Osijek-Baranja county (1.04). These are the highest rates among ESAC members.

Tetracyclines in Osijek-Baranja county were prescribed at 0.67 DID; this refers exclusively to doxycycline, since this was the only tetracycline the consumption of which was measured in the county. Such a low utilization is surprising, notably in comparison with Croatia as a whole (1.89 DID).

In contrast, sulfonamides were prescribed at 1.72 DIDs in Osijek-Baranja county and 1.71 DIDs in Croatia, with the real difference being even greater after including pre-school population in the DID value for the county. Such a high usage is unparalleled in any other European country. It is the second highest among the ESAC members in 2003: Iceland (1.92 DID)>Osijek Baranja county (1.89 DID)>Russian Federation (1.79 DID)>Croatia (1.71 DID) (6).

The consumption rates for fluoroquinolones were 1.43 DID in Osijek Baranja County and 1.51 DID in Croatia, mainly at the expense of norfloxacin (1.27 DID in the County; 1.49 DID in Croatia).

Around 75 200 prescription forms were analyzed in 3 years. A total of 47 370 prescriptions (63%) were issued for respiratory infections: 39 850 (53%) for infections of the upper respiratory tract and 7280 (9.69%) for infections of the lower respiratory tract (Table 3). The most frequent diagnoses were acute tonsillitis (ICD-10 code J03) with 14 680 prescriptions (19.52%); acute cystitis (N30) with 13 030 (17.33%); and acute pharyngitis (J02) with 12 560 (16.70%). There were no significant differences between the rural and urban group in regard to diagnoses registered on prescription forms: 22.09 vs 31.24% for upper respiratory tract infections ($t=0.56$, $P=0.05$), 4.06 vs 5.62% for lower respiratory tract infections ($t=0.78$, $P=0.05$), 10.84 vs 10.21% for urinary tract infections ($t=0.96$,$PP=0.05$), and 7.63 vs 7.88% for skin, soft tissue, and other infections ($t=0.96$, $P=0.05$). Eye infections, recorded as "acute conjunctivitis" (ICD-10 code H10) were present in 6390 (8.5%) of prescription forms; skin and soft tissue infections (pyodermias, skin abscesses and subcutaneous infections, and wounds and combustions) in 3580 (4.76%); acute enteral infections in 1180 (1.57%); other bacterial infections in 300 (0.40%), and undetermined conditions (fever of unknown origin) in 250 (0.33%) prescription forms.

The 10 most frequently prescribed antibiotics (in DIDs) were: amoxicillin – 4.00 DID (22.61% of total volume), co-amoxiclav – 3.69 (20.87%), co-trimoxazole – 1.72 (9.64%), cephalexin – 1.46 (8.27%), norfloxacin – 1.27 (7.13%), penicillin V – 1.24 (7.00%), azithromycin – 1.04 (5.88%), cefuroxime – 1.01 (5.73%), doxycycline 0.67 (3.78%), and nitrofurantoin – 0.48 (2.74%). Their total consumption was 16.58 DID (93.51% of all observed drugs). Of all of these, only ceftibuten was used at a somewhat greater volume (0.40 DID), while all others were prescribed on a much smaller scale.

Table 4 summarizes the utilization for upper respiratory tract infections, presented as total DDDs over all 3 years. Some drugs (co-trimoxazole, ceftibuten) were excluded from the analysis because their primary indication was different from respiratory infections, but their volume in upper respiratory syndromes nevertheless remained considerable (co-trimoxazole 14 064 DDD, ceftibuten 6548 DDD).

For acute pharyngitis and tonsillitis, the most frequently prescribed antibiotic was amoxicillin, with 76 762 DDD (36.51% of its overall consumption) for acute pharyngitis and 55 880 DDDs (26.58%) for acute tonsillitis. For both di-

TABLE 3. Representation of diagnoses on prescription forms according to International Classification of Diseases, 10th revision, Osijek-Baranja county, 2003-2005*

	Upper respiratory tract infection						Lower respiratory tract infection				Urinary tract infection			Skin soft tissue			
Code	J02-03	J00	J01	J04	J05-06	H65-66	J20	J15-18	J11	J41-42	N30	N10	N40-44	L01-04	S00-99	T00-99	Other
Number of prescript	27 240	752	4376	2782	2106	2707	6031	610	165	481	13032	346	2286	3580	676	677	7370
Percent of total (n = 75 200)	36.22	1	5.82	3.7	2.8	3.6	8.02	0.81	0.22	0.64	17.33	0.46	3.04	4.76	0.9	0.9	9.8

*ICD-10 codes (10): J02-J03 – acute pharyngitis and acute tonsillitis, J01 – acute sinusitis, J04 – acute laryngitis, J05-J06 – unspecified upper respiratory infection, H65-H66 – acute and chronic otitis media, J00 – common cold, J20 – acute bronchitis, J15-J18 – pneumonia, J11 – influenza, J41-J42 – chronic bronchitis, N30 – acute cystitis, N10 – acute pyelonephritis, N40-N44 – acute and chronic prostatitis, L01-L04 – skin and soft tissue infections, S00-S99 – wounds, T00-T99 – combustions, other: infectious diarrheas, infections affecting gastrointestinal system (cholecystitis, *Helicobacter pylory* erradication therapy etc.), accelerated erythrocyte sedimentation rate, fever of unknown origin. Acute and chronic conjunctivitis comprised 8.47% of all recorded diagnoses (in the "other" column).

TABLE 4. Antibiotics used in upper respiratory tract infections (total DDDs) with proportions of their total use (in percentages)*

Antibiotic	Total DDD	Upper respiratory infection	Acute pharyngitis	Acute tonsillitis	Acute sinusitis	Acute otitis media	Acute laryngitis	Non-specified URTI*
Amoxicillin	210 223	176 776 (84.08)	76 762 (37.50)	55 880 (26.95)	11 510 (5.50)	4380 (2.00)	12 533 (6.00)	8073 (3.90)
Co-amoxiclav	194 118	119 805 (61.71)	23 010 (12.85)	48 422 (25.10)	16 133 (8.30)	15 920 (8.20)	5505 (3.00)	4879 (2.50)
Cefalexin	76 927	46 983 (61.07)	16 283 (21.16)	11 320 (14.70)	8089 (10.51)	1661 (2.15)	3852 (5.00)	2882 (3.74)
Penicillin V	65 168	62 200 (95.44)	7778 (11.93)	51 322 (78.75)	784 (1.20)	697 (1.06)	1164 (1.78)	0
Azithromycin	54 726	38 423 (70.20)	6080 (11.10)	15 865 (28.98)	8871 (16.20)	2546 (4.65)	2996 (5.47)	1265 (2.31)
Cefuroxime	53 329	24 030 (45.05)	6082 (11.40)	4558 (8.54)	3929 (7.36)	6640 (12.45)	1236 (2.31)	591 (0.11)
Doxycycline	35 217	12 554 (35.64)	0	5408 (15.35)	1004 (2.85)	93 (0.26)	3442 (9.77)	1327 (3.76)
Total	689 708	480 771 (100)	135 995 (28.28)	192 775 (40.09)	50 320 (10.46)	31 937 (6.64)	30 728 (6.40)	19 017 (3.95)

*Abbreviations: DDD – defined daily doses; URTI – upper respiratory tract infections.

TABLE 5. Antibiotics used in lower respiratory tract infections (total DDDs) with proportions of their total use (in percentages)*

Antibiotic	Total consumption (DDD)	Consumption lower respiratory tract infections	Influenza	Pneumonia	Acute bronchitis	Chronic bronchitis	Asthma
Amoxicillin	210 223	12 897 (6.13)	873 (0.41)	209 (0.09)	10 944 (5.20)	232 (0.11)	584 (0.27)
Co-amoxiclav	194 118	35 273 (18.17)	404 (0.20)	7447 (3.83)	25 830 (13.30)	454 (0.23)	1141 (0.58)
Cephalexin	76 927	10 881 (14.14)	168 (0.21)	457 (0.59)	9827 (12.77)	104 (0.13)	329 (0.42)
Azithromycin	54 726	12 409 (22.67)	95 (0.17)	3311 (6.05)	8368 (15.29)	93 (0.17)	545 (0.99)
Cefuroxime	53 329	14 807 (27.76)	170 (0.31)	2588 (4.85)	11 295 (21.17)	296 (0.55)	460 (0.86)
Doxycyclin	35 217	9936 (28.21)	288 (0.81)	1338 (3.80)	7780 (22.09)	0	530 (1.50)
Ceftibuten	20 866	1317 (6.31)	0	189 (0.90)	978 (4.68)	45 (0.21)	95 (0.45)
Clarithromycin	9661	2355 (24.37)	0	1024 (10.60)	1175 (12.16)	154 (1.56)	0
Co-trimox	89 688	2801 (3.12)	75 (0.08)	245 (0.27)	1612 (1.49)	873 (0.97)	0
Total		102 676 (100)	2073 (2.19)	16 808 (16.36)	77 809 (75.78)	2251 (2.19)	3684 (3.58)

*DDD – defined daily dose.

agnoses, it was 132 642 DDD or 63.09% of its overall use, compared with just 62 200 DDD of penicillin V. If we add to amoxicillin other frequently prescribed antibiotics for sore throat (co-amoxiclav, cefalexin, cefuroxime, and azithromycin), the use of broad-spectrum drugs – β-lactams and macrolides (269 670 DDD) – exceeds that of penicillin V (62200 DDD) by 4.5 times (Table 4).

A wide range of drugs was used for the treatment of middle ear infections, with co-amoxiclav in the first place (49.84% of drugs for that indication), followed by cefuroxime (20.16%), amoxicillin (13.70%), azithromycin (8.00%), cephalexin (5.20%), and penicillin V (2.18%) (Table 4). Prescribing for acute sinusitis exceeded that for acute otitis media (50 320 DDD vs 31 937 DDD), with co-amoxiclav, again, as the most frequently used drug. The utilization for acute laryngitis (30 728 DDD) was very close to that for acute otitis media (31 937 DDD).

Acute bronchitis was a frequent indication for antibiotic use (75.80% of all diagnoses in this group) (Table 5). The most frequently used were co-amoxiclav (25 830 DDD or 13.30% of its total consumption), cefuroxime, amoxicillin, cephalexin, azithromycin, and doxycycline – all of them used between 7000 and 11 000 DDD. For pneumonia, a total of 16 808 DDD of antibiotics was prescribed (16.36%) (Table 5). As in the case of acute bronchitis, co-amoxiclav was the most represented antibiotic, with 7447 DDDs, together with azithromycin and cefuroxime-axetil.

Among urinary tract infections, the most frequent diagnosis was acute cystitis, with norfloxacin as the most frequently prescribed antibiotic (66 343 DDD), followed by co-trimoxazole (42 796 DDD) and nitrofurantoin (25 491 DDD). The remaining were β-lactams, tetracyclines, and even macrolides. The most frequently prescribed drugs for acute pyelonephritis were cefuroxime-axetil and co-amoxiclav, but their utilization rate was very low (2120 and 1381 DDDs).

For skin and soft tissue infections, wounds, combustions, and all other indications, the consumption rate was 45 052 DDD. As in the case of other diagnoses (eg, otitis media and pneumonia), a wide range of antibiotics was used – 12 in total, but most commonly, again, co-amoxiclav (20 085 DDDs or almost a half of a total consumption for this group of diagnoses), followed by amoxicillin (7720 DDD) and cephalexin (6918 DDD). "Other infections" included various diagnoses recorded on prescription forms, such as accelerated erythrocyte sedimentation rate, dry cough (ICD code R05), fever of unknown origin, and acute cholecystitis.

The majority of physicians (21 of 30, 70%) prescribed similar volumes of antibiotics across all categories, but important differences among individual prescribers emerged after detailed surveying of individual rates. Cefuroxime prescribing was the most inconsistent, with the highest utilization rate 38.5 times greater than the lowest, followed by norfloxacine (35.3 times), ceftibuten (29 times), and doxycycline (25 times). The use of co-trimoxazole was least heterogeneous (difference of 4.5 times).

DISCUSSION

This study is the first survey of prescribing practice in Osijek-Baranja county in Eastern Croatia. The pattern of prescribing was characterized by antibiotic overconsumption, together with a significant divergence from generally used guidelines regarding the choice of drugs. GPs prescribed mostly aminopenicillins, combined peni-

cillins, combined sulphonamides, and long-acting macrolides (azithromycin), while the use of doxycycline was among the lowest in Europe.

A high rate of antibiotic use (17.73 DID) places Osijek-Baranja county among the regions with greater overall consumption, especially given the low presence of pre-school children in the studied sample (567 out of 48 000), who are the most common users of antibiotics (12-17). Thus, the actual consumption in the County was probably higher than in Croatia as a whole (23.50 DID), putting it among the highest rates in Europe. Surprisingly, there were no differences in the total consumption between urban and rural physicians. This suggests that, although urban physicians have easier access to microbiological laboratories and supporting tests to confirm diagnoses, both groups of physicians showed similar prescribing behavior. Distinctions emerged as the highest and the lowest consumption rates for individual antibiotics and for individual prescribers, which indicates a great degree of discord regarding the place and role of individual drugs in the treatment of infective syndromes in the primary care setting. Such heterogeneity in the choice of antimicrobials arises apparently from physicians' noncompliance with international and domestic guidelines (18-21), the main purpose of which is precisely the opposite – homogenization of prescribing practice, aimed at impeding the development of antimicrobial resistance. There are probably many reasons for this, including insufficient education, pharmaceutical promotion, and lack of monitoring. Prescribing practices are affected, apart from education, by many factors: attitudes and prescribing habits of primary care practitioners; recommendations of consultants such as pediatricians, otorhinolaryngologists, and infectologists, who cannot themselves issue prescriptions; and pressure from patients and parents. Another likely reason for the observed variations among prescribers is the number of patients they see, as well as the age and morbidity patterns of the patients.

Physicians in Hungary, Czech Republic, Austria, and Slovenia prescribed much greater proportions of narrow-spectrum penicillins. This is an example that should be followed, because of their theoretically lower potential for resistance and lower cost. Co-amoxiclav was prescribed at 3.69 DID in Osijek-Baranja county (5.86 DID in Croatia), while in the UK it was only 0.89 DID – the lowest rate in Europe, not reported in any other ESAC member, including the Netherlands (1.39 DID). Co-amoxiclav not only has no indication as the first choice drug in any uncomplicated respiratory tract infection, but is much more expensive as well. According to Bisno et al (22), group A β-hemolytic streptococcus is the most frequent causative pathogen of acute bacterial pharyngitis, and is still universally susceptible to penicillin V. Penicillin V is, therefore, reliable enough to remain as the first option even in an era of antimicrobial resistance. Domestic guidelines also recommend this drug as a first choice (9). Practitioners in this survey prescribed for acute sore throat (ICD code J02 + J03) 328 770 DDD in total, with only 62 200 DDD (18.90%) of penicillin V, which is inappropriate according to international guidelines. Amoxicillin remains the first choice for most uncomplicated cases of acute otitis media and sinusitis, according to the guidelines of the American Academy of Pediatrics, being efficacious, inexpensive, and safe (23,24). In Osijek-Baranja county, co-amoxiclav was in the first place for both indications (15 920 DDD in acute otitis media, 16 133 DDD in acute sinusitis), while amoxicillin was the third in acute otitis media (behind co-amoxiclav and cefuroxime) and the second in acute sinusitis (behind co-amoxiclav). The global prevalence of ampicillin-resistant *H. influenzae* was about 20%, and in Croatia between 9 and 30% (2006) (25), which means that amoxicillin is trustworthy as initial drug in these indications, with co-amoxiclav only as an alternative in cases of treatment failure after amoxicillin or penicillin V.

Cephalexin was prescribed mostly in acute pharyngitis/tonsillitis (27 603 DDD or 35.88% of its total consumption), which is probably justified, because of its good activity against *S. pyogenes* in penicillin-allergic patients (26-28). In other respiratory tract infections (eg, acute sinusitis, otitis media, laryngitis), the consumption volume was 16 484 DDD (21.42% of the total quantity), which is inappropriate due to the unsatisfactory activity against other respiratory pathogens (29).

Cefuroxime (24 030 DDD in upper respiratory infections) was prescribed mainly in acute pharyngitis and tonsillitis (10 640 DDDs or 19.95% of its total use). Ceftibuten was represented in upper respiratory infections with 6548 DDD (31.38% of the total use), mostly for acute pharyngitis and tonsillitis (2457 DDDs), acute sinusitis, otitis media, and laryngitis. Such a high utilization of second and third generation cephalosporins is questionable, because of their higher potential for the development of resistance, and greater price (30). Interestingly, there was a relatively high-level use of co-trimoxazole for acute pharyngitis and tonsillitis (11 064 DDD or 12.33% of the total utilization), comparable to even cefuroxime (10 640 DDD) or azithromycin (21 945 DDD). Co-trimoxazole is not an option for that indication in

any clinical scenario because of its lack of activity against *S. pyogenes*.

Azithromycin was prescribed in acute sore throat at 21 945 DDD (40.09% of the total use). There is no scientific background for such a high consumption, due to the equally efficacious and inexpensive drugs as erythromycin and cefalexin. It is also presumed to have high potential for inducing antimicrobial resistance (31).

The prescribing pattern for lower respiratory tract infections was characterized by utilization of β-lactams, compared with macrolides (75 175 DDD vs 14 764 DDD), and marginal representation of tetracyclines (doxycycline: 9936 DDD or 28.21%), which is not in accordance with microbiological etiology and recommendations from international guidelines (19,32,33). The low-level use of amoxicillin for pneumonia is surprising (209 DDDs), as is the use of cephalexin for this indication (457 DDD). While the first has a significant place in international guidelines for use in community-acquired pneumonia without concomitant morbidity, the second one has no therapeutic role (14). Cefalexin, in the fourth place with 10 881 DDDs or 14.14% of total use, has little, if any, role in the treatment of lower respiratory tract infections.

The consumption rates in urinary tract infections varied between 6760 DDD (81.80%) for ciprofloxacin and 18 958 DDD for co-amoxiclav (9.76%). In the study of Huovinen et al (34), 65% of urinary tract infections in Finland was treated with trimethoprime (production in Croatia ceased in 1999), pivmecillinam (not registered in Croatia), and nitrofurantoin, all of them recommended as first line drugs. In Finland, practitioners used cheaper but still efficient drugs, while in Croatia the most represented was norfloxacin, which is not only much more expensive than co-trimoxazole and nitrofurantoin, but also carries greater potential for the development of antimicrobial resistance. Azithromycin, a macrolide, was utilized at 2849 DDDs (5.20%), despite the fact that macrolide antibiotics have no activity against Gram-negative microorganisms. Its main indication was chronic prostatitis.

A combination of amoxicillin with clavulanic acid was unjustifiably overused, both in Osijek-Baranja county and in Croatia as a whole, even compared with the "big spenders" France and Italy.

Consumption of azithromycin in the Osijek-Baranja county and Croatia as a whole was highest in Europe. The utilization of doxycycline in Osijek-Baranja county was much lower than in Croatia (0.68 DID vs 1.89 DID), belonging to the lowest rates in Europe. Sulfonamides in Osijek-Baranja county exceeded the rate not only of Croatia (1.72 DID vs 1.71 DID, but of all other countries as well, resulting in, again, the highest consumption in Europe. Overall antibiotic use in the Osijek-Baranja county was in the same range as in both Croatia as a whole and countries with higher consumption volume (Italy, France). The results of this study clearly show a necessity for a coordinated intervention – through continuous education of practitioners, audit of prescribing practice, or other measures, in order to correct inappropriate and oversized utilization, and place it in a framework of guidelines and scientifically based standards. Higher prevalences of resistant microorganisms reflect high consumption rates of certain antimicrobials with a significant potential for development of resistance (azithromycin, cefalosporins, combined penicillins).

The study has two important limitations. First, there were only 567 children aged 0-7 years in a population segment of 48 000 inhabitants of the county, because majority of children were under care of pediatric teams (not included in the investigation). This had a considerable influence on the comparisons of overall consumption rates between Osijek-Baranja county (17.73 DID), Croatia (23.50 DID), and European countries, in which the total population (all age groups) was included as a denominator in calculating DIDs. Such a small number of children contributed also to a relatively small proportion of respiratory infections (63%) in our sample, compared with the literature data (16-18), because of a well known fact that children with respiratory infections are the greatest consumers of antimicrobials. Second, the actual morbidity was not investigated, but only diagnoses recorded on prescription forms. It is possible, therefore, to come to a false conclusion that every visit to a physician, with, for example, respiratory infection symptoms, resulted in antibiotic prescription, which in reality is not the case.

The results of investigation point to two important conclusions: a) antimicrobial utilization on a regional level (as in this investigation), corresponds fairly well with the ESAC figures, on a state level or higher, and b) antimicrobial utilization data from a regional level are reliable tool for an approximation of consumption on a state level or higher, if the Anatomic Therapeutic Classification methodology is correctly implemented.

A practical approach to inappropriate prescribing in primary care setting would be, therefore, to follow

results and conclusions from the two models: 1) antimicrobial guidelines based on academic consensus ("theoretical reference model") and 2) antimicrobial consumption based on lower utilization level, attained in some European countries (Scandinavian countries, the UK, the Netherlands), as a "practical reference model."

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References

1 Lipsitch M, Samore MH. Antimicrobial use and antimicrobial resistance: a population perspective. Emerg Infect Dis. 2002;8:347-54. Medline:11971765 doi:10.3201/eid0804.010312

2 Nasrin D, Collignon PJ, Roberts L, Wilson EJ, Pilotto LS, Douglas RM. Effect of beta lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. BMJ. 2002;324:28-30. Medline:11777803 doi:10.1136/bmj.324.7328.28

3 Dagan R, Barkai G, Leibovitz E, Dreifuss E, Greenberg D. Will reduction of antibiotic use reduce antibiotic resistance?: The pneumococcus paradigm. Pediatr Infect Dis J. 2006;25:981-6. Medline:17006311 doi:10.1097/01.inf.0000239266.20642.26

4 Goossens H, Ferech M, Vander Stichele R, Elseviers M; ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005;365:579-87. Medline:15708101

5 Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ. 2010;340:c2096. Medline:20483949 doi:10.1136/bmj.c2096

6 ESAC European Map. Outpatient antibiotic use (ESAC I: 1997-2003), 2005. Available from: www.esac.ua.ac.be. Accessed: December 9, 2010.

7 Vander Stichele RH, Elseviers MM, Ferech M, Blot S, Goossens H; ESAC Project Group. European surveillance of antimicrobial consumption (ESAC): data collection performance and methodological approach. Br J Clin Pharmacol. 2004;58:419-28. Medline:15373935 doi:10.1111/j.1365-2125.2004.02164.x

8 Tambić Andrašević A, Tambić T, Kalenić S, Janković Katalinić V, Payerl Pal M. Antibiotic resistance in Croatia in 2007 [in Croatian]. Zagreb: Akademija medicinskih znanosti Hrvatske; 2007. Available from: http://iskra.novikod.com/upload/AMZH_2007.pdf. Accessed: December 9, 2010.

9 Tambić Andrašević A, Baudoin T, Vukelić D, Mimica Matanović S, Bejuk D, Puževski D, et al. ISKRA guidelines for sore throat: diagnostic and therapeutic approach – Croatian national guidelines [in Croatian]. ISKRA; 2008. Available from: http://www.mzss.hr/hr/content/download/4603/37168/file/Grlobolja_smjernice.pdf. Accessed: December 9, 2010.

10 World Health Organization. International Classification of Diseases (ICD), 10th revision, online version. Geneva: WHO. Available from: http://www.who.int/classifications/apps/icd/icd10online. Accessed: December 9, 2010.

11 About the ATC/DDD system; WHO Collaborating. Centre for Drug Statistics Methodology, 2008. Available from: http://www.whocc.no/atcddd/. Accessed: December 9, 2010.

12 Resi D, Milandri M, Moro ML; Emilia Romagna Study Group On The Use Of Antibiotics In Children. Antibiotic prescriptions in children. J Antimicrob Chemother. 2003;52:282-6. Medline:12865400 doi:10.1093/jac/dkg302

13 Thrane N, Olesen C, Schonheyder HC, Sorensen HT. Multiple prescriptions of antibiotics for children aged 0 to 5 years in relation to type of antibiotic. J Antimicrob Chemother. 1999;44:839-42. Medline:10590289 doi:10.1093/jac/44.6.839

14 Farber MO. Managing community-acquired pneumonia. Factors to consider in outpatient care. Postgrad Med. 1999;105:106-14. Medline:10223090 doi:10.3810/pgm.1999.04.668

15 Gonzales R, Bartlett JG, Besser RE, Cooper RJ, Hickner JM, Hoffman JR, et al. Principles of appropriate antibiotic use for treatment of uncomplicated acute bronchitis: background. Ann Intern Med. 2001;134:521-9. Medline:11255532

16 Chlabicz S, Małgorzata-Ołtarzewska A, Pytel-Krolczuk B. Respiratory tract infections: diagnosis and use of antibiotics by family physicians in north-eastern Poland. Int J Antimicrob Agents. 2004;23:446-50. Medline:15120721 doi:10.1016/j.ijantimicag.2003.10.009

17 Nyquist AC, Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. JAMA. 1998;279:875-7. Medline:9516004 doi:10.1001/jama.279.11.875

18 Mishra D, Sethi M, Mantan M. Factors affecting antibiotic prescribing pattern in pediatric practice. Indian J Pediatr. 2007;74:513. Medline:17526972 doi:10.1007/s12098-007-0093-z

19 Scottish Intercollegiate Guidelines Network. Community management of lower respiratory tract infections in adults. SIGN guideline, 2002. Available from: http://www.sign.ac.uk/pdf/sign59.pdf. Accessed: December 10, 2010.

20 Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A, et al. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J. 2005;26:1138-80. Medline:16319346 doi:10.1183/09031936.05.00055705

21 Tambić Andrašević A, Baudoin T, Vukelić D, Mimica Matanović S, Bejuk D, Puževski D, et al. ISKRA guidelines for sore throat: diagnostic and therapeutic approach – Croatian national guidelines [in Croatian]. ISKRA, 2007. Available from: http://

www.mzss.hr/hr/programi_i_projekti/nacionalne_smjernice/iskra_smjernica_za_grlobolju_dijagnosticki_i_terapijski_pristup. Accessed: December 11, 2010.

22 Bisno AL, Gerber MA, Gwaltney JM Jr, Kaplan EL, Schwartz RH. Diagnosis and management of group A streptococcal pharyngitis: a practice guideline. Infectious Diseases Society of America. Clin Infect Dis. 1997;25:574-83. Medline:9314443 doi:10.1086/513768

23 American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics. 2004;113:1451-65. Medline:15121972 doi:10.1542/peds.113.5.1451

24 Piglansky L, Leibovitz E, Raiz S, Greenberg D, Press J, Leiberman A, et al. Bacteriologic and clinical efficacy of high dose amoxicillin for therapy of acute otitis media in children. Pediatr Infect Dis J. 2003;22:405-13. Medline:12792379 doi:10.1097/00006454-200305000-00003

25 Tambić Andrašević A, Tambić T, Kalenić S, Janković V, Payerl Pal M. Antibiotic resistance in Croatia in 2005 [in Croatian]. Zagreb: Akademija medicinskih znanosti Hrvatske; 2006. Available from: http://www.amzh.hr/events/osjetljivost%20i%20rezistencija%20bakterija%20na%20antibiotike%20u%20rh/2005.html. Accessed: December 10, 2010.

26 Snow V, Mottur-Pilson C, Cooper RJ, Hoffman JR; American Academy of Family Physicians. American College of Physicians-American Society of Internal Medicine; et al. Principles of appropriate antibiotic use for acute pharyngitis in adults. Ann Intern Med. 2001;134:506-8. Medline:11255529

27 Linder JA, Bates DW, Lee GM, Finkelstein JA. Antibiotic treatment of children with sore throat. JAMA. 2005;294:2315-22. Medline:16278359 doi:10.1001/jama.294.18.2315

28 Bisno AL, Gerber MA, Gwaltney JM Jr, Kaplan EL, Schwartz RH; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Infectious Diseases Society of America. Clin Infect Dis. 2002;35:113-25. Medline:12087516 doi:10.1086/340949

29 Andes DR, Craig WA. Cephalosporins. In: Mandell GL, Bennett JE, Dolin R. Principles and practice of infectious diseases, 6th ed. New York: McGraw Hill; 2006. p. 297-300.

30 Guillemot D, Carbon C, Balkau B, Geslin P, Lecoeur H, Vauzelle-Kervroëdan F, et al. Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant Streptococcus pneumoniae. JAMA. 1998;279:365-70. Medline:9459469 doi:10.1001/jama.279.5.365

31 Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. Lancet. 2007;369:482-90. Medline:17292768 doi:10.1016/S0140-6736(07)60235-9

32 Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. Clin Infect Dis. 2000;31:347-82. Medline:10987697 doi:10.1086/313954

33 Mandell LA, Bartlett JG, Dowell SF, File TM Jr, Musher DM, Whitney C, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis. 2003;37:1405-33. Medline:14614663 doi:10.1086/380488

34 Huovinen P, Rautakorpi U-M, Klauka T, Makela MP, Nikkarinen T, Palva E, et al. Indication-based analysis of antibiotic use in primary care (poster). MIKSTRA, 2000. Available from: http://finohta.stakes.fi/NR/rdonlyres/BB5D7486-E0DA-46CE-B7D8-4F320BC3D521/0/poster_icaac2000.pdf. Accessed: December 10, 2010.