

Outpatient use of antibiotics in children in Slovenia

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Abstract

Background: Antibiotics are among the most common drugs prescribed in outpatient settings. It is estimated that up to 50 % of antibiotic prescriptions are unnecessary or inappropriate. To plan the actions to optimize the use of antibiotics we conducted a national antibiotic consumption study in children aged 0–18 years in the period between 2003 and 2015.

Methods: In this national retrospective research we analyzed outpatient antibiotic consumption using the ATC/DDD classification. The data on antibiotic use were stratified and analyzed by the pattern of prescription, age, gender and health region.

Results: The total consumption of antibiotics during the study period decreased by 35 %, from 979 to 636 prescriptions per 1000 children/year (PTY). The use of all antibiotic classes decreased (except for quinolones and nitrofurans derivatives) from 12.5 % to 8.1 %. Over the study period we found the highest consumption in children from 1 to 4 years (2184–1160 PTY). Amoxicillin was the most commonly prescribed antibiotic in children aged 0 to 4 years, penicillin V among those aged 5 to 14 years, and co-amoxiclav among adolescents aged 15 to 19 years. In northeastern health regions of Slovenia much more antibiotics were prescribed than in other regions. In 2015, 65 % of prescriptions were prescribed by paediatricians and school medicine specialists, 16 % by physicians without specialization, 14 % by GP/family doctors and 5 % by other specialists.

Conclusions: Despite the decrease in outpatient antibiotic use in children and adolescents in Slovenia, the overall and especially broad-spectrum antibiotic consumption (amoxicillin with clavulanic acid, azithromycin and second/third generation cephalosporins) is still too high. It is necessary to strengthen the activities to reduce prescribing, particularly for acute (upper) respiratory tract infections.

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1. Introduction

Antibiotics are the most common prescription drugs given to children with the highest incidence rates in pre-schools.^(1,2) There are large variations in antibiotic prescribing among countries and also within them.^(3,4) Prescribing antibiotics to children < 19 years varies

between less than 300 and over 1500 prescriptions per 1000 children/year (PTY) (Table 1) (1,5,6).

Antibiotic prescribing varies across paediatric practices in overall antibiotic prescribing rates and also in broad-spectrum antibiotic prescribing (7). Primary

paediatric care in Europe is provided by paediatricians or family doctors and general practitioners or both, and varies among countries as well (8). Acute respiratory tract infections followed by skin/cutaneous/mucosal and urinary tract infections are the most common conditions contributing to antibiotic prescribing in the ambulatory paediatrics (9).

To plan relevant activities that would limit and reduce the overuse of antibiotics of the total as well as of particular classes of antibiotics we conducted a retrospective national antibiotic consumption study in children aged 0–18 years in the period 2003–2015 characterising the patterns of antibiotic prescribing in relation to age, gender, health region, incidence of common infections and prescribers.

2. Methods

Slovenia is a small central European country with 2,064,188 inhabitants according to the January 2016 census data (10). It has 9 health regions with the populations varying from 71,218 to 656,831 (11). For the period 2003–2015 the data on outpatient antibiotic consumption

were analysed using the Anatomical Therapeutic Chemical classification with defined daily doses (ATC/DDD); WHO 2016. The results were expressed in DDD per 1000 inhabitants per day (DID) and PTY (12). The same definition of DDD was used for children and adults. The number of prescriptions of antibiotic for systemic use (JO1) and the incidence of infections were provided by the National Institute of Public Health (NIPH) of the Republic of Slovenia. The data on antibiotic consumption were analyzed by age, gender and health region. The analysis was retrospective and included the entire country. We did not need an approval from the Medical Ethics Committee.

3. Results

3.1. Total antibiotic consumption and pattern of consumption

The overall antibiotic consumption and its pattern during 2003–2015 expressed as PTY are shown in Table 2.

The consumption, expressed as PTY, decreased by 35 %; when expressed as DID it decreased by 26.5 % (from 17.92 to 13.18 DID).

During the study period there was a steady decrease with small temporary increases in different years. The use of all antibiotic classes decreased, except for nitrofurans derivatives (nitrofurantoin), polymyxins and quinolones. The highest decrease was seen in cephalosporins of 3rd and 2nd generations (by about 80 %), followed by macrolides and co-trimoxazole (60 %) and antistaphylococcal penicillins (57 %).

3.2. Prescriptions according to gender

In 2015 the amount of antibiotics prescribed to girls was by 5.6 % higher than

Table 1: Outpatient antibiotic prescribing rates (number of prescriptions per 100 children per year) in some European countries. (1,5,6).

Country	Year	Age (years)	PTY
Serbia	2013	0–18	1365
Greece	2010–13	0–18	1100
Italy (Emilia-Romagna)	2008	0–18	957
Slovenia	2015	0–18	636
Germany	2008	0–18	561
United Kingdom	2008	0–18	555
Denmark	2008	0–18	481
Sweden	2010	0–18	300
The Netherlands	2008	0–18	294

Legend: PTY – number of prescriptions per 1000 children per year.

that prescribed to boys (654 vs. 619 PTY). Macrolides, lincosamides, cephalosporins, quinolones, TMP/SMX, other antibiotics and aminoglycosides were more commonly prescribed to girls than boys.

3.3. Incidence of outpatient infections in children and adolescent (0–19 years)

The incidence rate and trend of specific diagnoses listed in the ICD-10 in the years 2005 and 2015 are shown in Table 3. Acute viral respiratory tract infections were the most common infections in both years, followed by upper respiratory tract infections (URTI), lower respiratory tract infections, skin and soft tissue infections and urinary tract infections.

3.4. Total consumption and pattern of consumption by age groups

Table 4 shows the prescriptions of antibiotics for systemic use per 1000 children/adolescents by age groups in 2015.

In the study period the highest incidence rate of antibiotic use was observed among children 1 to 4 years (2184–1160), followed by children 5 to 9 years (1203–723), then in children < 1 year (482–456), followed by children 15 to 19 years (566–398), and 10 to 14 years (602–350).

Amoxicillin was the most commonly prescribed antibiotic in children aged 0–4 years, penicillin V among those aged 5 to 14 years and co-amoxiclav among adolescents aged 15 to 19 years (Table 4).

Table 2: Number of prescriptions per 1000 children per year in 2003 and 2015 in Slovenia.

ATC code	ATC name	2003	2015	2003 vs. 2015
J01 A	TETRACYCLINES	5	4	- 20
J01 C	BETA-LACTAM ANTIBACTERIALS, PENICILLINS	657	515	- 21.7
CA	Penicillin with extended spectrum	270	222	-17.8–22.7–57–25
CE	Beta-lactamase sensitive penicillins	216	167	
CF	Beta-lactamase resistant penicillins	7	3	
CR	Combination of penicillins and beta-lactamase inhibitors	164	123	
J01 D	OTHER BETA-LACTAM ANTIBACTERIALS	86	17	- 80.2–50–81–80
DB	First-generation cephalosporin	2	1	
DC	Second-generation cephalosporin	79	15	
DD	Third-generation cephalosporin	5	1	
J01 E	SULPHONAMID AND TRIMETHOPRIM	58	23	- 60.3
J01 F	MACROLIDES AND LINCOSAMIDES	170	71	- 58.3–59.6–12.5
FA	Macrolides	166	67	
FF	Lincosamides	4.0	3.5	
J01 M	QUINOLONE ANTIBACTERIALS	3	3	+1.5
MA	Fluoroquinolones	3.22	3.27	
J01 X	OTHER ANTIBACTERIALS	-	3	
XB	Polymyxins	-	0	
XE	Nitrofurantoin derivatives	-	3	
Total		979	636	- 35

Legend: ATC, J01 – antibiotics for systemic use

3.5. Prescriptions by regions

Regional differences in incidence rates of treatment episodes within age group 0–18 years were identified. In the year 2015 there was an 83 % difference between the regions with the lowest and the highest total antibiotic consumption. The highest consumption was observed in the health region of Murska Sobota, in the northeast of Slovenia, and the lowest in the region of Nova Gorica, the westernmost part of the country (925 vs. 506 PTY). The median consumption was 688, and the average consumption 668 PTY.

3.6. Prescriptions by speciality

The differences in antibiotic prescriptions by different specialists were identified (Table 5). Amoxicillin was prescribed most commonly by all specialists followed by penicillin. It is a matter of

concern that physicians without specialization prescribed substantially more frequently co-amoxiclav. Paediatricians prescribed cephalosporins more often than other specialists did.

4. Discussion

In Slovenia, the total number of prescriptions for systemic use in children and in adolescents decreased by 35 %, and the consumption of different classes of antibiotics except for quinolones and nitrofurantoin derivatives from 12.5 % to 81 % during the period from 2003 to 2015 (Table 2). The decrease in the total antibiotic consumption is favourable but too small. When we benchmark the data with other countries we can see that in some countries (The Netherlands, Sweden), prescribe substantially fewer antibiotics (300 PTY vs. 636) are prescribed (Table 1). In both cited countries primary paediatric care is provided by family

Table 3: Causes of children and adolescents' (0–19 years) first outpatient visit in Slovenia in the years 2005 and 2015.

Diagnosis	ICD-10* code	Incidence rate/1000 in 2005	Incidence rate/1000 in 2015
Acute viral respiratory infection	J00, J04, B34.9, J06, J21, J22	628.5	587.2
Nonspecified acute pharyngitis	J02.9, J03.9	266.1	165.9
Acute otitis media (suppurative)	H66, H65	190.2 (24)	196.4 (32.7)
Acute bronchitis/bronchiolitis	J05, J20	74.4	83.6
Streptococcal pharyngitis	J0.2, J0.3	23.5	37.2
Suppurative skin or/and subcutaneous infection	L01, L02, L03, L08	31.6	34.5
Bacterial pneumonia	J13, J14, J15, J16, J17, J18	20.6	28.3
Urinary tract infection	N10, N30	12.1	13.6
Acute sinusitis	J01	14.1	8.9

* ICD-10—International classification of diseases, 10th revision.

doctors and general practitioners who have substantially shorter education in paediatrics, but they prescribe only half the amount of paediatric prescriptions. In the countries with lower antibiotic consumption, primary care physicians treat the most common infections, especially respiratory tract infections, less commonly. Rather than immediately prescribe an antibiotic, the physician should spend more time explaining to patients why an antibiotic is not needed and about the side effects including the development of resistance (2,4,6). Interventions to improve antibiotic prescribing in Slovenia have been reported recently (13).

A broad-spectrum penicillin co-amoxiclav is prescribed too often in all age groups, especially in adolescents. Co-amoxiclav is an alternative drug for the treatment of acute otitis media (OMA), acute bacterial rhinosinusitis and pneumonia, if amoxicillin monotherapy is not appropriate (14). We should remember to think critically before prescribing it and use amoxicillin instead, unless we are specifically concerned about the infection with amoxicillin-resistant bacteria (*Haemophilus influenzae*, *Moraxella catarrhalis*). It is important to avoid excessive or inappropriate use of co-amoxiclav in emergency departments and primary care settings which has been widely recognised (14). The reasons for curbing co-amoxiclav use are manifold, but include the long-term impact on antimicrobial resistance rates in the community, as well as possible patient-specific adverse effects (antibiotic-associated diarrhoea, including *Clostridium difficile*). A recent analysis has shown a positive relationship between the use of co-amoxiclav in the community and hospital care and the incidence of extended spectrum beta-lactamase (ESBL)-producing bacteria (15). The resistance mechanism

of pneumococcus against penicillin is not through beta-lactamase production, therefore the therapy of infections caused by penicillin-resistant pneumococci with co-amoxiclav is not appropriate. Instead, we should use higher doses of penicillin. Azithromycin is now recognized as a major driver of macrolide resistance due to its very long half-life and should not be used for the therapy of *Streptococcus pyogenes* infections; the use of macrolides with short half-life is recommended. In a 5-month retrospective study carried out in 2008/2009 Ahčan, who spent many years working at the department of paediatric infectious diseases, showed that penicillin V was the most commonly prescribed antibiotic (55.2%), followed by amoxicillin (33.1%), co-amoxiclav (3.2%), co-trimoxazole (3.2%), macrolides (2.7%) and antistaphylococcal antibiotics (2.7%) (16). Compared to other primary care paediatricians she prescribed substantially lower percentages of co-amoxiclav (3.2% vs. 19.5%), macrolides (2.7% vs. 6.4%), and higher percentage of narrow spectrum antibiotics (Table 5). The goal in Sweden is that at least 80% of antibiotics commonly used to treat respiratory tract infections in children 0–6 years of age should be penicillin V. In 2015 the proportion of penicillin V was 69% at the national level (4).

The highest incidence rate of antibiotic prescriptions was observed among children aged 1 to 4 years at 1160 per 1000 children in 2015. The most common cause of the high number of prescriptions are common respiratory tract infections in children attending day-care centres. Based on the data of the national Statistical Office of Slovenia, 78% of children aged 1–5 years are included in day-care centres. Every year the number of included children has increased (58% of children included in 2006) (17). The

number of prescribed antibiotics in Slovenia is too high in this age group. All countries with lower consumption of antibiotics than Slovenia have higher percentages of children included in day-care centres. Also the size of children groups is comparable with ours (18). Sweden has decreased the antibiotic consumption in children aged 0–6 years by 51 % since 2000, from 746 to 367 PTY (4). Also the counties with lower antibiotic consumption (200 PTY) continued to decrease the consumption significantly during 2014, which also suggests antibiotic overuse in other countries. A recent cohort study in the Stockholm County

has shown no increase in the number of complications in patients with OMA, tonsillitis and sinusitis as a consequence of a 33 % decrease in antibiotic use (19). A too high prescription incidence rate is also being observed in the age group less than one year of age. Slovenia has a one-year maternity leave and over 50 % of families have only one child (10). Respiratory tract infections are most commonly caused by viruses in this age group and antibiotics are likely prescribed unnecessarily. It is important to diminish the exposure of infants to individuals with symptomatic respiratory tract infections.

Table 4: Number of prescriptions per 1000 children (0–19 years) in 2015, by age groups and expressed in drug utilization 90 %.

Antibiotic	Age				
	0–1 year (%)	1–4 years (%)	5–9 years (%)	10–14 years (%)	15–19 years (%)
Amoxicillin	261 (57.2)	518 (44.6)	215 (29.6)	91 (26.0)	73 (19.6)
Penicillin V	26 (5.7)	250 (21,)	262 (36.2)	104 (29.7)	74 (19.9)
Co-amoxiclav	88 (19.2)	216 (18.6)	131 (18.0)	72 (20.6)	86 (23.0)
Azithromycin Mioamycin	21 (4.6)	23 (2.0)	57 (7.9)	38 (10.7)	44 (11.8)
Cefuroxime	15 (3.2)	20 (1.7)			
Co-trimoxazole	15 (3.2)	27 (2.3)		14 (4.0)	34 (9.2)
Doxycycline					11 (3.0)
Ciprofloxacin					9 (2.4)
Clindamycin					9 (2.4)
Number of prescriptions in DU 90 %	426 (93.4 %)	1054 (90.8 %)	665 (91.9 %)	319 (91.1 %)	340 (91.6 %)
Total antibiotic prescriptions	456	1160	723	350	371

Legend: DU – drug utilization.

Regional variations in antibiotic use in children and adults are apparent in each analyzed year. In health regions in northeastern Slovenia substantially more antibiotics are prescribed than in other regions. A retrospective study on the consumption of antibiotics for systemic use in children aged 0–14 years during the period 2006–2009 showed that in the regions with higher antibiotic consumption URTI and bronchitis were more frequently diagnosed. In 2006 OMA and urinary tract infections were diagnosed more commonly as well. The majority of these infections is caused by viruses, are self-limited but commonly treated with antibiotics. The region with the highest antibiotic consumption has more physician visits (5 visits per child per year) than the region with the lowest consumption (3 visits), which indicates the importance of parents' education and easy access to physicians. Primary care physicians are the most important source of information, they should educate parents when to visit the physician.

All over the world the differences in the frequency of prescriptions among individual physicians are observed (20). Gerber and co-workers have found a twofold difference in the total and a fourfold difference in prescriptions of broad spectrum antibiotics (7). Physicians who unusually prescribe high amounts of

antibiotics and/or broad-spectrum antibiotics need additional education. If education is not successful other interventions should be introduced to reduce inappropriate prescriptions. Electronic prescriptions enable a better control of the total and the pattern of prescriptions which has been recently reported (12). Benchmarking with other prescribers and introduction of accountable justification has decreased the consumption of antibiotics for acute respiratory tract infections (21). It would be useful to upgrade electronic prescriptions regarding the total (for example a warning at 80 % of the total average prescriptions) and the prescribing pattern. Recent data from the NIPH for 2015 show that 65 % of prescriptions for children and adolescents were written by paediatricians and school medicine specialists, 16 % by physicians in training, 14 % by GP/family doctors and 5 % by other specialists. These data show that the education of professionals should include all these specialists. We have prepared the guidelines for antibiotic therapy of common syndromes, followed by many presentations at professional meetings, yet physicians seem to be reluctant to adhere to the recommendations (22).

Antibiotic prescription is always considered appropriate for bacterial pneumonia, urinary tract infections and

Table 5: Structure of antibiotic prescribing (%) by speciality to children from 0 to 18 years in Slovenia in 2015.

Antibiotic/ Prescriber	Amoxicillin	Penicillin	Co- amoxiclav	Macrolides	Cephalosporins	Co- trimoxazole	Total PTY
Paediatrician	36.8	29.3	19.5	6.4	2.8	2.6	348
School doctor	31.9	30.4	18.4	9.9	1.4	2.8	65
General practitioner	43.5	22.7	17.8	6.9	2.0	3.0	51
Family doctor	42.0	27.0	16.2	5.4	1.3	2.7	37
Without specialty	31.9	23.3	26.2	5.8	1.4	3.4	100

Legend: number of prescriptions per 1000 children per year

streptococcal throat infections. The incidence of these infections is relatively low. More often the infections where recommendations allow the use of antibiotics in certain cases, such as acute suppurative otitis media, sinusitis (acute bacterial sinusitis), skin and soft tissue infections and bacterial lymphadenitis are being diagnosed. On the basis of many International guidelines, antibiotics are not indicated in nasopharyngitis, unspecified URTI, bronchitis, bronchiolitis, viral pneumonia, and non-suppurative acute otitis media. These infections are diagnosed the most frequently (21). AOM is diagnosed substantially more commonly in Slovenia than in the Netherlands where the incidence was 75/1000 inhabitants/year in patients < 18 years of age in 2010-2012 (23). Also the incidence of AOM episodes in five East European countries in children below 6 years of age in 2011/2012 was the highest in Slovenia (455.4/1000 persons per year), and the antibiotic prescription proportion was the highest in Slovenia as well (92.8 %) (24). These data show that AOM is overdiagnosed and overtreated with antibiotics. We urgently need additional education of primary care physicians on the correct diagnosis and appropriate therapy of AOM in Slovenia (25-27). Because physicians in training rarely see patients with AOM in hospitals, training in a simulation centre should be organized. If we treat 10 % of patients with URTI (prolonged course of suppurative rhinitis > 10 days), 30 % of AOM (suppurative AOM and part of non-suppurative, in infants < 6 months, bilateral in children < 2 years of age, after eardrum perforation, and/or new development of otorrhoea, severe course or in children with high risk for severe course), 20 % with acute bronchitis (suspected pneumonia, children with underlying diseases at high risk of complications) and

sinusitis (acute bacterial rhinosinusitis) and all cases of bacterial skin and soft tissue infections, bacterial pneumonia, UTI, streptococcal throat infections and other rare bacterial infections with antibiotics, the estimated use of antibiotics would be around 250 prescriptions /1000 inhabitants per year (28).

The limitation of the study is that we were not able to obtain the percentages of antibiotics prescribed for individual diagnosis and the percentages prescribed in working hours and in emergency departments. Regardless of the place of prescriptions it is important that antibiotics are prescribed only if they are needed, this is in documented or suspected bacterial infections, and where the benefit of antibiotic therapy is greater than the therapy without antibiotics.

When we prescribe antibiotics we should always, besides the benefit for the patient, take into account the future side effects and collateral damage of antibiotics. In Slovenia, we monitor the side effects of drugs including antimicrobials poorly. A recent Canadian study has shown that of all drugs, the side effects of antimicrobials are the most common cause for visiting an emergency department (29). When we prescribe antibiotics we should always bear in mind potential long-term side effects of antibiotics. Over the last few years many studies have been published confirming the correlation between antibiotic usage in early childhood and various autoimmune diseases (juvenile rheumatoid arthritis, chronic inflammatory bowel disease), obesity, which can present the tip of the iceberg from all long-term side effects.

The selection pressure of antibiotics on normal flora and pathogens, and secretion in the environment are well known but not sufficiently taken into account. In Slovenia, the levels of pneu-

mococcal resistance to penicillin and macrolides are higher in children because of a higher use of antibiotics in children than in adults. Higher regional consumption of penicillins is associated with higher resistance of *Streptococcus pneumoniae* to penicillin (3).

5. Conclusion

In Slovenia, the total consumption, especially the consumption of broad spectrum antibiotics such as co-amoxiclav, azithromycin and cephalosporins of the second and third generations is too high. The majority of antibiotics (more

than 80%) are prescribed by paediatricians, specialists of school medicine and physicians in training. To improve the prescription rates, the recommendations for antibiotic prescriptions should be followed. Self-education and more responsible antibiotic prescriptions in all age groups especially in preschool children are needed. All health regions in Slovenia should lower antibiotic consumption, especially northeastern regions. Antimicrobial resistance is such a great public health problem that we cannot permit inappropriate antibiotic prescriptions.

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