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Faculty of Pharmacy

Department of Clinical Pharmacy

Summary of the Ph.D. Thesis

VACCINATION AND RATIONAL ANTIBIOTIC USE: TWO ASPECTS TO COMBAT ANTIMICROBIAL RESISTANCE

'Pharmacoepidemiological Studies to Identify Problematic Areas'

Githa Fungie Galistiani

Supervisors:

Dr. Ria Benkő, PhD
Dr. Mária Matuz, PhD

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University of Szeged
Doctoral School of Pharmaceutical Sciences

Pharmacology, Biopharmacy, and Clinical Pharmacy Doctoral Programme
Programme director: **Prof. Dr. István Zupkó, DSc**

Department of Clinical Pharmacy
Supervisors: **Dr. Ria Benkő, PhD** and **Dr. Mária Matuz, PhD**

Githa Fungie Galistiani

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Defence Board:

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Members : **Dr. András Fittler**, **PhD**, University of Pécs, Institute of Pharmacy and Central Clinical Pharmacy

Dr. Réka Viola, PhD, University of Szeged, Faculty of Pharmacy, Institute of Clinical Pharmacy

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Member : **Dr. Anita Kovács, PhD**, University of Szeged, Faculty of Pharmacy, Department of Pharmaceutical Technology and Regulatory

Szeged

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1. INTRODUCTION

Antimicrobial resistance (AMR) is a major public health concern worldwide. One of the key strategies to reduce AMR is the prudent use of antimicrobials.

Antibacterials/Antibiotics are antimicrobial agents which are used to treat antibacterial infections. Drug utilization studies are needed to describe and understand the use of antibiotics in given population. The burden of infectious diseases in childhood is substantial with consequent frequent antibiotic prescribing.

Another approach to combat AMR is improving infection prevention and control, including vaccination. A published review stated that influenza vaccines can play an important role in reducing influenza-related antibiotic prescriptions and hence risk of AMR development.

Influenza vaccination has been recommended by the WHO for some specific populations (e.g., pregnant women and the elderly) Despite the well-recognised target population for seasonal influenza vaccination, there is some evidence suggesting that vaccination should be also prioritised among those with the highest number of social contacts, i.e. schoolchildren and active adults, to avoid transmission of infections and large outbreaks Additionally, protective immune response after vaccination may develop in higher rate in the young ones, compared to elderly with immunosenescence.

2. OBJECTIVES

2.1. *Cross-national comparative study of paediatric ambulatory antibiotic use: Hungary, Portugal and Norway*

To compare paediatric antibiotic use in the ambulatory care sector across three European countries: one from central/east (Hungary), one from the north (Norway), one from the south (Portugal) in 2014.

2.2. *Paediatric antibiotics use in ambulatory care in Hungary*

2.2.1. To explore the paediatric antibiotic use regarding the children's age and gender

2.2.2. To explore the paediatric antibiotic use regarding the prescribers' age and specialty

2.2.3. To explore the regional differences of paediatric antibiotic use in Hungary

2.2.4. To explore the seasonal variation of paediatric antibiotic use in Hungary

2.3. *Influenza vaccination among the active adult population in Hungary*

2.3.1. To analyse demographic characteristics relating to vaccination uptake

2.3.2. To investigate factors which motivated or discouraged vaccination uptake

2.3.3. To study the knowledge on influenza vaccination/influenza disease

2.3.4. To explore the active adult population' willingness to accept pharmacists as influenza vaccine administrators

3. METHODS

3.1. *Cross-national comparative study of paediatric ambulatory antibiotic use: Hungary, Portugal and Norway*

A retrospective, cross-national comparative study was conducted in three European countries with comparable data sources. The annual ambulatory care systemic antibiotic consumption (ATC: J01) data for 2014 were retrieved fromall countries. The analysis focused on children aged 0–19 years, but for comparative purposes,whole population data was also obtained. The commonly used age stratification was applied (0–4 years; 5–9 years; 10–14 years; 15–19 years) for subgroup analysis.

The same terminology and measurement assignment were used in all three countries: antibiotic use was evaluated by the Anatomical Therapeutic Chemical (ATC) classification and defined daily dose (DDD) measurement unit (version 2016). Data were expressed as number of packages per child inhabitant per year (packages/child/year) as these data for available for all countries plus as a complementary metrics in DDD per 1000 children and per day.

Population statistics on age were derived from Eurostat and refers to 1 January 2014. For Portugal, the population data were corrected for the mainland population.

Antibiotics have the same market status in all three countries; they are prescription only medicines. For all countries, data refers to ambulatory care consumption, including GPs, specialists, dentists, all private practices, and hospital emergency prescriptions for outpatients.

Data were obtained from the Hungarian National Health Fund Administration or in Hungarian: Nemzeti Egészségbiztosítási Alapkezelő (NEAK), the Norwegian Prescriptions Database (NorPD), and the National Reimbursed and Dispensed Medicines Database of Portugal.

The NEAK database contains a record for all reimbursed ambulatory care prescriptions dispensed at community pharmacies in Hungary. As NEAK is the only mandatory health insurance fund in Hungary (100% population coverage), and almost exclusively all antibacterial products are reimbursed agents, this database provides nearly 100% drug coverage for systemic antibacterial dispensing. The NorPD covers all inhabitants (100% population coverage), and all dispensed drug prescriptions (irrespective of reimbursement status) from the ambulatory care in Norway. Portugal database covers 100% of the Portuguese population who are residents of the mainland.

3.2. *Paediatric antibiotics use in ambulatory care in Hungary*

This was a population-based, retrospective study pertaining to year 2017. Data were obtained from the Hungarian National Health Fund Administration or in Hungarian: Nemzeti Egészségbiztosítási Alapkezelő (NEAK) which contains information on reimbursed drugs in ambulatory care.

Analysis was focused on children aged 0–19 years. Data were stratified by age group of patients (see Methods 3.1), age group of physicians (< 40 years, 40–65 years, 65 < years), specialty group of physicians (e.g., paediatrician GP, mixed GP, otolaryngologist), region (i.e., county), and month of antibiotic dispensation. Antibiotic use was expressed as the number of prescriptions per 100 inhabitants in the age group concerned per year or per month. Population data were derived from Eurostat. The proportion of broad-spectrum penicillins, cephalosporins and macrolides, as defined by the European Centre for Disease Prevention and Control (ECDC), was calculated.

3.3. *Influenza vaccination among the active adult population in Hungary*

The study was an observational cross-sectional study carried out in Hungary between March and July 2018. The self-administered questionnaire was distributed via social media, *Facebook*. Everyone who lives in Hungary, understands Hungarian and has a Facebook account was eligible to voluntarily take part in this study. No financial or other incentives were offered for participation. During the analysis, however, we focused only on the active adult population, aged 20 to 59 years.

The questions included general characteristics (e.g., age, sex, risk factors for influenza based on The Annual Vaccine Guideline of the Hungarian Ministry of Health), uptake of the seasonal influenza vaccine during the 2017/18 influenza season, factors motivating or discouraging uptake of the vaccine (see complete list of questions in **Table 6**), participants' knowledge in relation to influenza and influenza vaccination (see complete list of questions in **Table 7**) and the willingness of the participants to receive an influenza vaccination from their community pharmacist.

Descriptive, bivariate and multivariate statistical analyses were applied to describe all survey items. Descriptive statistics were used to describe all variables. Bivariate analyses, such as Pearson's chi-square test and Fisher's exact test, were used to compare categorical variables. Logistic regression was conducted to assess the potential associated factors of influenza vaccination uptake and adjusted odds ratios were reported. The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed using R software (R version 3.6.1).

4. RESULTS AND DISCUSSION

4.1. Cross-national comparative study of paediatric ambulatory antibiotic use: Hungary, Norway, and Portugal

4.1.1. Scale of use

In 2014, a total of 17,267,599 antibacterial packages were dispensed across the three countries. The population share of children versus antibiotic use share of children differed substantially in the three countries (see **Table 1**). Paediatric antibiotic use peaked in Hungary with 1.3 packages/child/year, followed by Portugal (0.8 packages/child/year) and Norway (0.3 packages/child/year).

Table 1 Total population and paediatric outpatient antibiotic use in Hungary, Portugal, and Norway in 2014

		Hungary		Norway		Portugal	
Population	All ages	9,877,365	(100.0%)	5,107,970	(100.0%)	9,869,783	(100.0%)
	0–19 years (%)	1,970,531	(19.9%)	1,256,379	(25.0%)	1,929,336	(19.5%)
	0–4 years (%)	455,202	(4.6%)	311,832	(6.1%)	426,971	(4.3%)
	5–9 years (%)	491,078	(4.9%)	310,769	(6.1%)	472,734	(4.8%)
	10–14 years (%)	479,536	(4.8%)	308,200	(6.0%)	509,777	(5.2%)
	15–19 years (%)	544,715	(5.5%)	325,578	(6.3%)	519,854	(5.3%)
Number of antibacterial packages	All ages	7,768,734	(100%)	2,188,551	(100%)	7,310,314	(100%)
	0–19 years (%)	2,495,781	(32.1%)	330,776	(15.1%)	1,459,298	(20.0%)
	0–4 years (%)	982,960	(12.7%)	111,116	(5.1%)	441,870	(6.0%)
	5–9 years (%)	647,115	(8.3%)	67,397	(3.1%)	471,822	(6.5%)
	10–14 years (%)	399,743	(5.1%)	41,473	(1.9%)	267,694	(3.7%)
	15–19 years (%)	465,964	(5.9%)	110,790	(5.1%)	277,912	(3.8%)
Number of antibacterial packages per inhabitant and per year	All ages	0.8		0.4		0.7	
	0–19 years	1.3		0.3		0.8	
	0–4 years	2.2		0.4		1.0	
	5–9 years	1.3		0.2		1.0	
	10–14 years	0.8		0.1		0.5	
	15–19 years	0.9		0.3		0.5	
DDD per 1000 inhabitants and per day	All ages	14.2		15.7		19.1	
DDD per 1000 children and per day	0–19 years	15.1		6.8		17.7	
	0–4 years	16.7		4.6		21.6	
	5–9 years	14.3		3.6		22.6	
	10–14 years	13.9		3.9		12.8	
	15–19 years	17.3		14.9		14.8	

A substantial difference was observed in paediatric antimicrobial use among Hungary, Portugal, and Norway. Similar cross-national comparison studies from various countries showed also substantial differences in antibiotic exposure: it peaked in South Korea with 3.4 prescriptions/child/year and were lowest in the Netherlands with 0.3 prescriptions/child/year.

In Hungary, children with or without their parents/caregivers often visit GP practises with self-limiting minor diseases just to obtain justification for being absent from school/day care and this consultation itself could increase the chance of being prescribed antibiotics. Explanation of the low paediatric antibiotic use in Norway can be that antibiotics are not reimbursed, exceptions are for specific diseases like sexually transmitted infections, tuberculosis, or to patients with chronic disorders such as cystic fibrosis. In Portugal, antibiotics are reimbursed comprehensively by a rate of 69%, which means that the out-of-pocket cost for parents is low. In Hungary, the reimbursement is very low (generally 25% of total price corresponding to 1–2 Euro in average). As a consequence, due to the low out-of-pocket price of antibiotics in Portugal and Hungary, there is no/limited financial barrier to fill in antibiotic prescriptions (i.e., low price may generate overuse).

4.1.2. Pattern of use

In all three countries, beta-lactam antibiotics and macrolides were most often used in paediatrics infections (**Figure 1**).

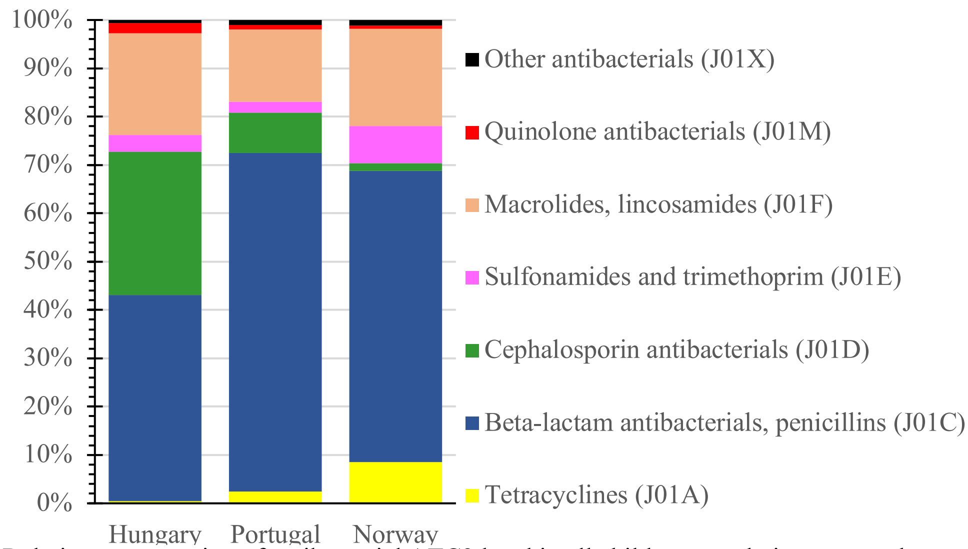

Figure 1. Relative consumption of antibacterial ATC3 level in all children population among three countries

However, the ATC3 level analysis revealed some differences: while in Norway and Portugal the relative use of the penicillin group was ~60% and ~70%, respectively, in Hungary their share from paediatric ambulatory use was only ~40%. In contrast, cephalosporins were used much more frequently in Hungary compared to other two countries (**Figure 2**). In Norway, the relative use of tetracyclines from the age of 10 years was substantially higher than in Hungary and Portugal (**Figure 2**).

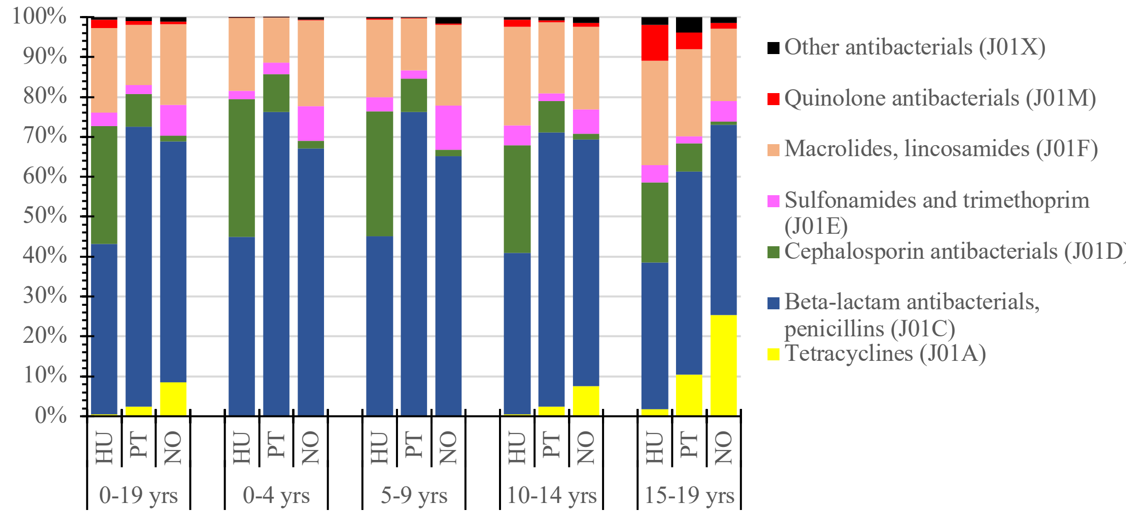

Figure 2. Relative consumption of antibacterial ATC3 level based on children's age subgroups in Hungary (HU), Portugal (PT), and Norway (NO)

In-depth data analysis (ATC4 level analysis) showed extreme differences in the pattern of use (**Figure 3A**). If a penicillin was prescribed in Norway, the narrow-spectrum penicillins (mainly the J01CE group) were used at a minimum of 50% in all paediatric age subgroups. In contrast, the relative share of narrow-spectrum penicillins was ~10% in Hungary and ranged between 2.9% and 19% in Portugal, depending on paediatric age subgroup. When we focused our analysis on cephalosporins (**Figure 3B),** we also revealed substantial differences: while in Norway first-generation cephalosporins were used almost exclusively in all paediatric age groups, in Hungary, first-generation cephalosporins were used marginally. In Portugal, first-generation cephalosporin's relative use creeped up by paediatric age groups in Portugal (from 16.7% to 30.2%; **Figure 3B**). Consequently, second- and third-generation cephalosporins were commonly prescribed for Hungarian and Portuguese children. Analysis of macrolide use (**Figure 3C**) showed that the old first-generation agent erythromycin was used extensively in Norway, while its use was quite limited in Hungary and marginal in Portugal. In contrast, in Portugal and in Hungary, azithromycin was used extensively. Of note, clindamycin use was present in all paediatric age groups in Norway, while its relative use gradually increased in Hungary from the age of 5 years.

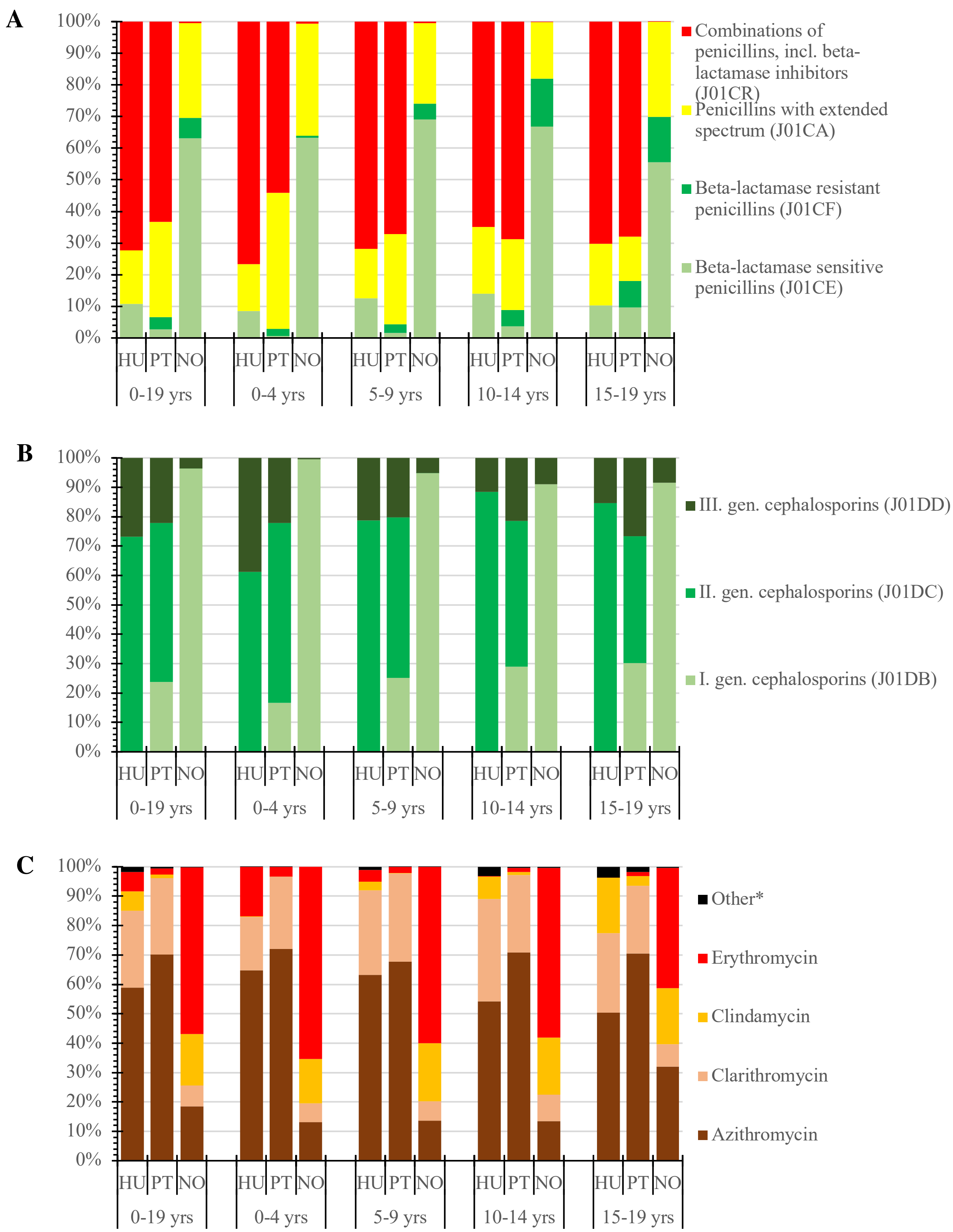

Figure 3. Relative consumption of penicillins (A), cephalosporins (B) and macrolides (C)

The observed differences in the patterns of use between the three countries cannot be explained by differences in bacterial resistances. The underuse of first line penicillins (amoxicillin, ampicillin, dicloxacillin, oxacillin, phenoxymethylpenicillin) in children was also recorded for Spain, Italy and South Korea.

The high use of penicillin combinations (i.e., amoxiclav) in Hungary is partly due to the fact that it was marketed earlier than amoxicillin alone, so doctors became used to it. Other reasons for this pattern could be the lack of antibiotic stewardship at all levels for prescribers: limitations of graduate education, lack of compulsory postgraduate courses, no incentives to prescribe more rationally, lack of feedback and the impact of pharmaceutical companies. In Hungary and in Portugal, the convenient dosage schedule of newer cephalosporins and also macrolides are often cited by doctors as an important influencing factor on antibiotic choice.

In contrast, in Norway, due to the strict legislation—prescribers must submit a special approval for prescribing—for products containing penicillin combinations (i.e., amoxiclav), their use is very limited and was even taken off the market between 2004 and 2017. The high absolute and relative use of tetracyclines (mainly lymecycline) in Norway is due to long-term treatment of acne vulgaris.

4.2. Paediatric antibiotics use in ambulatory care in Hungary

In total 6,792,714 antibiotic prescriptions were dispensed and redeemed at Hungarian pharmacies in 2017. Almost one-third (30.54%, N= 2,074,526) of these prescriptions were issued for children (**Table 2**), with a prescribing rate of 108.28 antibiotic prescriptions/100 children/year. Thirty active agents were used in the paediatric population in 2017, and the DU-90 segment (the number of active agents accounting for 90% of drug use) consisted of 8–11 antibacterials in various paediatric subgroups. Our study shows that almost one-third (30.81%) of all prescribed antibiotics in paediatric ambulatory care was comprised of amoxicillin and clavulanic acid (co-amoxiclav) (data not shown).

Table 2 Antibiotic exposure in ambulatory care in Hungary, 2017

Age groups	Number of Population	Number of antibiotic prescriptions	Percentage of total prescriptions redeemed (%)
0–4 years	461,739	849,139	12.50
5–9 years	474,702	511,965	7.54
10–14 years	486,424	341,209	5.02
15–19 years	493,069	372,213	5.48
All children and adolescents	1,915,934	2,074,526	30.54
All inhabitants	9,797,561	6,792,714	100.00

4.2.1. Paediatric antibiotic use regarding the children's age group and gender difference

Our study showed that on average every child received at least one course of antibiotic annually in 2017. Overall, paediatric (0–19 years old) antibiotic use in the ambulatory care was higher in Hungary (108.28 prescriptions/100 children/year) than Germany (0–14 years of age: 42.8 prescriptions/100 children in 2018), Finland (0–17 years of age: 37.4 prescriptions/100 children in 2016) and Denmark (0–19 years of age: with 32.57 prescriptions/100 children in 2017), but lower than in Serbia (0–18 years of age: 136.5 antibiotic prescriptions/100 children in 2013), and Greece (0–19 years of age: the annual rate was 110 prescriptions/100 children between 2010–2013). Besides the contributing factors related to prescribers, the patient and the healthcare system, a lack of clear national guidelines on a watchful waiting period for certain respiratory tract infections might explain the defensive use of antibiotics in childhood in Hungary.

Antibiotic exposure was the highest in the youngest age group (0–4 years: 183.9 prescriptions/100 children/year), as shown in **Table 2**. Antibiotic exposure decreased with increasing age in childhood, but there was a slight increment in the age group of late adolescents (15–19 years). Interestingly, boys in the youngest age group (0–4 years) were exposed to substantially higher antibiotic use compared to the girls. Concerning all children (0–19 years), antibiotic exposure was slightly higher in girls.

Regarding the patterns of antibiotic use (see **Table 3**), broad-spectrum penicillins, cephalosporins and macrolides were the most frequently prescribed antibacterials for all children (87.11 prescriptions/100 children/year of broad-spectrum vs. 16.82 and 4.35 prescriptions/100 children/year of unclassified and narrow-spectrum antibiotics, respectively). The B/N ratio was high across all paediatric age groups, and peaked in children aged 15–19 years. Similarly, the proportion of narrow-spectrum penicillins, cephalosporins and macrolides (N%, **Table 3**) was the lowest in this paediatric age group.

Table 3 Scale and characteristics of antibiotic use for children in ambulatory care in Hungary, 2017

Gender	Age groups (years)	Prescription/100 children/year				B/N	N %
		All antibiotics	B	N	Unclassified		
Girls and boys together	0–4	183.90	152.71	6.74	24.45	22.67	3.66
	5–9	107.85	89.01	5.74	13.10	15.50	5.32
	10–14	70.15	54.84	3.10	12.20	17.69	4.42
	15–19	75.49	55.70	2.00	17.79	27.86	2.65
	0–19	108.28	87.11	4.35	16.82	20.04	4.01
Girls	0–19	109.88	87.06	4.38	18.44	19.88	3.99
Boys	0–19	106.76	87.16	4.32	15.28	20.19	4.04
Girls	0–4	177.13	146.30	6.54	24.29	22.35	3.69
	5–9	107.26	87.81	5.73	13.71	15.32	5.34
	10–14	71.03	54.97	3.22	12.85	17.10	4.53
	15–19	87.78	62.53	2.19	23.06	28.54	2.50
Boys	0–4	190.31	158.78	6.92	24.61	22.96	3.63
	5–9	108.41	90.14	5.75	12.52	15.68	5.30
	10–14	69.31	54.73	2.99	11.59	18.30	4.32
	15–19	63.89	49.25	1.82	12.83	27.09	2.84

Broad- and narrow-spectrum categories defined by ESAC. B = broad-spectrum penicillins, cephalosporins and macrolides {J01(CR+DC+DD+(F-FA01))}. N = narrow-spectrum penicillins, cephalosporins and macrolides {J01(CE+DB+FA01)}. Unclassified: all other antibiotics. B/N = Ratio of the consumption of broad-spectrum penicillins, cephalosporins and macrolides to the consumption of narrow-spectrum penicillins, cephalosporins and macrolides. N% = the proportion of narrow-spectrum penicillins, cephalosporins and macrolides.

Overall, broad-spectrum penicillins, cephalosporins and macrolides were frequently prescribed for children in Hungary, with the highest proportion of broad-spectrum agents being prescribed for the youngest age subgroup (0–4 years). This might be explained by the frequent use of broad-spectrum penicillins (i.e., co-amoxiclav) for the treatment of acute otitis media. Similarly to our results, broad-spectrum penicillins, cephalosporins and macrolides were the most commonly prescribed antibiotics for children in many other countries, for instance in Greece, Korea, Lithuania, and Serbia.

In Hungary, co-amoxiclav was found to be the most frequently used antibiotic in children of all paediatric age groups. The frequent use of co-amoxiclav in Hungary may be explained by the reasons that we previously discussed (see **4.1.2.** paragraph 5). Although preferences in antibiotic use vary in different countries, co-amoxiclav is often the most widely used antibacterial agent in children, e.g., in Italy.

4.2.2. Paediatric antibiotic use according to prescribers' age and specialty

During the study period, paediatrician GPs were responsible for the majority (57.5%) of paediatric outpatient antibiotic prescriptions issued in ambulatory care (data not shown). As shown in red colour bar chart in **Figure 4** all physicians prescribed mainly broad-spectrum penicillins, cephalosporins and macrolides.

On the other hand, physicians aged 65 and older tended to prescribe less broad-spectrum agents than their younger colleagues. This might be explained by the fact that they were also familiar with older, narrow-spectrum agents, such as phenoxymethyl-penicillin (penicillin V). Overall, our study revealed that the majority of physicians prescribed more broad-spectrum antibiotics than narrow-spectrum agents. Similarly, the lack of therapeutic guidelines, the limited availability of narrow spectrum antibacterials on the Hungarian market and the influence of pharmaceutical companies might in part be responsible for the observed pattern in Hungary, but further research is required to better understand physicians' decision making about pediatric antibiotic prescribing.

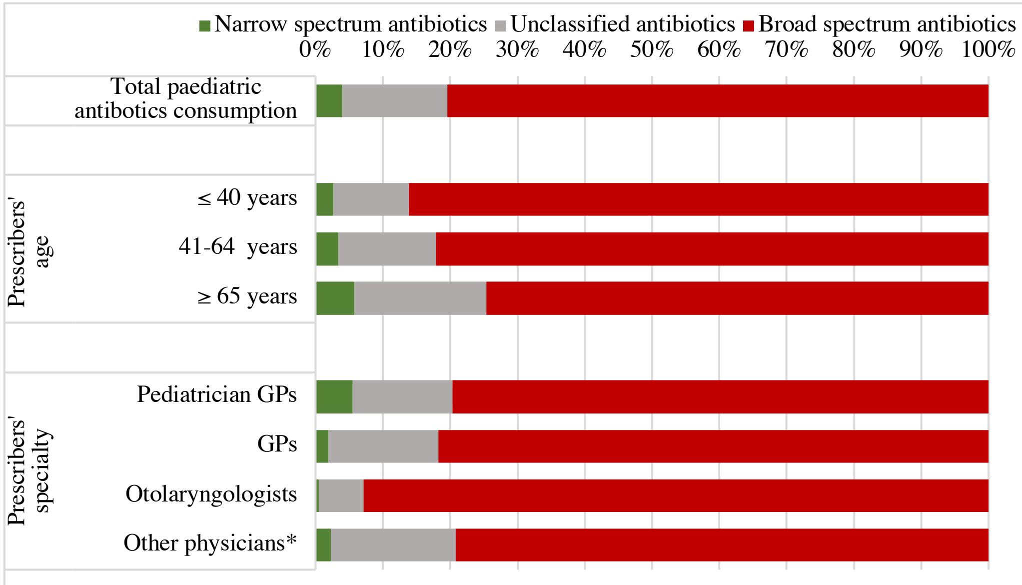

Figure 4 Use of antibiotics of broad-/narrow-spectrum categories defined by ESAC according to different prescribers' groups in the ambulatory care in Hungary, 2017. Broad-spectrum antibiotics: broad-spectrum penicillins, cephalosporins and macrolides {J01(CR+DC+DD+(F-FA01))}. Narrow-spectrum antibiotics: narrow-spectrum penicillins, cephalosporins and macrolides {J01(CE+DB+FA01)}. Unclassified antibiotics: all other antibiotics.

Otolaryngologists prescribed broad-spectrum penicillins, cephalosporins and macrolides more relatively often than other medical professionals. They prescribed broad-spectrum antibacterials more often than others, maybe because they treated more complicated cases.

4.2.3. Regional variation in paediatric antibiotic use

Both the scale and patterns of paediatric antibiotic use showed regional differences within Hungary. Regarding the scale of paediatric antibiotic consumption, an obviously increasing western to eastern gradient has been detected in all paediatric age groups, with ratio of maximum and minimum was 2.75 (175.6/63.8 prescriptions per 100 children per year) (see **Figure 5**). There was a more than 2.5-fold difference between the regions with the highest and the lowest paediatric antibiotic consumption. This is considerably higher than the 1.9-fold regional difference reported from Germany in 2018. The highest variation was observed in the youngest ones (0–4 years) with ratio of maximum and minimum was 3.5 (334.2/96 prescriptions/100 children/year).

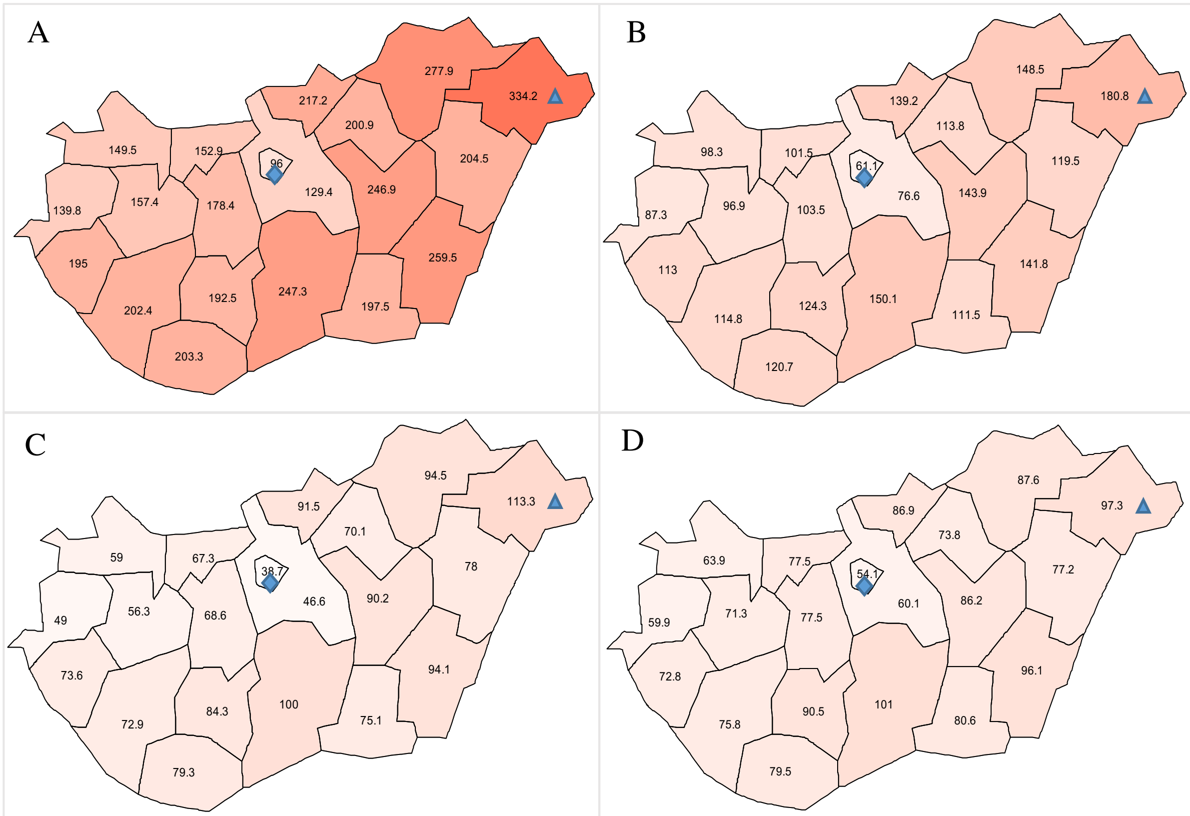

Figure 5 Regional variation of pediatric antibiotic use in different age groups in the ambulatory care in Hungary, 2017. A= 0–4 years, B= 5–9 years, C= 10–14 years, and D= 15–19 years, expressed as number of prescriptions/100 children/year (Triangle symbol for the maximum and diamond symbol for the minimum prescribing rate).

The findings that the lowest rate of paediatric antibiotic exposure was found for the capital city (Budapest), and an increasing western to eastern gradient in paediatric antibiotic use was evident, might be explained by factors such as paediatrician GPs availability and workload, or differences in the socio-economic status of patients. In line with our finding, a higher annual number of consultations per paediatrician GP (higher workload) was registered in those counties that were characterized by higher prescription rates compared to the capital city. Some chronic diseases with increased susceptibility to infections, like asthma and diabetes mellitus have a higher prevalence rate among children in counties with higher antibiotic use. Moreover, a recent publication on Hungarian primary healthcare availability reported that the most deprived areas were found in the north-eastern and south-western parts of Hungary, whereas the least deprived areas were in the north-western part of the country, as well as in the capital city and its neighbouring areas where the lowest rates of antibiotic exposure were detected in our study.

4.2.4. Seasonal variation in paediatric antibiotic use

Seasonal variation was substantial (see **Figure 6**), with monthly prescription rate peaking in January (16.65 prescriptions/100 children/month), while the lowest rate was observed in July (3.96 prescriptions/100 children/month). Seasonal variation was detectable in all paediatric age groups, with the highest monthly variation in the youngest ones (0–4 years).

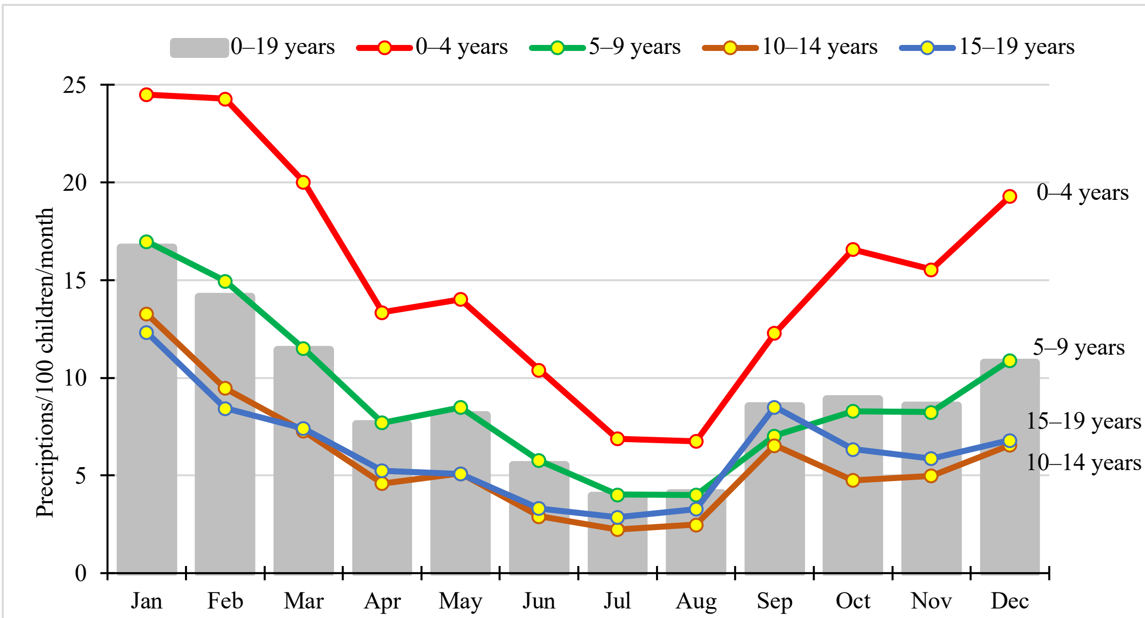

Figure 6 Seasonality of antibiotic use among children of different age groups (expressed as the number of prescriptions/100 children/month) in Hungary, 2017.

The highest monthly antibiotic consumption in the paediatric population was observed during the winter season, peaking in January. Seasonal fluctuation of outpatient antibiotic use in the general population across Europe has been described before, and it is most likely to be related to the higher incidence of viral respiratory infections in winter months. A previous cross-national comparison study in the pediatric population showed that seasonal peaks of antibiotic exposure in winter months were most pronounced in countries with high overall antibiotic utilisation, e.g., in Italy, followed by Germany. In our study a slightly increasing rate of antibiotic use was seen from August to September, which can be explained by childrens' attending school again after the summer holiday.

4.3. Influenza vaccination among the active adult population in Hungary

In total, 1842 questionnaires were filled. Of these, 1631 questionnaires were analysed and 211 were excluded since those were filled by participants who were not in the active adult (20-59 years old) population. The general characteristics of the participants and influenza vaccine uptake in 2017 are presented in **Table 4**.

Table 4 Bivariate analysis of participants' general characteristics and influenza vaccination uptake in 2017

Variable	Vaccination status: **Yes** (n = 200) Number	(Row %)	**No** (n = 1431) Number	(Row %)	**Total** Number	(Col.%)	Statistical test	*p*-value
Age (years) (mean ± SD)	37.5 ± 11.2		33.2 ± 10.5		33.7 ± 10.7		Welch's two Sample t-test	<0.001
Gender								
Male	50	(16.1)	260	(83.9)	310	(19.0)	Pearson's Chi-square test	0.0214
Female	150	(11.4)	1170	(88.6)	1320	(80.9)		
N/A	0	(00.0)	1	(100)	1	(00.0)		
Type of residence								
Village	33	(13.3)	225	(86.8)	258	(15.8)	Pearson's Chi-square test	0.7587
City	166	(12.1)	1205	(87.9)	1371	(84.1)		
N/A	1	(0.5)	1	(0.5)	2	(0.1)		
Educational level								
Primary	4	(15.4)	22	(84.6)	26	(1.6)	Fisher's exact test for count data	0.0146
Secondary	87	(10.1)	772	(89.9)	859	(52.7)		
Tertiary	109	(14.7)	635	(85.4)	744	(45.6)		
N/A	0	(0.0)	2	(100)	2	(0.1)		
Occupational risk factor [a]								
Yes	88	(17.2)	424	(82.8)	512	(31.4)	Pearson's Chi-square test	<0.001
No	112	(10.1)	1002	(89.9)	1114	(68.3)		
N/A	0	(0.0)	5	(100)	5	(0.3)		
Health risk factor [b]								
Yes	95	(15.1)	536	(84.9)	631	(38.7)	Pearson's Chi-square test	0.0063
No	105	(10.5)	895	(89.5)	1000	(61.3)		
Knowledge (N = 1609) (mean ± SD)	85.4 ± 9.7		70.7 ± 15.1		72.5 ± 15.3		Welch's two Sample t-test	<0.001

[a] Occupational risk factors include participants who have at least one of the following statuses: students in the health care field; work in health care services; social institution/long care term facility; nursery school/kindergarten; livestock or animal transfer (swine, poultry, horse); poultry processing or abattoir; work with immigrants/foreign people.
[b] Health risk factors include participants who had at least one of the following conditions in the previous year: heart failure; coronary artery disease; chronic pulmonary disease; immune disease; taking immunosuppressive drugs; inflammatory bowel disease; chronic liver disease; chronic kidney disease; pregnancy/planning pregnancy; disabled (physically); smoker.

4.3.1. Demographic characteristics relating to vaccination uptake

Overall, there were significant differences in age, gender, educational level, occupational risk factor, health risk factor and knowledge of vaccinated versus unvaccinated participants ($p<0.05$) in the bivariate analysis. Participants' type of residence was the only variable that showed no significant difference between vaccinated and unvaccinated participants (see **Table 4**). Furthermore, logistic regression showed that age, gender, health risk factor and knowledge about influenza were associated with influenza vaccination uptake (see **Table 5**).

Table 5 Logistic regression analysis to identify associated factors for influenza vaccination uptake (n = 1602)

	OR	95% CI	*p*-value
Age	1.028	1.012–1.044	0.001
Gender (male)	1.838	1.217–2.774	0.004
Occupational risk factor	1.211	0.838–1.751	0.309
Health risk factor	2.070	1.472–2.910	0.000
Educational level – Primary (reference)	-	-	-
Secondary	0.568	0.149–2.171	0.408
Tertiary	0.585	0.153–2.241	0.434
Knowledge	1.096	1.078–1.114	0.000

4.3.2. Factors which motivated or discouraged vaccination uptake

The reasons for obtaining or not obtaining the influenza vaccination are summarised in **Table 6** below.

Table 6 Participants' cited reasons for their vaccination status*

Reasons for being…	**Number**	**(%)**
Vaccinated, n = 200 (100%)		
To protect myself from the flu and its complications	190	(95.0)
To protect those with risk factors around me	122	(61.0)
I consider flu a severe disease	105	(52.5)
I belong to a risk group, I am prone to infections/diseases	69	(34.5)
I had severe influenza previously	31	(15.5)
Death due to influenza complications around me (in my neighbourhood)	7	(3.5)
Unvaccinated, n = 1431 (100%)		
Because I rarely get infectious diseases (including influenza)	968	(67.7)
Because I do not have a risk factor	700	(48.9)
Because nobody has a risk factor around me	587	(41.0)
Because I prefer alternative therapies (e.g. natural medicine)	511	(35.7)
I consider influenza a minor disease	463	(32.4)
Because I am afraid of the side effects	451	(31.5)
Because of the contradictory opinions on flu vaccine	411	(28.7)
I consider the vaccine ineffective	380	(26.6)
Because I prefer medical therapy	361	(25.2)
Previous bad experience with flu vaccine among family members/acquaintance	341	(23.8)
Because I forgot and missed it	263	(18.4)
Because I am afraid of the needles	172	(12.0)
I received the flu vaccine previously, but it was ineffective because I got the flu	156	(10.9)
Influenza vaccine is contraindicated to me	93	(6.5)
I received the flu vaccine previously, but I experienced major/serious side effects	85	(5.9)

**Participants' could give more than one reason*

The most frequently cited reasons for having an influenza vaccination were 'self-protection' and 'to protect those with risk factors around', which were also noted in other studies, followed by 'consider flu as a severe disease'. These stated reasons imply that vaccinated people are more likely to be aware of the negative impacts of influenza disease. Of note, social responsibility was an important motivating factor for influenza vaccination.

4.3.3. Knowledge of influenza vaccination/influenza disease

The participants' knowledge on certain questions is summarised in **Table 7**. Most participants (93.6%) knew that influenza is an infectious disease. On the other hand, approximately half of the participants (47.4%) believed that influenza vaccination can cause flu, and just over half of them (51.6%), (calculated from the sum of 'wrong' and 'unknown' answers) were not knowledgeable about the safety of influenza vaccine ingredients (see **Table 7**).

In total, only 30.6% of all participants gave the correct 'FALSE' answer to the statement 'flu vaccine can cause influenza disease'; however, the vaccinated group showed better knowledge compared with the knowledge of the unvaccinated group (54.5% vs 27.3%) (see **Table 7**). Moreover, vaccinated participants scored higher for each knowledge question in comparison with the scores of non-vaccinated participants. This higher level of knowledge was identified as one of the factors associated with influenza vaccine uptake ($p < 0.05$) (see **Table 5).**

Table 7 Participants' knowledge about influenza and influenza vaccination

Questions	Correct answers	Answer by participants	Vaccinated n = 200 (100%) Number	(%)	Unvaccinated n = 1431 (100%) Number	(%)	Total n = 1631 (100%) Number	(%)
Influenza is an infectious disease	True	Correct	194	(97.0)	1333	(93.2)	1527	(93.6)
		Wrong	4	(2.0)	57	(4.0)	61	(3.7)
		Do not know	0	(0.0)	30	(2.1)	30	(1.8)
		NA	2	(1.0)	11	(0.8)	13	(0.8)
Influenza vaccination is recommended annually for the risk groups	True	Correct	194	(97.0)	1122	(78.4)	1316	(80.7)
		Wrong	0	(0.0)	87	(6.1)	87	(5.3)
		Do not know	3	(1.5)	205	(14.3)	208	(12.8)
		NA	3	(1.5)	17	(1.2)	20	(1.2)
Influenza vaccination is highly/specially recommended for the elderly	True	Correct	189	(94.5)	988	(69.0)	1282	(78.6)
		Wrong	1	(0.5)	148	(10.3)	119	(7.3)
		Do not know	6	(3.0)	280	(19.6)	209	(12.8)
		NA	4	(2.0)	15	(1.1)	21	(1.3)
Influenza vaccination is highly/specially recommended for those with chronic diseases	True	Correct	185	(92.5)	1093	(76.4)	1173	(71.9)
		Wrong	4	(2.0)	118	(8.3)	152	(9.3)
		Do not know	9	(4.5)	203	(14.2)	289	(17.7)
		NA	2	(1.0)	17	(1.2)	17	(1.0)
Elderly and those with certain chronic diseases can get the flu vaccination for free	True	Correct	183	(91.5)	1009	(70.5)	1192	(73.1)
		Wrong	4	(2.0)	48	(3.4)	52	(3.2)
		Do not know	11	(5.5)	360	(25.2)	371	(22.8)
		NA	2	(1.0)	14	(1.0)	16	(1.0)
Influenza is a synonym for common cold	False	Correct	179	(89.5)	1239	(86.6)	1418	(86.9)
		Wrong	9	(4.5)	106	(7.4)	115	(7.1)
		Do not know	7	(3.5)	73	(5.1)	80	(4.9)
		NA	5	(2.5)	13	(0.9)	18	(1.1)
In case of fever the vaccination should be postponed	True	Correct	177	(88.5)	1176	(82.2)	1353	(83.0)
		Wrong	7	(3.5)	41	(2.9)	48	(2.9)
		Do not know	13	(6.5)	199	(13.9)	212	(13.0)
		NA	3	(1.5)	15	(1.1)	18	(1.1)
The best method to prevent influenza is the influenza vaccination	True	Correct	172	(86.0)	619	(43.3)	791	(48.5)
		Wrong	12	(6.0)	453	(31.7)	465	(28.5)
		Do not know	13	(6.5)	339	(23.7)	352	(21.6)
		NA	3	(1.5)	20	(1.4)	23	(1.4)
Time to onset of action is 2 weeks for influenza vaccination in case of adults	True	Correct	163	(81.5)	841	(58.8)	1004	(61.6)
		Wrong	6	(3.0)	68	(4.8)	74	(4.5)
		Do not know	29	(14.5)	501	(35.0)	530	(32.5)
		NA	2	(1.0)	21	(1.5)	23	(1.4)
Influenza vaccine contains safe ingredients	True	Correct	159	(79.5)	606	(42.4)	765	(46.9)
		Wrong	8	(4.0)	258	(18.0)	266	(16.3)
		Do not know	31	(15.5)	544	(38.0)	575	(35.3)
		NA	2	(1.0)	23	(1.6)	25	(1.5)
Influenza can be prevented by high dose vitamin C (min. 500 mg daily) instead of vaccination	False	Correct	156	(78.0)	662	(46.3)	818	(50.2)
		Wrong	12	(6.0)	407	(28.4)	419	(25.7)
		Do not know	30	(15.0)	344	(24.0)	374	(22.9)
		NA	2	(1.0)	18	(1.3)	20	(1.2)
Antibiotics work against influenza	False	Correct	155	(77.5)	953	(66.6)	1108	(67.9)
		Wrong	24	(12.0)	321	(22.4)	345	(21.2)
		Do not know	18	(9.0)	144	(10.1)	162	(9.9)
		NA	3	(1.5)	13	(0.9)	16	(1.0)
The flu vaccination can weaken the immune system	False	Correct	151	(75.5)	652	(45.6)	803	(49.2)
		Wrong	24	(12.0)	439	(30.7)	463	(28.4)
		Do not know	22	(11.0)	320	(22.4)	342	(21.0)
		NA	3	(1.5)	20	(1.4)	23	(1.4)
Influenza can be prevented by herbs (e.g. honey, ginger tea) instead of vaccination	False	Correct	143	(71.5)	672	(47.0)	815	(50.0)
		Wrong	13	(6.5)	374	(26.1)	387	(23.7)
		Do not know	41	(20.5)	368	(25.7)	409	(25.1)
		NA	3	(1.5)	17	(1.2)	20	(1.2)
You should not take influenza vaccination if you have already got influenza	False	Correct	117	(58.5)	625	(43.7)	742	(45.5)
		Wrong	49	(24.5)	421	(29.4)	470	(28.8)
		Do not know	32	(16.0)	370	(25.9)	402	(24.7)
		NA	2	(1.0)	15	(1.0)	17	(1.0)
The flu vaccination can cause flu	False	Correct	109	(54.5)	390	(27.3)	499	(30.6)
		Wrong	62	(31.0)	711	(49.7)	773	(47.4)
		Do not know	27	(13.5)	308	(21.5)	335	(20.5)
		NA	2	(1.0)	22	(1.5)	24	(1.5)
In case of egg allergy, the flu vaccination can be taken	True	Correct	58	(29.0)	323	(22.6)	381	(23.4)
		Wrong	61	(30.5)	264	(18.5)	325	(19.9)
		Do not know	79	(39.5)	822	(57.4)	901	(55.2)
		NA	2	(1.0)	22	(1.5)	24	(1.5)

4.3.4. Willingness to accept pharmacists as influenza vaccine administrators

Overall, almost one-third (29.1%; 474/1631) of all participants would accept an influenza vaccination from a pharmacist. **Table 8** shows that the willingness to accept pharmacists as vaccine administrators was significantly higher among participants who had been vaccinated during the last influenza season ($p < 0.05$).

Table 8 Bivariate analysis of general characteristics and participants' willingness to be vaccinated by a pharmacist (n = 1631)

Variables	**Willingness to be vaccinated by a pharmacist**		**Statistical test**	***p-value***
	Yes n = 474 (100%) **Number (%)**	**No** n = 1157 (100%) **Number (%)**		
Age (years)				
(*mean* ± *SD*)	32.5 ± 10.8	34.2 ± 10.6	Welch's two sample t-test	0.0029
Gender				
Male	132 (42.6)	178 (57.4)	Pearson's Chi-square test	<0.001
Female	341 (25.8)	979 (74.2)		
N/A	1 (100)	0 (0.0)		
Type of residence				
Village	61 (23.6)	197 (76.4)	Pearson's Chi-square test	0.0375
City	412 (30.0)	959 (70.0)		
N/A	1 (50.0)	1 (50.0)		
Education level				
Primary	14 (53.9)	12 (46.1)	Pearson's Chi-square test	0.0192
Secondary	245 (28.5)	614 (71.5)		
Tertiary	214 (28.8)	530 (71.2)		
N/A	1 (50.0)	1 (50.0)		
Occupational risk [a]				
Yes	122 (23.8)	390 (76.2)	Pearson's Chi-square test	0.0014
No	352 (31.6)	762 (68.4)		
N/A	0 (0.0)	5 (100)		
Health conditions risk [b]				
Yes	179 (28.4)	452 (71.6)	Pearson's Chi-square test	0.6238
No	295 (29.5)	705 (70.5)		
Vaccinated				
Yes	116 (58.0)	84 (42.0)	Pearson's Chi-square test	<0.001
No	358 (25.0)	1073 (75.0)		
Knowledge (n = 1609)				
(mean ± SD)	79.3 ± 12.4	69.8 ± 15.5	Welch's two sample t-test	<0.001

[a] Occupational risk factors include participants who have at least one of the following statuses: students in the healthcare field; work in health care services; social institution/long care term facility; nursery school/kindergarten; livestock or animal transfer (swine, poultry, horse); poultry processing or abattoir; work with immigrants/foreign people.

[b] Health risk factors include participants who had at least one of following conditions in the previous year: heart failure; coronary artery disease; chronic pulmonary disease; immune disease; taking immunosuppressive drugs; inflammatory bowel disease; chronic liver disease; chronic kidney disease; pregnancy/planning pregnancy; disabled (physically); smoker.

5. CONCLUSIONS

The scale and pattern of paediatric ambulatory antibiotic use differed largely among Hungary, Portugal and Norway. Undesirable pattern of antibiotic use (i.e., low consumption of narrow-spectrum agents) begins in childhood in Hungary and Portugal. In 2017, high paediatric antibiotic exposure with a suboptimal pattern was detected in Hungary, especially among children of the youngest age group (0–4 years). The considerable regional variation and the disproportionately high seasonality of antibiotic use in children may also suggest suboptimal prescribing habits. The revealed characteristics of paediatric antibiotic use can support planning antibiotic stewardship interventions and can serve as a basis for more detailed qualitative research.

Influenza vaccine uptake among active adults was low in Hungary. Increased public awareness and improved knowledge about influenza vaccination and/or influenza disease is necessary to achieve higher influenza vaccination uptake rates. Based on the insufficient knowledge of participants concerning the effectiveness and safety of the influenza vaccine, combined with the level of acceptance among participants to obtain an influenza vaccination from a pharmacist, we recommend that both the educational role played by pharmacists should be extended, while vaccine administrator role should be considered and implemented.

PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

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PRESENTATIONS RELATED TO THE SUBJECT OF THE THESIS

1. **Galistiani GF**, Matuz M, Babarczy B, Papp R, Hajdu A, Benkő R. 2020. Variations in antibiotic prescribing for children—Hungary, 2017. *European Drug Utilization Research Group (EuroDURG) Conference 2020*. Szeged, Hungary. March 4-7, 2020.
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3. **Galistiani GF,** Matuz M, Csatordai M, Doró P, Schváb K, Benkő R. 2019. Preliminary study on influenza vaccination uptake in the active population. *The 14th Congress of the European Association for Clinical Pharmacology and Therapeutics (EACPT).* Stockholm, Sweden. June 29-July 2, 2019.