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ORIGINAL ARTICLE

Cross-national comparison of paediatric antibiotic use in Norway, Portugal and Hungary

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Abstract
A cross-national comparison was performed on paediatric (0-19 years) antibiotic use in Hungary, Norway and Portugal to explore and compare the scale and pattern of paediatric antibiotic use in these three European countries. Ambulatory care systemic antibiotic use (ATC: J01) was retrieved from national databases for year 2014. The main outcome measure was number of antibacterial packages per child inhabitant per year (packages/child/year) and was further stratified by age groups. Paediatric antibiotic use peaked in Hungary with 1.3 packages/child/year, followed by Portugal (0.8) and Norway (0.3). This ranking was retained and was most prominent in the 5- to 9-year and 10- to 14-year age groups. The pattern of antibiotic use in different paediatric age groups varied also substantially between countries. Narrow-spectrum penicillins were much commonly used in Norway in all paediatric age subgroups in comparison with Hungary and Portugal. Newer, broad-spectrum cephalosporins and macrolides were widely prescribed for Hungarian and Portuguese children in all paediatric subgroups in contrast to Norway, while tetracyclines were commonly prescribed for Norwegian adolescents. The scale and pattern of paediatric antibiotic use in Hungary and Portugal were very different compared with Norway. The high antibiotic exposure and the high consumption of broad-spectrum penicillins begin in childhood in Hungary and Portugal which underpins the responsibility of paediatric GPs.

KEYWORDS
ambulatory care, antibacterials, antimicrobial management, children, public health

1 | INTRODUCTION AND BACKGROUND

The public health burden of infectious diseases in childhood is substantial.[1] Young children are more prone to acquire infections due to immature immune system and anatomical characteristics (eg narrower passages in the sinus, middle ear and bronchi). Infection transmission is also more prevalent in childhood due to close physical contact, scarce use of coughing/sneezing etiquette, etc.[2-4] Antimicrobial resistance is considered as an important public health issue,[5-8] and rational use is a factor that may restrain this.

Despite that antibiotics are among the most commonly prescribed drugs for children and adolescents,[2,9,10] information on paediatric antibiotic use is still limited. Countries with electronic health record databases have reported overprescribing for non-severe infections nationally[11-13] but comprehensive and comparable, country-wide paediatric antibiotic use data have only been published for a limited number of European countries,[14-16] while few

European countries published paediatric antibiotic use data on a certain region.[17,18] From an antibiotic stewardship point of view, more cross-national drug utilisation studies are needed to get an overview of possible variations in antibiotic use in children.

The present study aimed to compare paediatric antibiotic use in the ambulatory care sector across three European countries: one from south, one from north and one from central/east. For two of these countries, Hungary and Portugal, data on paediatric antibiotic use were not available and published before.

2 | METHODS

2.1 | Study design, setting

A retrospective, cross-national comparative study was conducted in three European countries with comparable data sources (see below). The level of geographical analysis was national census data for all the three countries. The annual ambulatory care systemic antibiotic consumption (ATC category: J01) data for 2014 were retrieved from national data sources. The analysis focused on children aged 0-19 years, but for comparative purposes, data were also obtained for the whole population (including paediatrics, adults, elderly). The commonly used age stratification was applied (0-4 years; 5-9 years; 10-14 years; 15-19 years) for subgroup analysis. A template Excel sheet was provided to fill in data in a standardised format.

The same terminology and measurement assignment was 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) and as a complementary metrics in DDD per 1000 children and per day. For this later, sum of DDDs were divided by the children population of the specific age subgroup than further divided by 365 and finally multiplied by 1000.

As the number of packages proved to be a good proxy for number of prescriptions/treatments,[19,20] this was our main measurement unit. In Hungary, only one antibiotic product can be prescribed on each prescription (this is usual practice, but not a legal restriction on this in Portugal and in Norway) and because doctors in these three countries most often prescribe monotherapy and almost exclusively one package at once, the number of packages serves as a good proxy to the number of treatments/prescriptions).

Moreover, to picture the burden of antibiotics in these countries, cross-national variation in DDDs/packages in different age groups was chosen as a volume metric. It has been argued that DDDs are not suited to describe antibiotic use among children since the dose depends on the child's age and body-weight. However, on aggregated data and in cross-national comparisons among children, the DDDs may give a good estimate for variations in volume of use, that is high/low dosing or length of treatment.

Population statistics on age were derived from Eurostat and refers to 1 January 2014.[21] For Portugal, the population data were corrected for the mainland population (population of autonomous regions was excluded).

Antibiotics have the same market status in all 3 countries; they are prescription-only medicines. For all countries, data include ambulatory care consumption, including hospital emergency prescriptions for outpatients.

2.2 | Background information

2.2.1 | Hungary

National data were obtained from the Health Fund Administration (HFA). The HFA database contains a record for all reimbursed ambulatory care prescriptions dispensed at community pharmacies in Hungary. As HFA is the only mandatory health insurance fund in Hungary (with 100% population coverage), and as almost exclusively all antibacterial products are reimbursed agents, this database provides nearly 100% drug coverage for systemic antibacterial dispensing. In Hungary, the majority (1 425 000; 76%) of children are registered at a paediatrician GP; the rest are registered at mixed GP practises (ie care for both adults and children).

2.2.2 | Norway

Data for Norway were retrieved from the Norwegian Prescription Database (NorPD). The NorPD covers all inhabitants (100% drug coverage), and all dispensed drug prescriptions (irrespective of reimbursement status) from the ambulatory care in Norway have been included since 2004. In Norway, the GP offices are the first line healthcare services and provide health care for all citizens (including children).

2.2.3 | Portugal

To retrieve Portuguese data, the National Reimbursed and Dispensed Medicines Database was used. As in Hungary and Norway, this database covers 100% of the Portuguese population who are residents of the mainland. As all antibiotics currently marketed are reimbursed in Portugal, the data set provides 100% drug coverage for systemic antibacterials. In Portugal, ambulatory care treatment for children is managed by GPs and private paediatricians.

2.3 | Ethics

As crude data were aggregated at the active agent level and not at individual patient level, no ethical approval was needed.

3 | RESULT

3.1 | Scale of use

During the study period, a total of 17 267 599 antibacterial packages were dispensed across the three countries (Table 1). The population share of children vs antibiotic use share of children differed substantially in the three countries. In Portugal, both the population share of children (19.5%) and ambulatory antibiotic use share of this age group were very similar (~20%). Hungary had similar rate for paediatric population share compared to Portugal (~19.9%) but the proportional antibiotic use of this age group was much higher (32.2%). Norway had the highest rate of young people (24.6%), and the share of this age group from total ambulatory care antibiotic use was the lowest (15%).

The scale of antibiotic use differed greatly in the three countries (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). This ranking was retained when we focused our analysis on paediatric age subgroups. The differences between countries were most prominent in the 5- to 9-year and 10- to 14-year age groups: Hungarian children in these age groups were prescribed 5 times more packages of antibacterials during the study year.

3.2 | Pattern of use

In all three countries, beta-lactam antibiotics and macrolides were most often used in paediatric infections. 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 the other two countries (Figure 1A). In Norway, the relative use of tetracyclines from the age of 10 years was substantially higher than in Hungary and Portugal (Figure 1A).

In-depth data analysis (ATC4 level analysis) showed extreme differences in the pattern of use (Figure 1B). If a penicillin was prescribed in Norway, the narrow-spectrum

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

		Hungary	Norway	Portugal
Population	All inhabitants (all ages)	9 877 365 (100.0%)	5 107 970 (100.0%)	9 869 783 (100.0%)
	0-19 y (%)	1 970 531 (19.9%)	1 256 379 (25.0%)	1 929 336 (19.5%)
	0-4 y (%)	455 202 (4.6%)	311 832 (6.1%)	426 971 (4.3%)
	5-9 y (%)	491 078 (4.9%)	310 769 (6.1%)	472 734 (4.8%)
	10-14 y (%)	479 536 (4.8%)	308 200 (6.0%)	509 777 (5.2%)
	15-19 y (%)	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 y (%)	2 495 781 (32.1%)	330 776 (15.1%)	1 459 298 (20.0%)
	0-4 y (%)	982 960 (12.7%)	111 116 (5.1%)	441 870 (6.0%)
	5-9 y (%)	647 115 (8.3%)	67 397 (3.1%)	471 822 (6.5%)
	10-14 y (%)	399 743 (5.1%)	41 473 (1.9%)	267 694 (3.7%)
	15-19 y (%)	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 y	1.3	0.3	0.8
	0-4 y	2.2	0.4	1.0
	5-9 y	1.3	0.2	1.0
	10-14 y	0.8	0.1	0.5
	15-19 y	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 y	15.1	6.8	17.7
	0-4 y	16.7	4.6	21.6
	5-9 y	14.3	3.6	22.6
	10-14 y	13.9	3.9	12.8
	15-19 y	17.3	14.9	14.8

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 1C), 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 1C). Consequently, second- and third-generation cephalosporins were commonly prescribed for Hungarian and Portuguese children.

Analysis of macrolide use (Figure 1D) 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.

The top five list of antibacterials underpins our previous findings (Table 2). In Norway, two narrow-spectrum agents, phenoxymethylpenicillin and pivmecillinam[22] were among the five most used agents, while in the other two countries all widely used agents were classified as broad-spectrum agents. Of note, the share of the top one agent, co-amoxiclav, was considerably high both in Hungary and Portugal (Table 2).

4 | DISCUSSION

This is the first study providing data on paediatric antibiotic use in Hungary and Portugal and update available Norwegian data. Moreover, this is a cross-national study which complements well what is known from aggregated international surveillance data[23,24] and can help tailor interventions.

The observed 4-fold and 2.5-fold higher overall paediatric antibiotic consumption in Hungarian and Portuguese outpatients (in number of packages/child/year) in comparison with Norwegian outpatients was not anticipated as the scale of national ambulatory antibiotic use data in Hungary and Norway is very similar according to ESAC-Net data.[23,24] Also, our results pertaining to all ages showed much smaller disparities. As paediatric antibiotic overuse can lead to serious long-term consequences as coeliac disease, inflammatory bowel disease, atopic diseases and obesity, overuse must be avoided as much as possible.[25-27] With the complementary measurement unit: DDD per 1000 children per day, the ranking was different This can be explained by the higher DDD content of packages used by younger children in Portugal compared to the other two countries and may indicate either higher doses or longer duration of treatment or simply more waste.

4.1 | Scale of use

We observed a substantial, up to 5-fold, difference in paediatric antimicrobial use in the three countries. Similar cross-national comparison studies[16,28] from various countries showed also substantial differences in antibiotic exposure: it peaked in South Korea with 3.4 prescribed courses per child-year and were lowest in the Netherlands with 0.3 prescriptions/child/year.

As written in the methods section in detail, in the two countries, Hungary and Norway (paediatrician), GPs provide care for children, while in Portugal children are managed by GPs and private paediatricians..According to national health statistics,[29] the registered number of annual consultation rates was 6731 for one paediatrician GP in Hungary, 3267 for one GP in Portugal and 320 per GP in Norway.[30] This points to the fact that the health structure and physician seeking behaviour is very different in Hungary and Portugal in comparison with Norway.

Healthcare seeking behaviour is influenced by knowledge and health beliefs.[31] A recent systematic review proved that consultation rates for paediatric infections can be decreased by educating parents.[32] The recent Eurobarometer survey showed that in Hungary and Portugal, the level of knowledge on antibiotics is low.[33] A potential explanation for low level of knowledge on antibiotics can be previous inappropriate prescribing by doctors. In Hungary, 25% of surveyed people told that they were prescribed antibiotics for sore throat, and 17% for fever, while in Portugal 22% of respondents told that they were prescribed antibiotic for the flu.[33] Misleading advertisement may also have responsibilities: in Hungary, during the previous years the over-the-counter dorithricin-containing lozenges (local antibiotic) was massively advertised on TV as a “throat-saver antibiotic” and conveyed the wrong message that antibiotics are needed to treat sore throat.

In Hungary, children with parents 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. To decrease the workload of paediatric GPs, the Hungarian government considers to increase the number of days that can be justified by parents for their children being absent from school/day care, which may indirectly lower antibiotic use. In Norway, the opposite policy for 16- to 18-year-olds was introduced recently (ie more strict absence rules), which generated a 30% increase in GP consultation rates and significantly increased antibiotic prescribing.

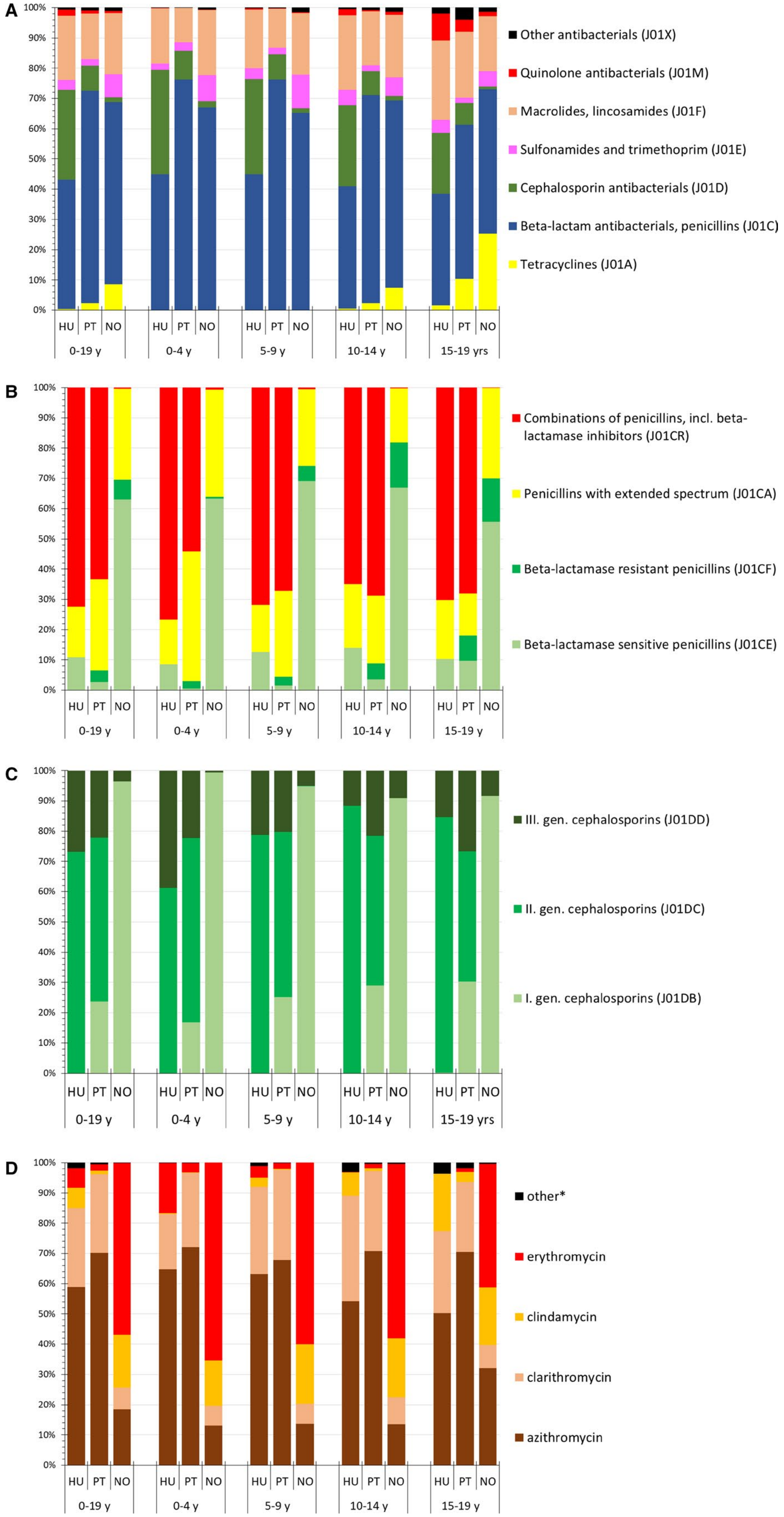

FIGURE 1 Relative consumption of antibacterial subclasses (A), penicillins (B), cephalosporins (C) and macrolides (D)

In Portugal, several measures have been taken since 2013-2014 to rationalise antibiotic use (eg Regional Control and Prevention of Antimicrobial Resistance Program (PPCIRA), guideline development and dissemination), some of these specially focusing on children. Antibiotic consumption data presented in this study may not reflect the impact of the above-mentioned measures since 2014 was the year when major changes in Portugal occurred.

Another 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. Furthermore, especially the narrow-spectrum antibiotics are cheap, and if price is influencing, this could explain the low volume of use as well as the narrow-spectrum pattern. 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 (ie low price may generate overuse).

It has been shown previously for hospital care that the higher the number of available antibacterial products, the higher the use.[34] We examined the number of available antibacterial products and the number of available antibacterial products with paediatric (liquid oral) formulations but we did not find any relation with the scale of use (Table 3).

TABLE 2 The toplist of antibacterials used (Unit: number of antibacterial packages/child/year)

Drug name	Unit	%[a]	Cumulative %[a]
Hungary			
Co-amoxiclav	0.36	28.38	28.38
Azithromycin	0.15	11.56	39.94
Cefuroxime	0.14	10.97	50.91
Amoxicillin	0.08	6.66	57.57
Cefprozil	0.08	6.01	63.58
Norway			
Phenoxymethylpenicillin	0.11	43.51	43.51
Amoxicillin	0.04	14.88	58.40
Erythromycin	0.03	13.14	71.54
Pivmecillinam	0.02	5.86	77.39
Trimethoprim	0.01	4.99	82.38
Portugal			
Co-amoxiclav	0.34	44.31	44.31
Amoxicillin	0.16	21.11	65.41
Azithromycin	0.08	10.56	75.97
Clarithromycin	0.03	3.92	79.89
Cefuroxime	0.02	2.94	82.82

[a]Total packages.

4.2 | Pattern of use

The observed differences in the patterns of use between the three countries cannot be explained by differences in bacterial resistance. For example, the penicillin resistance of a common respiratory pathogen Streptococcus pneumoniae is different in the three countries[35] as penicillin-resistant pneumococci are more prevalent in Hungary and in Portugal than in Norway. The mechanism of penicillin resistance in pneumococci is a result of alterations in penicillin-binding proteins and not due to production of beta-lactamase enzymes, so the addition of clavulanic acid to aminopenicillin will not help overcome this resistance. Moreover, all three countries have implemented a routine paediatric vaccination programme for streptococci, which may diminish the differences in pneumococci resistance. The underuse of first line penicillins in children was also recorded for Spain, Italy and South Korea.[16]

The high use of penicillin combinations 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

TABLE 3 Availability of antibacterials and antibacterial products on national markets for ambulatory care (2014)

	Hungary	Norway	Portugal
Number of antibacterial agents (exclude those that are marketed, but no use in 2014, for all ages)	56	52	36
Number of antibacterial products (exclude those that are marketed, but no use in 2014, for all ages)	247	322	413
Number of antibacterial agents available in liquid oral formulations (suspensions, syrups, oral solutions)	13	14	14
Number of liquid oral antibacterial products (suspensions, syrups, oral solutions)	36	37	78

of compulsory postgraduate courses, no incentives to prescribe more rationally, lack of feedback and the impact of pharmaceutical companies.[36] Of note, if narrow-spectrum agents (eg penicillin V) are rarely used, it will create a vicious circle, as has been the case in Hungary: the community pharmacies often do not stock them, which limits availability and hence future prescription and at the end the product will be withdrawn from the market, as happened with many narrow-spectrum penicillin products in Hungary during the last few years.[37] In Hungary and in Portugal, the convenient dosage schedule of newer cephalosporins and also macrolides is 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 (ie 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.[38]

4.3 | Strengths and limitations

The strength of this cross-national comparative study is the population coverage and the low risk of bias. We carefully checked for the potential sources of bias by the recently published Cross National Comparison checklist.[39] Also, we provided a thorough discussion of the findings. As some antibacterials (eg those with highest price from every antibiotic subgroup) are not reimbursed in Hungary, and therefore not included in the used data source, the scale of paediatric antibiotic use in Hungary is an underestimation of the real use. Age linkage may be missing for a few patients, but this limitation applies for all national databases and has a very low rate. Nevertheless, these limitations do not influence our conclusions. The differences in hospital/ambulatory care mix (especially to which healthcare sector nursing homes and long care treatment facilities belong) are also encountered as a potential source of bias in cross-national comparisons but due to the focus of this work this is irrelevant to our study.

5 | CONCLUSIONS

The scale and pattern of paediatric ambulatory antibiotic use differed largely between the three countries. Some of these differences were not anticipated at all, based on the similar scale of ambulatory antibiotic use in Hungary and Norway based on surveillance data. Portuguese and Hungarian children are exposed to more systemic antibiotics and more broad-spectrum antibiotics, while in Norway the use of newer, broad-spectrum agents is efficiently inhibited. Undesirable pattern of use (ie low consumption of narrow-spectrum agents) begins in childhood in Hungary and Portugal, which underpins the outstanding responsibility of paediatricians/paediatrician GPs to shape antibiotic use.

CONFLICT OF INTEREST

None of the authors have anything to disclose.

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