Antibiotic Use in Children – A Cross-National Analysis of 6 Countries

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Objectives To describe the rates of pediatric antibiotic use across 6 countries on 3 continents.

Study design Cross-national analysis of 7 pediatric cohorts in 6 countries (Germany, Italy, South Korea, Norway, Spain, and the US) was performed for 2008-2012. Antibiotic dispensings were identified and grouped into subclasses. We calculated the rates of antimicrobial prescriptions per person-year specific to each age group, comparing the rates across different countries.

Results A total of 74 744 302 person-years from all participating centers were included in this analysis. Infants in South Korea had the highest rate of antimicrobial consumption, with 3.41 prescribed courses per child-year during the first 2 years of life. This compares with 1.6 in Lazio, Italy; 1.4 in Pedianet, Italy; 1.5 in Spain; 1.1 in the US; 1.0 in Germany; and 0.5 courses per child-year in Norway. Of antimicrobial prescriptions written in Norway, 64.8% were for first-line penicillins, compared with 38.2% in Germany, 31.8% in the US, 27.7% in Spain, 25.1% in the Italian Pedianet population, 9.8% in South Korea, and 8% in the Italian Lazio population.

Conclusions We found substantial differences of up to 7.5-fold in pediatric antimicrobial use across several industrialized countries from Europe, Asia, and North America. These data reinforce the need to develop strategies to decrease the unnecessary use of antimicrobial agents. *(J Pediatr 2016;■■:■■-■■).*

Antimicrobial agents are the most commonly prescribed therapeutic agents in the pediatric population globally.[1,2] Antibiotic overuse is a major public health problem and the single most important factor in the emergence of antibiotic resistance among respiratory bacterial pathogens through selection pressure.[3] Recent studies have associated antibiotic use in infancy with a multitude of negative health-related consequences, including long-term reduction in microbiota diversity, increased risk for atopic diseases, obesity, and inflammatory bowel diseases.[2,4-7] Thus, as a public health policy, there is little doubt that overzealous prescribing habits and inappropriate use of antibiotics should be minimized individually and on a population level.

In recent years, as awareness of the potential adverse results associated with overuse of antibiotics are being increasingly recognized, antibiotic prescribing rates for children have declined.[8] Country-specific campaigns to promote judicious antibiotic use likely made an important contribution to this change in pediatric practice.[9,10] Nevertheless, it is still estimated that 50% of all pediatric antimicrobial prescriptions are unnecessary.[10,11] Furthermore, some evidence has emerged that the downward trend in antibiotic prescription rates in children recently has been attenuated and reached a plateau, suggesting the need for renewed focus on proper pediatric antimicrobial usage.[12]

There is great variability in the use of antimicrobial medications across countries, with the lowest prescription rates reported in northern European nations, and higher rates in southern Europe and the US.[13-15] Limited data exist that compare pediatric antibiotic consumption rates across countries, but some studies have suggested that the same global pattern exists.[1,2,10,16,17]

In the current study, we aimed to investigate the rates of pediatric antibiotic use and compare results across 6 countries, 4 in Europe, 1 in North America, and 1 in Asia.

NorPD	Norwegian Prescription Database

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Table I. Classification of antibiotics

First-line penicillin	Amoxicillin, ampicillin, dicloxacillin, oxacillin, penicillin V potassium
Second-line penicillin	Amoxicillin-clavulanate
First-generation macrolide	Erythromycin, erythromycin-sulfisoxazole
Second-generation macrolide	Azithromycin, clarithromycin, roxithromycin
Cephalosporin	Cefaclor, cefadroxil, cefdinir, cefditoren, cefixime, cefpodoxime, cefprozil, ceftibuten, cefuroxime, cephalexin, cephradine
Other	Ciprofloxacin, clindamycin, doxycycline, gatifloxacin, gemifloxacin, levofloxacin, linezolid, lomefloxacin, loracarbef, metronidazole, minocycline, moxifloxacin, nitrofurantoin, norfloxacin, ofloxacin, sulfisoxazole, telithromycin, tetracycline, trimethoprim, trimethoprim/sulfamethoxazole

Listed are the most commonly used medications from each subgroup. For a full list of medications and The Anatomical Therapeutic Chemical codes, see reference.[18]

Methods

A cross-national, retrospective analysis of 7 cohorts in 6 countries was performed for 2008-2012. Investigators in Germany, Italy, Norway, South Korea, Spain, and the US collaboratively developed a study protocol and independently selected the study cohorts. The German pediatric cohort was identified by using claims data from the Scientific Institute of the AOK. The AOK (Allgemeine Ortskrankenkassen) is the biggest German health fund, covering about 30% of the total German population. The study protocol was approved by the Institutional Review Board of the Brigham and Women's Hospital, and each participating center's institutional review board when needed. Patient informed consent was not required because datasets were de-identified, and only aggregate data was shared.

Two Italian pediatric cohorts were selected: Pedianet and the Lazio cohort. Pedianet is a population-based database that collects clinical data about pediatric patients under the care of about 300 family pediatricians throughout the country. The Lazio cohort was identified using data from public health information systems covering approximately 95% of the pediatric population registered in the Lazio Regional Health System, including information on drug claims, mortality, and hospital admissions.

Drug use data from Norway were retrieved from the Norwegian Prescription Database (NorPD), a complete register that covers all dispensed outpatient prescriptions for the entire population in Norway. Antibiotics are prescription-only medicines in Norway; hence, all antibiotics purchased from pharmacies are covered. Data from South Korea were based on complete filled prescription data from the Health Insurance Review and Assessment Service database, which includes the entire Korean population. The Spanish cohort was constructed using the claims and electronic medical records data from the Valencia Health Agency, which covers about 97% of the nearly 5 million inhabitants of the Valencia region. For the US, claims data from a nationwide commercial health insurer (United HealthCare, Hopkins, Minnesota) were used to identify the study cohort. Detailed information about the data sources can be found in the **Appendix** (available at www.jpeds.com).

All children from birth to age 18 years in the study populations (except Germany where data are provided for 2 months to 18 years of age, and Italy-Pedianet, from birth to 12 years of age) were included in the study. No exclusion criteria were applied. Years were defined as January 1 to December 31 of the calendar year and within each study year we calculated the number of subjects in each of the age categories: <3, 3-5, 6-12, and 13-18 years. A child could contribute data to only one age group in a single year based on his or her age on January 1.

Antibiotic Medications

Analyses were based on filled outpatient prescriptions. The dispensings of antibiotics were identified according to a prespecified list of National Drug Codes based on The Anatomical Therapeutic Chemical classification system, group J01 (antibacterials for systemic use).[18] Antibacterials were cross-indexed by using generic or brand name and grouped into antibiotic subclasses. Subclass groupings included first-line penicillins, second-line penicillins, first-generation macrolides, second-generation macrolides, and cephalosporins. All other antibiotics were classified as "other" (**Table I**). Antitubercular, antihelminthic, and antifungal agents, as well as topical antibiotics were excluded.

Data Analyses

Each study team independently conducted all the prespecified analyses and shared aggregate results only. We first calculated the number of total yearly cohort-specific antimicrobial prescriptions per age group. We then calculated the rates of antimicrobial prescriptions per person-year specific to each age group. Aggregate results from each participating team were then analyzed to compare the rates across different countries. We used the Pearson χ^2 test to compare the rate across the countries.

Results

During the study period (2008-2012, except for South Korea, where data were obtained from 2009 to 2011), the total number of person-years observed across all 6 countries including 7 sites was 10 880 716 for children aged <3 years; 11 560 297 for children aged 3-5 years; 29 421 539 for children aged 6-12 years; and 24 324 993 for children aged 13-18 years (**Table II**).

Children in South Korea had the highest rate of antimicrobial consumption, with 3.41 prescribed courses per child-year during the first 2 years of life and 2.62 courses per child-year between ages 3 and 5, decreasing to 0.74 and 0.32 courses per child-year at ages 6-12 and 13-18, respectively. Among children aged 0-2 years, the rate of antimicrobial consumption per child-year was 1.6 in Lazio, Italy and 1.4 in Pedianet, Italy, 1.5 in Spain, 1.1 in the US, 1.0 in Germany, and the lowest, at 0.5,

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Table II. Antibiotic courses per child-year in participating countries (2008-2012*)

Age groups	Country	No. of subjects	Prescribed antimicrobial courses per child-year
0-2 years	US	1 502 945	1.06
	Korea	3 666 303	3.41
	Italy (L)	872 767	1.62
	Italy (P)	162 869	1.38
	Germany	3 035 082	1.04
	Spain	717 618	1.55
	Norway	923 132	0.45
3-5 years	US	1 604 146	1.05
	Korea	4 024 356	2.63
	Italy (L)	865 379	1.40
	Italy (P)	164 327	1.55
	Germany	3 234 164	0.98
	Spain	753 981	1.05
	Norway	913 944	0.44
6-12 years	US	4 074 074	0.66
	Korea	11 565 635	0.74
	Italy (L)	1 653 508	0.75
	Italy (P)	268 260	0.76
	Germany	8 150 566	0.52
	Spain	1 579 772	0.52
	Norway	2 129 724	0.21
13-18 years	US	3 082 213	0.67
	Korea	9 527 049	0.32
	Italy (L)	1 974 319	0.53
	Germany	8 298 169	0.58
	Norway	1 443 243	0.28

Italy (L), Lazio region; *Italy (P)*, Pedianet database.
For full information about the participating countries see **Appendix**.
*Data for Korea are for 2009-2011.

in Norway. For children aged 0-2, compared with Norway, the relative antimicrobial prescription rate per child-year was 7.57 in South Korea, 3.44 in Spain, 3.61 in Lazio, Italy, 3.07 in Pedianet, Italy, 2.35 in the US, and 2.31 in Germany (**Table III**).

Antimicrobial Group-Specific Consumption

Considering all age groups from birth to 12 years of age, 64.8% of antimicrobial prescriptions in Norway were for first-line penicillins, compared with 39.6% in Germany, 31.8% in the US, 25.3% in Spain, 26.5% in the Italian Pedianet population, 9.8% in South Korea, and 8.5% in the Italian Lazio population. Second-line penicillins were the most commonly used antimicrobial agent in South Korea (44.8%), Italy (40.9% and 30.6% of prescriptions in Lazio and Pedianet, respectively), and Spain (35.1%). Only 8.5% of prescriptions in the US, 2.2% in Germany, and 0.1% in Norway were for second-line penicillins. First-generation macrolides were used uncommonly, except in Norway and Germany (15.8% and 9.2% of prescriptions, respectively). Second-generation macrolides constituted 25% of the US prescriptions, 24.1% in Lazio, Italy, 21.3% in Pedianet, Italy, 18.6% in Spain, and 17.5% of South Korean antimicrobial agents prescribed. Cephalosporins were commonly used in Germany (35.2%), the US (26.4%), South Korea (26.2%), Italy (Lazio 25.8% and Pedianet 21.3%), and Spain (20.1%), whereas their use was reported rarely from Norway (1.7%). Summarizing data from all participating countries, the most commonly used antimicrobial agent was second-line penicillin (31.1% of all prescriptions), followed by cephalosporins (26.7%) and first-line penicillins (19.5%) (**Table IV**).

Discussion

This study presents comprehensive comparative person-specific data on rates of antimicrobial prescription among pediatric populations in 6 countries on 3 continents. Our results showed significant between-country variability, with prescription rates being highest in South Korea, followed by Italy, Spain, and the US. Norway and Germany had the lowest prescription rates across all age groups.

Previous reports from South Korea, mainly relying on adult data, have shown consistently high antimicrobial consumption rates.[19] However, our current findings, suggesting that an average toddler in South Korea is prescribed 3.41 antimicrobial courses a year, a rate that is 7.5-fold the prescription rate in Norway, are surprising in their magnitude. It has been shown previously that South Korea has extremely high rates of antibiotic resistance.[20,21] Subsequently, legislation aimed at reducing antibiotic overuse was passed in 2000 and 2006, but overuse still seems to be prevailing, as also has been described in other countries in East Asia.[22,23]

Within the remainder of our cohort, significant differences in antimicrobial consumption rates also were

Table III. Relative rates of antimicrobial use per child-year in participating centers among children 0-2 years of age (2008-2012*)

		Korea	Italy (L)	Spain	Italy (P)	US	Germany	Norway
		3.41	1.62	1.55	1.38	1.06	1.04	0.45
Korea	3.41	1.000	2.097	2.199	2.463	3.216	3.272	7.566
Italy (L)	1.62	0.477	1.000	1.048	1.174	1.533	1.560	3.607
Spain	1.55	0.455	0.954	1.000	1.120	1.463	1.488	3.441
Italy (P)	1.38	0.406	0.851	0.893	1.000	1.306	1.328	3.072
US	1.06	0.311	0.652	0.684	0.766	1.000	1.018	2.353
Germany	1.04	0.306	0.641	0.672	0.753	0.983	1.000	2.312
Norway	0.45	0.132	0.277	0.291	0.326	0.425	0.432	1.000

For full information about the participating centers see **Appendix**.
*Data for Korea are for 2009-2011.

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Table IV. Antibiotic use by subgroup in the study period

Ages, yrs	Country	No. of prescribed antimicrobial courses	First-line penicillin (%)	Second-line penicillin (%)	First-generation macrolide (%)	Second-generation macrolide (%)	Cephalosporin (%)	Other (%)
0-2	US	1 591 500	36.6	6.3	0.2	19.0	29.1	8.8
	Korea	12 485 617	11.4	45.2	0.5	16.5	25.3	1.0
	Italy (L)	1 417 118	11.9	39.6	0.0	23.2	24.7	0.5
	Italy (P)	212 504	31.2	29.1	0.1	17.8	21.7	0.1
	Germany	3 091 583	36.2	2.2	10.8	7.4	42.2	1.1
	Spain	1 111 468	27.7	34.4	0.3	16.7	20.6	0.3
	Norway	415 495	66.6	0.1	16.4	5.5	1.8	9.6
	Total	20 325 285	19.4	33.6	2.3	15.6	27.4	1.7
3-5	US	1 676 435	28.3	11.0	0.1	25.3	26.9	8.4
	Korea	10 584 628	9.7	48.0	0.5	18.3	22.3	1.2
	Italy (L)	1 212 348	6.2	42.9	0.0	24.2	26.2	0.5
	Italy (P)	240 998	24.8	30.8	0.1	21.9	22.3	0.0
	Germany	3 082 249	41.3	2.1	9.7	9.5	35.9	1.5
	Spain	792 447	24.1	35.0	0.3	18.5	21.6	0.5
	Norway	397 936	63.5	0.1	15.5	5.9	1.7	13.3
	Total	17 987 041	18.6	34.5	2.3	17.6	24.8	2.1
6-12	US	2 683 736	31.3	8.2	0.1	28.3	24.5	7.6
	Korea	8 588 244	7.8	40.3	0.5	17.7	32.1	1.6
	Italy (L)	1 248 015	6.7	40.5	0.0	25.0	26.7	1.1
	Italy (P)	192 356	23.6	32.0	0.2	24.5	19.6	0.2
	Germany	4 060 969	40.8	2.1	7.6	16.6	29.4	3.5
	Spain	827 916	23.3	36.0	0.4	21.1	18.0	1.2
	Norway	454 012	64.1	0.1	15.6	5.2	1.5	13.5
	Total	18 055 248	20.9	25.6	2.4	19.4	28.4	3.2
13-18	US	2 071 453	16.6	6.1	0.1	26.5	16.4	34.2
	Korea	3 026 074	6.1	31.6	0.6	12.5	43.8	5.5
	Italy (L)	1 038 254	6.7	35.2	0.1	27.0	20.9	10.0
	Germany	4 555 020	30.6	2.2	1.5	26.0	17.5	22.3
	Norway	567 542	48.3	0.0	11.3	9.5	1.1	29.8
	Total	10 962 743	18.2	14.1	0.8	21.8	24.4	18.2
0-12	US	5 951 671	31.8	8.5	0.1	25.0	26.4	8.1
	Korea	31 658 489	9.8	44.8	0.5	17.5	26.2	1.2
	Italy (L)	3 877 481	8.5	40.9	0.0	24.1	25.8	0.7
	Italy (P)	645 858	26.5	30.6	0.1	21.3	21.3	0.1
	Germany	10 234 801	39.6	2.2	9.2	11.7	35.2	2.2
	Spain	2 731 831	25.3	35.1	0.3	18.6	20.1	0.6
	Norway	1 267 443	64.8	0.1	15.8	5.5	1.7	12.1
	Total	56 367 574	19.6	31.3	2.3	17.5	26.9	2.3

observed, with 0- to 2-year-olds from the Lazio region in Italy and Valencia, Spain, consuming an average of 1.62 and 1.55 antibiotic courses per year, respectively, about 3.5 times the rate of consumption of 0.45 per child-year described in Norway. Similar trends were observed across all age groups. Global patterns of antimicrobial use in pediatric patients are similar to those described among adults, with higher prescription rates in Asian and Southern European countries, followed by the US and central European countries, and the lowest rates in Scandinavia and other Northern European countries.[13,15,24,25]

In general, in countries with lower antimicrobial prescription rates, a higher proportion of narrow-spectrum agents are used, perhaps reflecting an overall pattern of conservatism in antibiotic use. Thus, among all pediatric antimicrobial prescriptions in Norway, 64% are first-line penicillins, whereas in South Korea, Spain, and Italy the most commonly prescribed agent was a second-line penicillin, mostly amoxicillin with clavulanic acid (this combination is regulated in the Norwegian market, and prescribers must submit a special application, which might explain its extremely limited use). Similarly, high use of second-generation macrolides (most commonly azithromycin) was seen in the US (25% of prescriptions), Italy (23%), Spain (18.6%), and South Korea (17.5%) in contrast with Germany (14%) and Norway (6%). It is easy to understand why, in countries with higher resistance rates, providers are more inclined to prescribe broad-spectrum antimicrobial agents. However, this prescribing pattern exerts constant selection pressure, encouraging the development of increasing resistance.[26-29] Furthermore, a healthy and diverse gut microbiome has been shown to have a central role in maintaining health, and its perturbation has been associated with a variety of disease states.[30] Studies have shown the detrimental effects of antibiotics on the microbial gut variability, lasting for up to 18 months after antibiotic use,[31] suggesting that the use of narrow-spectrum antimicrobial agents, with less "collateral damage," may have this additional clinical benefit.

The main strength of our study lies in the use of large population-based datasets, covering national or regional populations, maximizing the generalizability of the findings. However, limitations should be noted. First, even though each study site worked from individual-level patient data, the combined dataset on which the current analysis is based did not

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assess the extent to which antibiotic use was linked with repeat administration to the same patients. Previous pediatric population-based studies have shown that "heavy antibiotic users" contribute little to the overall prescription rates,[32] and this is unlikely to explain the differences in rates we observed. Second, we were unable to link the antimicrobial prescriptions to specific recorded diagnoses, and thus could not ascertain the appropriateness of individual prescriptions. However, even a recorded diagnosis of "otitis media" cannot be used to validate the actual presence of that condition. In addition, the use of antibiotics for this condition, even when it is known to be present, remains controversial. Previous studies have found similar rates of bacterial infections requiring antimicrobial prescriptions in a comparison that included several of our participating countries. Thus, our finding of marked differences in usage rates across different countries suggests that physicians in many areas of the world still prescribe antimicrobial agents inappropriately. Finally, comparing antimicrobial use between countries is plagued by inconsistencies in units of measurement.[33] In adult studies, this is addressed most commonly by using daily defined doses of medication. The weight-based dosing in children makes this approach impractical, and the World Health Organization has recommended against the use of daily defined doses in pediatric studies.[34] Accordingly, experts have recommended using alternative measures such as number of packages or prescriptions.[32,35] In our study we used data on the number of antibiotic prescriptions. Although these data do not provide an exact quantitative measure of use, they provides useful metrics for assessing antimicrobial prescribing practices between countries.

These data showing up to 7.5-fold differences in pediatric antimicrobial use across several industrialized countries from Europe, Asia, and North America reinforce the need to develop strategies to decrease the unnecessary use of antibiotics. Cross-national prescription data such as these can be a useful tool to inform future efforts. ■

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Appendix

South Korea

Data from South Korea were based on National Patients Sample database by the Health Insurance Review and Assessment Service from January 1, 2009, to December 31, 2011. These Health Insurance Review and Assessment-National Patients Sample data, a nationally representative sample of whole National Health Insurance claims data, were constructed using a sex- and age-stratified random sampling from approximately the entire 50 million Koreans. The database contains anonymized codes representing each individual together with information on patients (age, sex, diagnoses), medical institutions (type of institution, region), physician specialties, medical procedures, and prescribed drugs. Information on prescribed drugs included generic name, domestic medicine code, prescription date, quantity, strength, and route of administration. All diagnoses are recorded using the *International Classification of Diseases, Tenth Revision, Clinical Modification*.

Italy – Pedianet

Pedianet is an Italian population-based, nationwide database that collects demographic and clinical data, including drug prescriptions, clinical diagnoses, diagnostic tests, and specialist referrals, for children who are under the care of about 300 family pediatricians throughout the country. Data are generated during routine patient care with the software JuniorBit (Sosepe, Padova, Italy) and are stored in separate files that can be linked through a unique anonymous patient identifier. The parents of the children included in the database provide written informed consent for their data to be collected and used for research purpose.

Italy – Lazio

The Lazio cohort was identified using data from public health information systems covering approximately 95% of the pediatric population registered in the Lazio Regional Health System, including information on drug claims, mortality, and hospital admissions.

Germany

German data were contributed by the "Scientific institute of the AOK." The AOK is the biggest health fund in Germany, covering about 24 million insurants (approximately 30% of the German population). The database includes demographic patient data such as age, sex, and residence, as well as claims data from ambulatory and inpatient care and data on drug prescriptions (date of prescription, type, and amount of dispensed drug). For the current study, antibiotic courses were defined by the date of an antimicrobial prescription.

Norway

Data on the use of antibiotics in Norwegian children are retrieved from the NorPD, a nationwide prescription database covering the whole population of Norway. The database collects all prescriptions being dispensed to outpatients in Norway since January 1, 2004. The Norwegian Institute of Public Health hosts the database.

Through the national personal identification number, the prescription data are linked to sociodemographic data such as age and sex. Drugs dispensed at hospitals and nursing homes are registered, but at an institutional base and these data cannot be linked to the individual use in outpatients. Therefore, antibiotics used in institutions are not included in this analysis.

In Norway, antibiotics are prescription-only drugs and all dispensed antibiotics to individuals are captured in NorPD. The data from NorPD gives us the exact population prevalence of antibiotic use in ambulatory care. More information on NorPD is available at www.fhi.no.

As a main rule, antibiotics are not reimbursed. Exceptions are antibiotics for chronic infections and infections regarded to be threat to public health (e.g., tuberculosis). The proportion of antibiotic prescriptions being reimbursed in 2012 were 3.5%, 4.1%, 5.4%, and 6.5%, respectively, for age groups <3 years, 3-5 years, 6-12 years, and 13-18 years.

US

The US cohort included enrollees in United HealthCare, a commercial US health plan. This plan insures primarily working adults and their family members. The database contains longitudinal claims information including medical diagnoses, procedures, hospitalizations, physician visits, and pharmacy dispensing on its approximately 14 million subscribers across the US on a yearly basis.

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