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RESEARCH

Drug use in children: cohort study in three European countries

Miriam C J M Sturkenboom, professor in analysis of observational data,[1,2] Katia M C Verhamme, assistant professor in pharmacoepidemiology,[1] Alfredo Nicolosi, director, senior associate research scientist,[3,4] Macey L Murray, teaching and research fellow,[5] Antje Neubert, postdoctoral research fellow,[5] Daan Caudri, researcher,[1] Gino Picelli, analyst,[6] Elif Fatma Sen, PhD student,[1] Carlo Giaquinto, head of clinical research unit,[7] Luigi Cantarutti, director,[8] Paola Baiardi, director,[9] Maria-Grazia Felisi, researcher,[9] Adriana Ceci, scientific coordinator,[9] Ian C K Wong, professor of paediatric medicines research,[5] on behalf of the TEDDY European Network of Excellence

[1]Department of Medical Informatics, Erasmus University Medical Centre, 3000 CA Rotterdam, Netherlands
[2]Department of Epidemiology, Erasmus University Medical Centre, Rotterdam, Netherlands
[3]Department of Epidemiology and Medical Informatics, Institute of Biomedical Technologies, National Research Council, 20090 Segrate, Milan, Italy
[4]GH Sergievsky Center, School of Public Health, Columbia University, New York, NY 10032, US
[5]Centre for Paediatric Pharmacy Research, School of Pharmacy and Institute of Child Health, University of London, London WC1N 1AX
[6]International Pharmacoepidemiology and Pharmacoeconomics Research Centre, 20033 Desio, Italy
[7]Department of Paediatrics, University Hospital, Padua, Italy
[8]Società Servizi Telematici 35138 Padua, Italy
[9]Consorzio per Valutazioni Biologiche e Farmacologiche, 27100 Pavia, Italy

Correspondence to:
M C J M Sturkenboom
m.sturkenboom@erasmusmc.nl

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ABSTRACT

Objective To provide an overview of drug use in children in three European countries.

Design Retrospective cohort study, 2000-5.

Setting Primary care research databases in the Netherlands (IPCI), United Kingdom (IMS-DA), and Italy (Pedianet).

Participants 675 868 children aged up to 14 (Italy) or 18 (UK and Netherlands).

Main outcome measure Prevalence of use per year calculated by drug class (anatomical and therapeutic). Prevalence of "recurrent/chronic" use (three or more prescriptions a year) and "non-recurrent" or "acute" use (less than three prescriptions a year) within each therapeutic class. Descriptions of the top five most commonly used drugs evaluated for off label status within each anatomical class.

Results Three levels of drug use could be distinguished in the study population: high (>10/100 children per year), moderate (1-10/100 children per year), and low (<1/100 children per year). For all age categories, anti-infective, dermatological, and respiratory drugs were in the high use group, whereas cardiovascular and antineoplastic drugs were always in the low use group. Emollients, topical steroids, and asthma drugs had the highest prevalence of recurrent use, but relative use of low prevalence drugs was more often recurrent than acute. In the top five highest prevalence drugs topical inhaled and systemic steroids, oral contraceptives, and topical or systemic antifungal drugs were most commonly used off label.

Conclusion This overview of outpatient paediatric prescription patterns in a large European population could provide information to prioritise paediatric therapeutic research needs.

INTRODUCTION

Recent years have seen growing concerns about the incompleteness of the evidence relating to the efficacy and safety of drugs used in children. Almost all of the drugs prescribed to children are the same as those originally developed for adults. They are often prescribed on an unlicensed or "off label" basis (percentages ranging from 11-80%[1]) simply by extrapolating data for adults, without conducting any paediatric clinical, kinetic, dose finding, or formulation studies in children. Diseases in children, however, might be different from their adult equivalents, and the processes underlying growth and development might lead to a different effect or an adverse drug reaction unseen in adults (Reye's syndrome is an outstanding example).

To provide legitimate and appropriate treatment for children's diseases, new legislation was approved in the United States in 2003 and the European Union in 2007.[2] Both the Food and Drug Administration (FDA) and the European Medicines Agency for the Evaluation of Medicinal Products (EMEA) now offer extensions of drug licences to companies who provide evidence concerning the efficacy and safety in children of new drugs or off label drugs.[3-6] The World Health Organization underlines the need for these actions and in December 2007 launched a global campaign to "make medicines child size" to address the need for improved availability and access to safe child specific medicines for all children.[7]

We investigated the current use of paediatric drugs in children in three European countries, using population based data on primary care prescriptions.

METHODS

Setting

The primary care of children is entrusted to general practitioners in the UK and the Netherlands and to paediatricians in Italy.[8,9] Access to health care is free in Italy and the UK and fully covered by healthcare insurance in the Netherlands. In these countries, primary care physicians are responsible for children's health care, which means that all clinical information

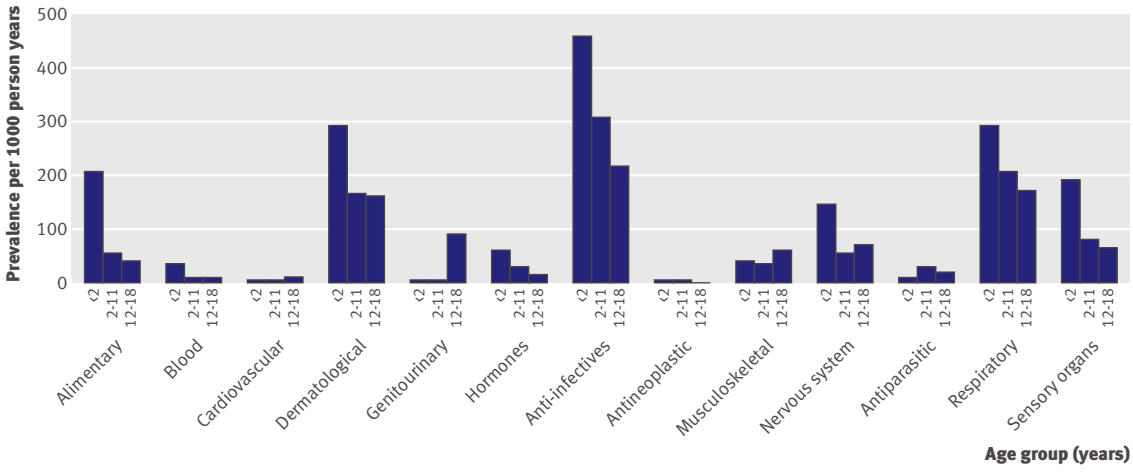

Fig 1 | One year prevalence of drug prescriptions by age (<2, 2-11, 12-18 years), and anatomical class

concerning the patients (including summaries of specialist and hospital care) is kept in their medical records. As all children need to be registered with a general practitioner in the Netherlands and UK and with a family paediatrician in Italy, the databases are population based.[9]

Data collection

We used the same protocol to study prescription patterns in the three countries, making use of the Pedianet database (paediatric electronic medical records from 150 paediatricians since 2000) in Italy,[10] the integrated primary care information (IPCI) database (comprising adult and paediatric electronic medical records from more than 400 doctors since 1996) in the Netherlands,[8 11 12] and the IMS disease analyser database (IMS-DA: electronic medical records on adults and children from 670 doctors) in the UK.[13] All of these databases include the complete automated medical records of primary care physicians and have been used and proved valid for pharmacoepidemiological research.[9] The age and sex distribution in the various databases is representative for the country of origin.

Study population and drug prescriptions

The dynamic study population in each country consisted of all children aged 0-18 years (0-14 years in Italy) who had a database history of at least six months or who were born during the study period (1 January 2000 to 31 December 2005). We calculated the person time of follow-up for each child, stratified by calendar year and age group. Age was assessed on 1 January of each year and grouped according to the guidelines of the International Conference of Harmonization (ICH) as <2, 2-11, and 12-18.[14] We could not further stratify the youngest age category into newborns (<1 month) and infants (1-24 months) as exact dates of birth were not available because of privacy regulations. Each child was followed from the start of the study period or the date of registration with the primary practice (whichever was the latest) until the cancellation of registration with the practice or the end of the study period. We used the person time accumulated in each calendar year as the denominator to calculate prevalence rates. Over the study period children could contribute to more than one age category.

All prescribed drugs in children during follow-up were retrieved from the prescription data in the database. The drug prescriptions were grouped on the basis of the WHO Anatomical Therapeutic Chemical (ATC) classification system, which made comparison between countries possible.

Statistical analysis

We estimated user prevalence rates (per 1000 person years) by counting the number of children using a specific drug in a specific calendar year. The prevalence rates were calculated by age and country to account for differences in distributions between populations and to allow for direct comparisons within groups. User prevalence rates should be interpreted as the number of children per 1000 who use a specific class of drug in one year. We could not calculate prevalence of drug use for children aged 15-18 in Italy because all of children were censored at the age of 15. We used person years rather than individuals as the denominator because of the dynamic nature of age and the population.

For each anatomical class of drug we assessed the age and country specific user prevalence rates for all individual drugs in 2005. We evaluated the five drugs with the highest prevalence per anatomical class in each country for off label status considering age only. A drug was considered to be off label for age if the child's age at the time of use was below the lowest approved age mentioned in the summary of product characteristics of that drug in each country.[15] Within each therapeutic drug level, we separately estimated the prevalence of children presenting "recurrent/chronic" (three or more prescriptions a year) versus "non-recurrent" or "acute" drug use (less than three prescriptions a year), and the ratio between them to

identify the treatments more commonly used for chronic than acute paediatric diseases. We used χ^2 test to compare user prevalence rates.

RESULTS

Study population

Our population of 675 868 children generated 2 334 673 person years of follow-up (table 1); the mean individual follow-up was 3.5 years. Most of the children (66%) came from the IMS database in the UK, 19% from Italy, and 15% from the Netherlands. The databases recorded more than five million paediatric prescriptions. In all three countries the prescription rate was highest for the children aged under 2 and, in each age group, was significantly higher in the UK and Italy than in the Netherlands (P<0.001) (table 1).

Table 1 | Characteristics of study population

Patients	No of children*	No (%) of person years	No of prescriptions	Prescriptions/ person year
Italy				
<2 years	56 000	87 408 (22)	286 597	3.3
2-11 years	103 195	296 148 (73)	690 688	2.3
12-14 years	18 154	22 599 (6)	35 883	1.6
Females	61 962	194 744 (48)	462 580	2.4
Males	67 525	211 412 (52)	550 588	2.6
2000	11 188	369 (0)	1150	3.1
2001	73 364	45 330 (11)	140 764	3.1
2002	95 712	78 850 (19)	220 207	2.8
2003	103 987	94 131 (23)	242 261	2.6
2004	106 555	96 388 (24)	206 535	2.1
2005	102 911	91 086 (22)	202 251	2.2
Total	129 487	406 156 (100)	1 013 168	2.5
UK				
<2 years	95 060	106 250 (6)	494 353	4.7
2-11 years	262 306	855 678 (52)	2 011 153	2.4
12-18 years†	229 959	683 900 (42)	1 549 372	2.3
Females	219 669	804 646 (49)	2 047 616	2.5
Males	225 153	841 182 (51)	2 007 262	2.4
2000	307 884	288 450 (18)	659 067	2.3
2001	306 923	286 483 (17)	677 373	2.4
2002	305 088	285 664 (17)	670 690	2.3
2003	303 594	280 085 (17)	679 216	2.4
2004	287 287	259 219 (16)	674 389	2.6
2005	265 273	245 927 (15)	694 143	2.8
Total	444 822	1 645 828 (100)	4 054 878	2.5
Netherlands				
<2 years	25 694	36 601 (13)	78 983	2.2
2-11 years	62 326	159 010 (56)	208 134	1.3
12-18 years	40 364	87 078 (31)	147 250	1.7
Females	49 709	138 262 (49)	230 466	1.7
Males	51 850	144 427 (51)	203 901	1.4
2000	56 423	48 752 (17)	76 319	1.6
2001	53 274	46 822 (17)	76 059	1.6
2002	57 998	50 219 (18)	81 919	1.6
2003	62 216	49 279 (17)	73 462	1.5
2004	60 315	50 882 (18)	75 399	1.5
2005	52 252	36 735 (13)	51 209	1.4
Total	101 559	282 689 (100)	434 367	1.5

*Number of children in various age groups does not add up to total as one child can contribute to more than one category.

Drug use by anatomical class

The highest prevalence rates among the children aged under 2 were for anti-infective drugs, respiratory drugs, and dermatological drugs, which were used by 48%, 30%, and 30% of the children, respectively (fig 1). The other common prescriptions were for gastrointestinal drugs (user prevalence of 20%), drugs for the nervous system (14%) and drugs for sensory organs (19%). Blood and blood forming organs, hormonal, and musculoskeletal system drugs were used in 1-10% of the children, and cardiovascular, genitourinary, antineoplastic, and antiparasitic drugs by less than 1%.

Among the children aged 2-11, the prevalence of use of anti-infective, respiratory, and dermatological drugs decreased to 30%, 21%, and 17%, respectively. The prevalence was 1-10% for gastrointestinal, hormonal, musculoskeletal system, nervous system, antiparasitic, and sensory organ drugs; and less than 1% for blood and blood forming organs, cardiovascular, genitourinary, and antineoplastic drugs.

In adolescents (12-18 years), anti-infective, respiratory, and dermatological drugs were used by more than 10% per year. Most of the other drug classes were used by 1-10%, but the prevalence of use of cardiovascular and antineoplastic drugs was less than 1%.

Regarding sex differences, in the youngest age groups, most of the drugs were equally prescribed to both sexes or more commonly prescribed to boys than girls (rate ratio <1), particularly anti-infective and respiratory drugs. This pattern reversed in adolescence, when user prevalence for almost all drug classes (except non-sex hormones) was higher among girls than boys. This sex pattern, which was consistent across countries, was most pronounced for genitourinary drugs, with a user prevalence more than 60 times higher in girls because they include oral contraceptives, which accounted for 95% of the use of genitourinary drugs in girls. The use of drugs for blood and blood forming organs (mainly iron preparations) was also markedly higher among adolescent girls.

The age trend of prevalence of use was consistent across countries, although there were some variations in the age specific rates (fig 2). In particular, the UK showed the highest prevalence of alimentary drug use in children aged under 2, and the prevalence of prescriptions of dermatological drugs was threefold to fourfold higher in the UK and the Netherlands than in Italy (both P<0.001). The prevalence of genitourinary drug use (almost all oral contraceptives) was high in adolescent girls in the Netherlands (P<0.001). In Italy, the use of hormones (almost all systemic corticosteroids) was 10-fold higher in children aged <2 (P<0.001) and fivefold higher in those aged 2-11 (P<0.001); respiratory drug use was also greater in Italy than in the other two countries (P<0.001). The prevalence of the use of anti-infective drugs and drugs for musculoskeletal disorders was much lower in the Netherlands; the prevalence of prescriptions for

Table 2 | **Prevalence of acute use (<3 prescriptions per year) and recurrent use (≥3 prescriptions per year) by age and therapeutic level (prevalence per 1000 person years), ranked by the ratio of recurrent to acute use***

Anatomical and therapeutic class (ATC)	Acute use				Recurrent use				Ratio recurrent/ acute	Total prevalence
	<2	2-11	12-18	All ages	<2	2-11	12-18	All ages		
Gastrointestinal										
Drugs used in diabetes (A10)	0.0	0.2	0.3	0.2	0.0	0.9	2.5	1.3	7.0	1.5
Digestives, including enzymes (A09)	0.1	0.0	0.0	0.0	0.1	0.2	0.2	0.2	4.9	0.2
Bile and liver therapy (A05)	0.1	0.0	0.0	0.0	0.1	0.1	0.1	0.1	1.7	0.1
Mineral supplements (A12	1.1	0.8	0.5	0.7	0.2	0.3	0.2	0.2	0.3	1.0
Laxatives (A06)	24.7	13.3	6.2	12.0	3.3	4.7	1.8	3.6	0.3	15.6
Drugs for acid related disorders (A02)	27.0	3.5	9.6	7.9	12.6	0.8	1.7	2.3	0.3	10.1
Vitamins (A11)	24.2	3.6	1.4	4.9	3.5	0.7	0.5	0.9	0.2	5.8
Antiemetics and antinausea (A04)	1.4	0.6	3.7	1.8	0.7	0.1	0.2	0.2	0.1	2.0
Drugs for functional gastrointestinal disorders (A03)	25.9	10.6	9.7	11.8	1.4	0.4	0.9	0.6	0.1	12.4
Stomatological preparations (A01)	56.3	6.6	4.2	10.7	3.2	0.2	0.2	0.5	0.0	11.2
Antidiarrhoeal (A07)	64.9	11.6	3.2	14.0	1.9	0.3	0.6	0.5	0.0	14.5
Blood and blood forming organs										
Antithrombotic agents (B01)	0.2	0.2	0.3	0.3	0.2	0.3	0.3	0.3	1.1	0.5
Antianaemic preparations (B03	20.8	3.6	6.8	6.4	2.9	0.5	1.2	1.0	0.2	7.4
Antihaemorrhagics (B02)	5.5	1.0	1.6	1.6	0.2	0.1	0.2	0.1	0.1	1.8
Cardiovascular system										
Agents acting on renin-angiotensin system (C09)	0.1	0.1	0.1	0.1	0.1	0.2	0.3	0.2	2.5	0.3
Lipid modifying agents (C10)	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.1	1.7	0.1
Diuretics (C03)	0.6	0.1	0.1	0.2	0.6	0.1	0.2	0.2	1.2	0.4
Calcium channel blockers (C08	0.0	0.0	0.2	0.1	0.0	0.0	0.2	0.1	0.8	0.2
β blocking agents (C07	0.1	0.2	2.2	0.8	0.1	0.2	0.7	0.3	0.4	1.2
Cardiac therapy (C01)	1.3	2.2	1.6	1.9	0.2	0.3	0.3	0.3	0.2	2.2
Dermatological										
Anti-acne preparations (D10)	0.3	1.0	31.2	11.2	0.0	0.1	15.0	5.2	0.5	16.3
Emollients and protectives (D02)	98.8	45.1	25.6	43.8	48.5	21.8	8.1	19.8	0.5	63.6
Antipsoriatics (D05)	3.9	3.1	4.8	3.7	0.2	0.5	2.0	1.0	0.3	4.7
Corticosteroids, dermatological preparations (D07)	140.4	74.1	55.9	74.4	24.4	11.9	8.7	12.0	0.2	86.5
Preparations for treatment of wounds and ulcers (D03)	1.1	0.7	1.0	0.8	0.0	0.1	0.1	0.1	0.1	0.9
Antiseptics and disinfectants (D08)	3.9	2.4	2.8	2.7	0.1	0.1	0.2	0.1	0.1	2.8
Antifungals for dermatological use (D01)	50.8	18.4	19.6	22.0	1.6	0.6	1.5	1.0	0.0	23.0
Antibiotics and chemotherapeutics (D06)	43.6	36.4	23.6	32.8	0.8	0.9	0.9	0.9	0.0	33.7
Other dermatological preparations (D11)	5.3	8.9	9.8	8.9	0.2	0.1	0.4	0.2	0.0	9.1
Genitourinary system and sex hormones										
Sex hormones, modulators of genital system (G03)	1.7	0.4	32.3	11.3	0.3	0.1	49.7	17.0	1.5	28.3
Urologicals (G04)	0.5	1.1	1.8	1.3	0.1	0.6	0.6	0.5	0.4	1.8
Gynaecological anti-infectives and antiseptics (G01)	1.1	1.3	9.2	4.0	0.0	0.0	0.5	0.2	0.0	4.2
Systemic hormonal preparations, excluding sex hormones and insulins										
Thyroid therapy (H03)	0.3	0.2	0.3	0.2	0.4	0.5	1.1	0.7	3.1	0.9
Pituitary and hypothalamic hormones (H01)	0.1	2.2	1.5	1.7	0.0	1.3	1.4	1.2	0.7	3.0
Corticosteroids for systemic use (H02)	51.0	23.2	8.0	20.7	6.0	2.2	1.0	2.2	0.1	22.9
Pancreatic hormones (H04)	0.0	0.3	0.7	0.4	0.0	0.0	0.1	0.0	0.1	0.4
Anti-infectives for systemic use										
Antibacterials for systemic use (J01)	340.0	241.4	166.3	225.6	95.2	47.0	27.6	45.2	0.2	270.7
Antimycobacterials (J04)	0.5	0.5	0.3	0.4	0.1	0.0	0.0	0.0	0.1	0.5
Vaccines (excluding routine childhood vaccinations) (J07)	11.8	10.6	14.3	12.0	0.8	0.4	1.0	0.6	0.1	12.6
Antimycotics for systemic use (J02)	1.1	0.6	3.7	1.7	0.0	0.0	0.2	0.1	0.0	1.8
Antivirals for systemic use (J05)	9.8	4.2	1.7	3.9	0.1	0.0	0.1	0.1	0.0	4.0
Antineoplastic and immunomodulating drugs										
Immunosuppressive agents (L04)	0.0	0.0	0.1	0.1	0.0	0.1	0.4	0.2	3.8	0.3
Antineoplastic agents (L01)	0.0	0.1	0.1	0.1	0.0	0.1	0.1	0.1	0.9	0.2
Musculoskeletal system										
Muscle relaxants (M03)	0.1	0.1	0.2	0.1	0.0	0.1	0.2	0.2	1.7	0.2
Anti-inflammatory and antirheumatic products (M01)	38.8	32.0	53.6	40.0	1.2	1.2	3.0	1.8	0.0	41.8
Nervous system										
Antiepileptics (N03)	0.7	0.7	0.8	0.7	1.1	2.6	3.6	2.8	3.9	3.5
Psychoanaleptics (N06)	0.1	1.1	6.8	2.9	0.0	1.7	6.8	3.3	1.1	6.2

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Table 2 cont

Anatomical and therapeutic class (ATC)	Acute use				Recurrent use				Ratio recurrent/ acute	Total prevalence
	<2	2-11	12-18	All ages	<2	2-11	12-18	All ages		
Antiparkinsonian (N04)	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	1.1	0.1
Psycholeptics (N05)	7.3	2.2	5.0	3.6	0.4	0.4	1.6	0.8	0.2	4.5
Other nervous system drugs (N07)	0.1	0.2	2.0	0.8	0.0	0.0	0.4	0.2	0.2	1.0
Analgesics (N02)	109.9	55.0	38.7	54.9	24.2	8.5	5.6	9.0	0.2	63.9
Anaesthetics (N01)	2.1	4.2	4.2	4.0	0.1	0.1	0.2	0.1	0.0	4.1
Antiparasitic products										
Ectoparasiticides (P03)	2.9	14.9	10.6	12.2	0.1	1.5	0.8	1.1	0.1	13.4
Antiprotozoals (P01)	1.8	1.7	2.2	1.9	0.0	0.0	0.0	0.0	0.0	1.9
Anthelmintics (P02)	4.4	12.2	3.1	8.4	0.1	0.2	0.0	0.1	0.0	8.5
Respiratory system										
Drugs for obstructive airway diseases (R03)	126.3	69.3	39.2	64.7	34.8	39.1	31.8	36.2	0.6	100.9
Other respiratory system products (R07)	45.4	55.1	53.0	53.4	2.8	8.1	14.1	9.6	0.2	63.0
Antihistamines for systemic use (R06)	50.4	29.1	17.4	27.3	3.5	2.1	2.6	2.4	0.1	29.7
Nasal preparations (R01)	79.1	36.2	43.7	43.0	3.9	2.1	4.4	3.1	0.1	46.1
Cough and cold preparations (R05)	4.1	2.2	1.7	2.2	0.2	0.1	0.0	0.1	0.0	2.3
Throat preparations (R02)	1.1	1.4	4.0	2.3	0.0	0.0	0.1	0.0	0.0	2.3
Sensory system										
Ophthalmological (S01)	164.9	60.7	42.9	64.9	10.3	3.1	4.0	4.1	0.1	69.0
Ophthalmological and otological preparations (S03)	3.2	3.5	4.0	3.7	0.1	0.2	0.1	0.1	0.0	3.8
Otological (S02)	15.7	15.0	13.5	14.6	0.4	0.5	0.6	0.5	0.0	15.1

ATC=WHO Anatomical Therapeutic Chemical classification system.
*Excluding therapeutic levels with prevalence of both acute and recurrent use <0.1/1000 person years.

drugs for the nervous system (including paracetamol, which can be prescribed in UK) was much higher in the UK; and the use of drugs for the sensory organs was much less in Italy.

Prevalence of drug use in therapeutic class

Within the most commonly used anatomical drug classes, antibacterials accounted for most of the anti-infective drug use; and the therapeutic classes anti-asthmatics, other respiratory products, and nasal preparations were the most commonly used drugs in the respiratory group (table 2). The therapeutic classes with the highest prevalence of use among the dermatological drugs were topical corticosteroids and emollients and barrier creams. Many therapeutic classes in the group of alimentary drugs (laxatives, antidiarrhoeal drugs, drugs for acid disorders) had a considerable prevalence of use. The most commonly prescribed drugs in the other classes were antianemia medications, cardiac drugs (mainly digoxin), sex hormones, oral corticosteroids, non-steroidal anti-inflammatory drugs, analgesics, and ophthalmological drugs.

Ranking of user prevalence rates specific for age over the entire range of drugs showed that antibacterials are the most commonly prescribed drugs in all age groups (table 3) and are prescribed to at least twice as many children as the second most commonly used drug in each age category. The second most commonly used drug changed by age from ophthalmological drugs (< 2 years) to drugs for obstructive airway disease (2-11) to sex hormones (12-18).

When we ranked the therapeutic classes within each anatomical class on the basis of the ratio between recurrent (chronic) and non-recurrent (acute), we observed a different pattern (table 2). The drugs with a ratio of >1 (indicating mostly chronic/recurrent use) were often those with a low prevalence of use (except for sex hormones): antidiabetics, digestives, bile and liver therapy, antithrombotic agents, agents acting on the renin-angiotensin system, lipid lowering drugs, sex hormones, thyroid therapeutic agents, immunosuppressive agents, muscle relaxants, antiepileptics, and psychoanaleptics (table 2). In absolute terms, emollients, topical corticosteroids, sex hormones, anti-infectives, and drugs for obstructive airway disease showed the highest prevalence of recurrent use.

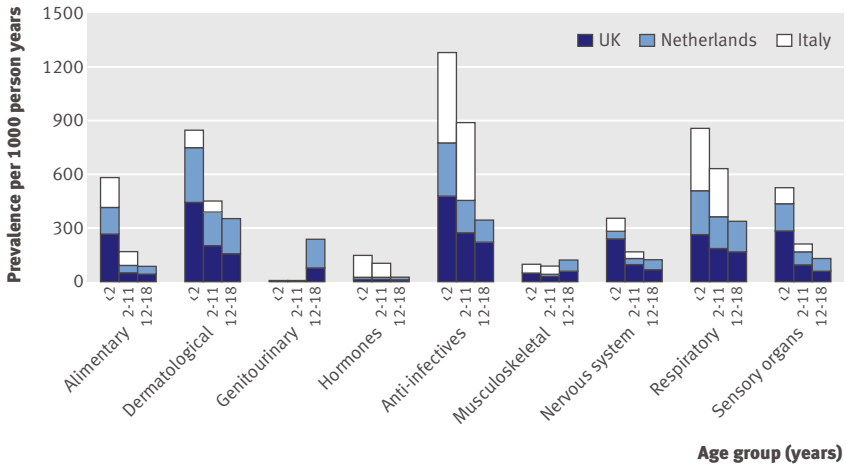

Fig 2 | **Year prevalence of drug use (per 1000 person years) by age (<2, 2-11, 12-18), country, and anatomical class for most prevalently used drug classes (data for Italy excluded age category 12-18)**

Most commonly used drugs in each anatomical class

In the most commonly used anatomical classes (dermatology, anti-infectives, and respiratory system),

the most common individual dermatological drugs were fusidic acid (except for Italy), topical steroids, and topical imidazole/triazole derivatives (tables 4, 5, and 6). The topical triazoles/imidazoles were off label in most countries for at least one or more age categories. In the anti-infectives group (J), penicillin derivatives (amoxicillin, co-amoxiclav, and phenoxymethylpenicillin) followed by macrolides (erythromycin, clarithromycin) were the most common, cefalexin (UK, <2 year) was the only off label drug. Oral aciclovir was one of the top five anti-infective drugs in Italy. Among the respiratory drugs, salbutamol and inhaled steroids (beclometasone, fluticasone, flunisolide), antihistamines (cetirizine, loratidine, clorpheniramine), and xylometazoline were most commonly prescribed. Beclometasone, xylometazoline, and cetirizine were off label in the youngest children (<2 years) in the UK and the Netherlands.

In the moderately used drugs (gastrointestinal, genitourinary, nervous system, and sensory system drugs), the most commonly prescribed alimentary tract drugs (A) were laxatives (lactulose), miconazole, domperidone, and mebeverine. Only ranitidine and laurilsulfate were off label in children <2 years. For the genitourinary drugs, the top five in the Netherlands and UK were oral contraceptives and topical antifungals (miconazole), whereas in Italy (up to age 12) oestrogens, drugs to treat incontinence, and antiseptics were the most commonly prescribed. The percentage of off label use of oral contraceptives and antifungals was high in the Netherlands and the UK. Among drugs for the nervous system, paracetamol is clearly the most used (but probably underestimated because of high over the counter use); methylphenidate (Netherlands and UK), lidocaine (Netherlands), pizotifen (UK), fluoxetine (UK) diazepam, niaprazine (Italy), and valproic acid (Italy) were also in the top five of at least one country. None of them was used off label, except diazepam for children under 12 in the Netherlands. In the group of sensory organ drugs many different drugs were used in the various countries, the most commonly prescribed drugs in the Netherlands (fusidic acid, levocabastine) and the UK (chloramphenicol) were off label.

The low prevalence drugs comprised many classes (groups blood, cardiovascular, hormonal, antineoplastic, musculoskeletal, antiparastic). In the blood forming organs group (B), phytomenadione, iron, tranexamic acid, platelet inhibitors, and vitamin K antagonists were most commonly prescribed. Salicylic acid derivatives were off label. In the cardiovascular drug group topical steroids (antihaemorrhoid creams), topical anaesthetics (lidocaine, oxetacaine), β blockers (propranolol, atenolol), furosemide, disopyramide, adrenaline (epinephrine), and enalapril were most common. Furosemide, β blockers, adrenaline, and topical (antihaemorrhoidal) steroids were off label in at least one country. For the non-sex hormones, desmopressin, oral steroids (dexamethasone, prednisolone and prednisone), levothyroxine and glucagons) were the most commonly prescribed drugs. Only the oral steroids were off label (Netherlands and UK only). The most commonly prescribed antineoplastic and immunomodulating drugs differed substantially between countries but were almost always off label. In the musculoskeletal drug group non-steroidal anti-inflammatory drugs were the most commonly prescribed, with important sequence differences between countries but little off label use except in Italy, where the number one and two drugs (ibuprofen and morniflumate) were off label. In all countries the number one antiprotozoal drug was mebendazole, with little off label drug use.

Table 3 | Top 10 most commonly used therapeutic classes in various age categories

Therapeutic class (ATC)	Users/1000 person years
<2 years	
Antibacterials for systemic use (J01)	435
Ophthalmologicals (S01)	175
Corticosteroids, dermatological preparations (D07)	165
Drugs for obstructive airway diseases (R03)	161
Emollients and protectives (D02)	147
Analgesics (N02	134
Nasal preparations (R01)	83
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents (A07)	67
Stomatological preparations (A01)	59
Corticosteroids for systemic use (H02)	57
2-11 years	
Antibacterials for systemic use (J01)	288
Drugs for obstructive airway diseases (R03)	108
Corticosteroids, dermatological preparations (D07	86
Emollients and protectives (D02)	67
Ophthalmologicals (S01)	64
Analgesics (N02	63
Other respiratory system products (R07)	63
Nasal preparations (R01)	38
Antibiotics and chemotherapeutics (D06)	37
Anti-inflammatory and antirheumatic products (M01)	33
12-18 years	
Antibacterials for systemic use (J01)	194
Sex hormones and modulators of genital system (G03)	82
Drugs for obstructive airway diseases (R03)	71
Other respiratory system products (R07)	67
Corticosteroids, dermatological preparations (D07)	65
Anti-inflammatory and antirheumatic products (M01)	57
Nasal preparations (R01)	48
Ophthalmologicals (S01)	47
Anti-acne preparations (D10	46
Analgesics (N02)	44

ATC=WHO Anatomical Therapeutic Chemical classification system.

DISCUSSION

We have provided a unique overview of primary care prescription patterns in a large multinational European paediatric population. The data could be used to improve the prioritisation of research into long term safety of paediatric drugs, as well as efficacy and effectiveness studies in paediatric medicine. Off label use in some of the most commonly and recurrently

Table 4 | Most commonly used drugs (use per 1000 children per year) by anatomical level and age in 2005 plus paediatric licensing status in Netherlands

Drug class and name	<2 years		2-11 years		12-18 years		Total users /1000
	No/1000	% off label	No/1000	% off label	No/1000	% off label	
Alimentary tract (A)							
Lactulose	92	0	332	0	58	0	482
Domperidone	79	0	222	0	73	0	374
Miconazole	200	0	30	0	8	0	238
Nystatin	130	0	11	0	3	0	144
Laurilsulfate	20	100	80	0	17	0	117
Blood and blood forming organs (B)							
Ferrous fumarate	2	0	60	0	57	0	119
Phytomenadione	41	0	2	0	3	0	46
Carbasalate calcium	1	100	12	100	0	NA	13
Cardiovascular (C)							
Hydrocortisone (haemorrhoids)	12	100	29	100	10	100	51
Lidocaine	3	100	30	0	13	0	46
Propranolol	0	NA	5	0	18	0	23
Adrenaline (epinephrine)	0	NA	17	0	4	0	21
Enalapril	0	NA	2	0	5	0	7
Dermatological (D)							
Fusidic acid	194	100	1013	100	311	100	1518
Hydrocortisone	284	100	734	100	269	100	1287
Miconazole	273	0	337	0	204	0	814
Triamcinolone	36	100	360	100	292	100	688
Ketoconazole	48	100	168	100	139	100	355
Genitourinary system and sex hormones (G)							
Levonorgestrel/oestrogen	1	100	3	100	1034	100	1038
Cyproterone/oestrogen	0	NA	4	100	321	100	325
Norethisterone	0	NA	2	100	98	100	100
Miconazole	4	100	14	100	58	100	76
Lynestrenol	0	NA	4	100	57	100	61
Systemic hormonal preparations (H)							
Desmopressin	0	NA	94	0	49	0	143
Prednisolone	14	100	41	100	31	100	86
Levothyroxine sodium	1	0	13	0	16	0	30
Prednisone	0	NA	11	100	7	100	18
Dexamethasone	4	0	6	0	2	0	12
Anti-infectives for systemic use (J)							
Amoxicillin	763	0	1870	0	302	0	2935
Co-amoxiclav	133	0	657	0	155	0	945
Clarithromycin	131	0	489	0	137	0	757
Azithromycin	47	0	246	0	111	0	404
Pheneticillin	22	0	211	0	161	0	394
Antineoplastic and immunomodulating agents (L)							
Fluorouracil	0	NA	6	100	3	100	9
Azathioprine	0	NA	0	0	3	0	3
Triptorelin	0	NA	2	100	0	100	2
Methotrexate	0	NA	1	0	0	0	1
Ciclosporin	0	NA	1	0	0	0	1
Musculoskeletal system (M)							
Diclofenac	0	NA	29	0	233	0	262
Naproxen	0	NA	10	0	171	0	181
Ibuprofen	0	NA	29	0	131	0	160
Diclofenac, combinations	0	NA	2	100	12	100	14
Bufexamac	3	100	8	100	3	100	14
Nervous system (N)							
Methylphenidate	0	NA	125	0	140	0	265
Paracetamol	38	0	99	0	32	0	169
Lidocaine-prilocaine	3	0	110	0	14	0	127
Carbasalate calcium	0	NA	27	0	79	0	106
Diazepam	8	100	39	100	34	0	81
Antiparasitic drugs, insecticides, and repellents (P)							
Mebendazole	1	0	87	0	14	0	102

Table 4 cont at the top of the next page

Table 4 cont

Drug class and name	<2 years		2-11 years		12-18 years		Total users /1000
	No/1000	% off label	No/1000	% off label	No/1000	% off label	
Metronidazole	2	100	21	0	20	0	43
Proguanil, combinations	0	NA	4	0	10	0	14
Permethrin	1	0	8	0	3	0	12
Respiratory system (R)							
Salbutamol	311	0	1053	0	448	0	1813
Fluticasone	159	0	702	0	201	0	1062
Desloratadine	14	0	447	0	366	0	827
Xylometazoline	154	100	356	0	143	0	654
Levocetirizine	0	NA	177	0	302	0	479
Sensory organs (S)							
Fusidic acid	342	100	441	100	263	100	1049
Levocabastine	2	100	130	100	156	100	291
Hydrocortisone/anti-infectives	12	0	129	0	70	0	211
Lidocaine	33	100	135	0	16	0	185

NA=not assessable.

used drugs is high (such as oral contraceptives) and these should be considered for prioritisation.

Prioritisation of research on drug safety in paediatrics

We recommend two important assessments in prioritising research needs in medicines for children: public health assessment,[16] comprising the severity and prevalence of disease and the availability of treatment alternatives; and assessment of use. This may comprise the frequency or volume of use and the licensing/labelling status of medicines for children. The use of off label and unlicensed medicines implies that there are no proper labelling and dosing recommendations, which can potentially be harmful to children.[17-20] Therefore off label and unlicensed medicines should be a higher priority for research than licensed/on label medications, especially if no data on safety and efficacy in children are available. We focused on assessing the volume and labelling status to provide knowledge to experts and facilitate research prioritisation that includes both the public health as well as the assessment of use.

Our data on use support the conclusions of the recently published EMEA consensus/expert derived list of research priorities concerning off patent medicinal products,[16] which emphasised the need for paediatric studies of the safety of topical, systemic, and inhaled steroids. Steroids are associated with impaired growth,[21] abnormalities in glucose meta bolism,[22] and adrenal suppression.[23 24] Of these, growth retardation is the most common and is of particular concern in children. The extent of growth suppression varies with the method of administration (such as inhaled or oral) and the duration of treatment, as well as with the type and dose of glucocorticoid used.[21 25] EMEA also lists topical and systemic antifungals (imidazoles/triazoles), acid reducing drugs, and antineoplastic drugs as research priorities. These drugs are often or recurrently used and are mostly off label. Many other drugs listed did not appear as commonly used drugs in our study and, on the basis of frequency of use in primary care alone, would not be considered as priorities but apparently were considered priorities for other reasons. On the other hand, sex hormones are not listed on the priority list, whereas they are commonly and recurrently prescribed, mostly off label. Few long term safety studies on the use of sex hormones in adolescents are available and to our knowledge there are no randomised controlled trials on their safety and efficacy in this age group. The use of oral contraceptives in adolescents has been associated with an increased risk of lower bone mineral density, higher serum cholesterol concentrations, triglyceridaemia,[26-28] cardiovascular events (such as myocardial infarction and stroke), and venous thromboembolism.[29-33] As the use of sex hormones in young adolescents is relatively high, leading to a long duration of use, further studies on the efficacy and long term safety effects of these drugs in young women are warranted.

Although patterns of drug use and labelling status can inform decisions on prioritisation of research, these data inform also us about suboptimal use and might even uncover undesirable prescribing practices. For example, fusidic acid and chloramphenicol are often used and often off label (tables 4-6). In the Netherlands, fusidic acid is prescribed for the treatment of conjunctivitis, similar to chloramphenicol in the UK. The beneficial effect of antibiotics in the treatment of this condition, however, has not been proved.[34 35] Indeed acute bacterial conjunctivitis is often a self limiting condition, and topical antibiotic use offers only marginal benefit in improving clinical outcomes; hence the emphasis should be on educating clinicians not to prescribe such treatment rather than a call for more research.[36 37] Another example underlining the need for education rather than research is the cough and cold medications. These drugs are not only available over the counter but are also often prescribed, which should be strongly discouraged because of reports of death and lack of efficacy.[38]

Patterns of drug use

We found that the prevalence of the most commonly prescribed drugs in primary care is highest in children

Table 5 | Most commonly used drugs (use per 1000 children per year) by anatomical level and age in 2005 plus paediatric licensing status in UK

Drug class and name	<2 years		2-11 years		12-18 years		Total users /1000
	No/1000	% off label	No/1000	% off label	No/1000	% off label	
Alimentary tract (A)							
Lactulose	797	0	2565	0	565	0	3927
Miconazole	566	0	134	0	31	0	731
Ranitidine	145	100	133	0	343	0	622
Mebeverine	0	NA	57	0	524	0	581
Domperidone	103	0	136	0	247	0	486
Blood and blood forming organs (B)							
Folic acid	141	100	48	0	368	0	558
Tranexamic acid	0	NA	9	0	295	0	304
Aspirin	12	100	52	100	37	0	103
Warfarin	1	100	17	100	25	100	46
Phytomenadione	26	0	10	0	7	0	43
Cardiovascular (C)							
Adrenaline (epinephrine)	6	100	580	0	383	0	970
Propranolol	4	0	27	0	262	0	293
Furosemide	18	100	38	0	19	0	76
Atenolol	2	100	31	100	42	100	78
Enalapril	0	NA	26	0	37	0	63
Dermatological (D)							
Hydrocortisone	2425	0	7311	0	2574	0	12 310
Fusidic acid	880	0	3936	0	1457	0	6273
Clobetasone butyrate	232	0	1888	0	1080	0	3200
Clotrimazole	828	100	1617	0	627	0	3073
Betamethasone	74	0	967	0	1360	0	2401
Genitourinary system and sex hormones (G)							
Clotrimazole	61	100	182	100	801	0	1046
Norethisterone	0	NA	4	100	1019	100	1025
Levonorgestrel	0	NA	0	0	946	0	946
Medroxyprogestrogen	0	NA	1	100	693	0	695
Desogestrel	1	100	0	100	268	100	272
Systemic hormonal preparations (H)							
Desmopressin	0	NA	467	0	312	0	779
Levothyroxine	19	0	89	0	159	0	267
Glucagon	0	NA	77	0	108	0	185
Dexamethasone	19	100	44	0	8	0	72
Somatropin	0	NA	28	0	26	0	54
Anti-infectives for systemic use (J)							
Phenoxymethylpenicillin	518	0	6057	0	5710	0	12285
Flucloxacillin	897	0	6043	0	4223	0	11 163
Erythromycin	1287	0	5265	0	3386	0	9938
Trimethoprim	351	0	2623	0	2122	0	5096
Cefalexin	345	100	1597	0	1098	0	3041
Antineoplastic and immunomodulating agents (L)							
Azathioprine	0	NA	16	0	65	0	81
Methotrexate	0	NA	10	0	24	0	34
Ciclosporin	0	NA	13	100	8	0	22
Tacrolimus	0	NA	5	0	9	0	14
Goserelin	0	NA	2	100	2	100	6
Musculoskeletal system (M)							
Ibuprofen	1085	0	5404	0	4251	0	10 740
Diclofenac	2	0	41	0	1247	0	1290
Mefenamic acid	0	NA	11	0	1278	0	1289
Naproxen	0	NA	4	0	143	0	147
Ketoprofen	0	NA	15	100	70	0	86
Nervous system (N)							
Paracetamol	4292	0	11 085	0	2832	0	18 209
Methylphenidate	0	NA	286	0	433	0	719
Pizotifen	0	NA	207	0	430	0	637
Fluoxetine	0	NA	6	0	398	0	404
Diazepam	4	0	124	0	266	0	394

Table 5 cont at the top of the next page

Table 5 cont

Drug class and name	<2 years		2-11 years		12-18 years		Total users /1000
	No/1000	% off label	No/1000	% off label	No/1000	% off label	
Antiparasitic drugs, insecticides, and repellents (P)							
Mebendazole	24	100	1695	0	349	0	2069
Phenothrin	3	0	201	0	53	0	257
Permethrin	35	0	845	0	400	0	1280
Malathion	40	0	1088	0	372	0	1500
Respiratory system (R)							
Salbutamol	1309	100	12 403	0	8321	0	22 034
Beclometasone	256	100	6332	0	3963	0	10 552
Cetirizine	24	100	3382	0	4145	0	7552
Chlorphenamine	578	0	3945	0	959	0	5482
Loratadine	1	0	1992	0	2261	0	4254
Sensory organs (S)							
Chloramphenicol	4155	100	7161	0	2192	0	13 509
Cromoglicic acid	53	100	1875	0	2630	0	4559
Fusidic acid	1316	0	1951	0	540	0	3807
Nedocromil	0	NA	265	0	465	0	730
Hydrocortisone	101	100	236	0	57	0	395

NA=not assessable.

aged under 2, that the most commonly used drugs (anti-infectives, dermatologicals, and respiratory drugs) are the same in all three age categories, and that almost all other drugs are used by less than 10% of children a year. In general, we can categorise three groups of drug use: drugs used by more than 10% of children a year, those used by 1-10%, and those used by less than 1%. The use of the high prevalence drug classes decreases with age but remains high, whereas the use of the lowest prevalence drug groups increases to a moderate prevalence rate in adolescence, except in the case of cardiovascular and antineoplastic agents. Only a few therapeutic drug classes accounted for most use in a specific anatomical class: antibacterials, topical corticosteroids, antiasthma and antianaemia medications, cardiac drugs, sex hormones, oral corticosteroids, non-steroidal anti-inflammatory drugs, analgesics, and ophthalmological drugs. Relatively speaking, the high prevalence drugs were more often used for acute use. Only 12 drug classes (antidiabetics, digestives, bile and liver therapy, antithrombotic agents, drugs affecting the renin-angiotensin system, lipid lowering drugs, sex hormones, thyroid therapeutic agents, immunosuppressive agents, muscle relaxants, antiepileptics, and psychoanaleptics) were prescribed more often for recurrent than acute use.

We observed an age related sex reversal: prevalence rates for drug use were consistently higher in adolescents girls than in adolescent boys (except in the case of non-sex hormones), whereas the opposite was true in the younger age categories. This agrees with findings from previous Dutch and Danish studies.[39 40]

Interestingly, the percentage of off label use varied highly between countries, and similar drugs differed in off label status between countries. This confirms that the differences in the paediatric status of the drugs, instead of the different prescription habits or medical cultures as postulated by many authors, represent the real reason for the variability reported by years and from many European studies and surveys on the off label use in children.[41]

Previous studies

Our study was population based, had a large sample size, and covered different European countries. Previous European studies have been country or region specific and have concentrated on specific conditions, except for studies from Sweden, the Netherlands, and Denmark in the late 1990s and a recent Italian study covering data from 2000-6.[40 42-44] These studies took all types of drugs into account but the methods to calculate prevalence and ranking (on the basis of number of dispensed boxes or user prevalence) and age ranges varied largely, which complicates direct comparisons. The overall results—highest drug use in lowest age category, ranking of the most commonly used drugs (anti-infectives, respiratory, and dermatological drugs), and sex pattern (more prescriptions for girls than boys after the age of 10)—are consistent with our findings.[39 40 45]

Potential of multi-country database studies

We have shown the potential of studying the primary care prescribing of a wide range of drugs using multiple databases. As all databases include outcome data, such as morbidity and mortality, they can also be used for studies of paediatric drug safety. The country specific estimates provide insights into prescription differences and allow a search for high prevalence countries regarding drug prescribing.

Limitations

We captured only outpatient, primary care drug prescriptions and not use of over the counter drugs (which resulted in a substantial underestimation of the use of paracetamol and phytomenadione, and potentially other drugs such as cough and cold medications). In the Netherlands, the UK, and Italy, most health

Table 6 | Most commonly used drugs (use per 1000 children per year) by anatomical level and age in 2005 plus paediatric licensing status in Italy

Drug class and name	<2 years		2-11 years		Total users /1000
	No/1000	% off label	No/1000	% off label	
Alimentary tract (A)					
Domperidone	250	0	649	0	899
Sodium fluoride	571	0	192	0	763
Cimetropium bromide	341	0	124	0	465
Nystatin	139	0	133	0	272
Lactitol	45	0	168	0	213
Blood and blood forming organs (B)					
Electrolytes	124	0	151	0	275
Tranexamic acid	4	0	168	0	172
Phytomenadione	88	0	9	0	97
Ferrous gluconate	6	0	62	0	68
Ferrous sulphate	0	NA	48	0	48
Cardiovascular (C)					
Epinephrine	16	0	56	0	72
Hydrocortisone	0	NA	14	0	14
Furosemide	9	0	4	0	13
Oxetacaine	0	NA	8	0	8
Disopyramide	0	NA	1	0	1
Dermatological (D)					
Betamethasone/antibiotics	205	0	431	0	636
Mometasone	240	0	362	0	602
Mupirocin	90	0	313	0	403
Clotrimazole	175	100	118	100	293
Econazole	90	100	83	100	173
Genitourinary system and sex hormones (G)					
Conjugated oestrogens	57	0	26	0	83
Oxybutynin	0	NA	37	0	37
Benzydamine	2	100	19	100	21
Povidone-iodine	1	100	14	100	15
Estriol	9	100	5	100	14
Systemic hormonal preparations (H)					
Betamethasone	1430	0	2064	0	3494
Prednisone	5	0	240	0	245
Desmopressin	0	NA	120	0	120
Dexamethasone	18	0	6	0	24
Levothyroxine	5	0	17	0	22
Anti-infectives for systemic use (J)					
Amoxicillin	2573	0	3603	0	6176
Co-amoxiclav	1760	0	4210	0	5970
Azithromycin	666	0	2616	0	3282
Clarithromycin	683	0	2385	0	3068
Aciclovir	309	0	739	0	1048
Antineoplastic and immunomodulating agents (L)					
Pidotimod	11	0	80	0	91
Leuprorelin	0	NA	7	100	7
Triptorelin	0	NA	6	100	6
Methotrexate	0	NA	5	100	5
Ciclosporin	0	NA	3	100	3
Musculoskeletal system (M)					
Ibuprofen	508	100	1399	100	1907
Morniflumate	118	100	446	100	564
Ketoprofen	8	0	354	0	362
Flurbiprofen	19	0	220	0	239
Niflumic acid	62	0	168	0	232
Nervous system (N)					
Paracetamol	603	0	491	0	1094
Paracetamol, combinations	255	0	506	0	761
Niaprazine	158	0	39	0	197
Diazepam	41	0	85	0	126
Valproic acid	4	0	39	0	43

Table 6 cont at the top of the next page

Table 6 cont

Drug class and name	<2 years		2-11 years		Total users /1000
	No/1000	% off label	No/1000	% off label	
Antiparasitic drugs, insecticides, and repellents (P)					
Mebendazole	38	0	479	0	517
Pyrantel	11	0	145	0	156
Mefloquine	8	0	16	0	24
Albendazole	1	0	22	0	23
Permethrin	0	NA	13	0	13
Respiratory system (R)					
Beclometasone	1584	0	2849	0	4433
Salbutamol	1202	0	1932	0	3134
Flunisolide	615	0	1256	0	1871
Cetirizine	234	0	1435	0	1669
Salbutamol combinations	537	0	725	0	1262
Sensory organs (S)					
Tobramycin	441	0	515	0	956
Anti-infectives, combinations	117	0	256	0	373
Dexamethasone and anti-infectives	42	100	229	100	271
Nedocromil	43	0	156	0	199
Combinations of different antibiotics	90	0	75	0	165

NA=not assessable.

problems are dealt with in primary care,[8] and as drug prescriptions by a specialist for a chronic disease are often continued by general practitioners or paediatricians, most of them are picked up. Drugs given in hospital and the monitoring of chemotherapeutic and biological drugs are unlikely to be fully captured by our databases. Despite differences in the absolute prevalence rates of drug prescribing and the types of drugs prescribed, age and sex patterns were consistent in the three countries. As the UK accounted for 60% of the study population, however, the pooled results are inevitably dominated by UK prescription patterns so we conducted stratified analyses as much as possible. Because of the nature of the databases, we studied drug prescriptions rather than drug intake, and so the prevalence of actual drug exposure might be lower than estimated here.

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Ethical approval: The use of IMS data for this study has been reviewed by an independent scientific and ethics committee.
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WHAT IS ALREADY KNOWN ON THIS TOPIC

Most previous research on drug use in children has focused on specific high use areas such as antibiotics and respiratory and neuropsychiatric drugs, therefore most of these drugs have a paediatric licensing status

Paediatric expert groups have been established by the European Medicines Evaluation Board (EMEA) to identify those drugs that are important for the paediatric community and that require additional efficacy and safety data

WHAT THIS STUDY ADDS

Data on frequency of prescriptions and off label status of drugs could provide objective evidence for the prioritisation of research in paediatric drugs

Information on the safety and efficacy of some of the most commonly used drugs in children (such as oral contraceptives, steroids, and triazoles/imidazoles) is lacking, and not all such drugs are on the list of research needs

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