



# A survey of medicine use in children and adolescents in Austria

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## Abstract

Aims of this survey were to evaluate prescription patterns for children and adolescents in primary and hospital care settings in Austria and to identify the medicines used most frequently in this population. Prescription data were assessed for the year 2014: for primary care, reimbursement data were obtained from Austrian health insurances; for hospital care, information on medicines dispensed to pediatric wards from hospital pharmacies. Frequencies of medicine use were analyzed by Anatomical Therapeutic Chemical classification system, age groups, and care setting. In primary care, anti-infectives (25%) and medicines for the respiratory system (14%) and for the nervous system (13%); in hospitals, anti-infectives (23%) and medicines for the nervous system (13%) and alimentary tract (12%) were prescribed most frequently. Amoxicillin/beta-lactamase inhibitor, ibuprofen, and paracetamol were the most frequent substances in both primary and hospital care settings. Based on the top 80% prescribed substances, a hit list of 150 pediatric medicines was defined for Austria.

**Conclusion:** This is the first representative and comprehensive survey of medicine use in children and adolescents in Austria, allowing comparison of prescription patterns to other European countries and assessing temporal trends in the future. Moreover, it serves as basis for planned measures to improve rational use of pediatric medicines.

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**What is Known:**

- Large knowledge gaps exist for medicine use in children and adolescents concerning appropriate dosing, efficacy, and safety aspects.
- Off-label medicine use is common in the treatment of children and adolescents.

**What is New:**

- We present a comprehensive survey of current prescription patterns for children and adolescents in Austria and define a hit list of pediatric medicines, as basis for developing an evidence-based information platform for health care professionals.
- Anti-infectives, medicines for respiratory tract system, and pain medication are most frequently prescribed.

**Keywords** Pediatric medicine · Survey · Austria · Primary care · Hospital

**Abbreviations**

ATC	Anatomical Therapeutic Chemical (classification system)
DDD	Defined daily dose
HVB	Main Association of Austrian Social Security Institutions (= Hauptverband der Oesterreichischen Sozialversicherungstraeger)
NSAID	Non-steroidal anti-inflammatory drug

**Introduction**

Several surveys on medicine use in children and adolescents performed over the last 20 years have demonstrated a low degree of evidence for most medicines used in children [2, 12, 18–21, 25]. Surveys assessing prescribing patterns in children by therapeutic area and age groups and identifying specific information deficits regarding dosing, efficacy, and safety provide the basis to define priorities for research into pediatric medicines [5, 17, 24]. Previous pediatric drug utilization studies assessed medicine use either in primary care [17, 21, 25] or in hospital care [16, 18, 24]. Apart from one study investigating prescription frequencies in inpatient and outpatient care of a pediatric teaching hospital [6], a comprehensive study of both primary and hospital care settings within the same country and time period has not been performed to date. For Austria, no representative, nationwide information on pediatric medicine use has been available so far.

The primary aim of the present survey was to evaluate prescription patterns for children and adolescents in primary and hospital care settings in Austria. A secondary aim was to identify the medicines used most frequently in this population, as basis for a future project to develop an evidence-based information platform on pediatric medicines for Austria.

**Methods**

Data on medicines prescribed for children and adolescents in Austria were obtained for the year 2014 from the following data sources:

1. Data of medicines prescribed by primary care physicians and reimbursed by Austrian health insurances were

obtained from the umbrella organization of 19 Austrian statutory health insurance funds, the “Main Association of Austrian Social Security Institutions” (HVB). These funds cover medical insurance for more than 95% of the Austrian population. There is a prescription fee per drug package (€5.40 in 2014) that has to be paid by the patient in the pharmacy. Medicines with a price below the prescription fee are not contained in the reimbursement database. An exception is medicines prescribed to patients with prescription fee exemptions (amounting to 6.1% of pediatric patients in 2014), and prescription data of exempted patients are included in the data set. The prescription behavior of doctors in the outpatient sector is influenced by a “Guideline for economic prescription.” This guideline should be observed by doctors and—in a nutshell—implies that if several medicines are equally suitable from a medical viewpoint, the cheaper one should be prescribed.

2. Data on medicine use in the hospital care setting was provided by Austrian hospital pharmacists, listing all medicines dispensed to pediatric wards in the respective hospital. Hospital dispensing data were obtained from 13 general hospitals with pediatric departments across Austria (3 university hospitals, 10 secondary care hospitals). Hospital data covered about 50% of all pediatric hospital beds in Austria, including regular pediatric wards, intermediate-care units, intensive care units, neonatology units, and psychiatric and surgical wards caring for children.

**Data preparation and coding**

Data for primary care setting were provided from HVB as summary data of reimbursement frequencies for individual medicines but without information on individual patients, single or multiple/repeated prescription, or indication for prescription. We took reimbursement data as proxy for prescription frequencies. Data were provided at level 5 of the Anatomical Therapeutic Chemical (ATC) classification system. Extemporaneous preparations and medicines without ATC code (medicines not listed as medicines in the Austria Codex, i.e., medical devices, food supplements) were listed separately, coded as “Z,” and excluded from further analyses because active ingredients of these preparations were unknown.

Data for hospital care setting were medicines dispensed to pediatric wards. For lack of individual patient data and difficulties to define child-adapted daily doses, dispensing data were used as proxy for prescription frequencies. For a relative quantification based on the available information, we chose the following pragmatic definition: one package of dispensed medicine reflects one prescription. The data set did not provide information on individual patient characteristics (e.g., age) or indication for prescription. For data analysis, up-front filters were used to focus on medicines relevant for medical treatment: we excluded products for enteral (baby) nutrition, diagnostics, care products (e.g., washing lotions), and hygienic products (antiseptics and disinfectants), as well as the following subgroups from ATC class “blood and blood forming organs” (B): solutions for parenteral nutrition (B05BA), solutions affecting the electrolyte balance (B05BB), irrigating solutions (B05C), peritoneal dialysis (B05D), i.v. solution additives (B05X), hemodialysis and hemofiltration (B05Z). Extemporaneous preparations and other medicines without ATC code were excluded from further analyses.

## Data analysis

In both primary and hospital care settings, descriptive analyses were performed for ATC level 1 (anatomical main group), ATC level 2 (therapeutic main group), and ATC level 5 (chemical substance). On ATC level 2, the 10 most frequently prescribed drug groups were described (top 10). On ATC level 5, we identified the chemical substances that covered 80% of the total number of prescriptions in either care setting (top 80%). Prescription frequencies were compared between primary and hospital care settings. For the primary care setting, the data were provided by HVB in age subsets of 0–2, 3–4, 5–6, 7–9, 10–14, and 15–19 years. We combined these into three age subgroups (0–2, 3–9, and 10–19 years) to allow comparison of our results to those reported in the literature [25]. In the hospital care setting, prescription frequencies were normalized to individual hospital size, i.e., frequencies per ATC group in relation to overall dispensing of medicines for children and adolescents in the respective hospital. Chi-square test was used to compare frequencies between primary and hospital care settings, applying Bonferroni correction for multiple testing. Data preparation was done in SAS Enterprise Guide, data analysis with SPSS V.17.0.

## Results

### Study population/data coverage

Primary care prescription data were available for 1,665,952 insured children and adolescents aged 0–19. This corresponds to approximately 20% of total number of persons with

medical insurance in Austria in 2014. In total, 4,636,209 prescriptions were reimbursed for patients aged 0–19. The average number of prescriptions per child was 2.8 overall and was decreasing with increasing age, with 3.6, 2.9, and 2.5 prescriptions per child for age groups 0–2, 3–9, and 10–19 years, respectively. Analysis of medicines prescribed in hospitals was based on 328,391 dispensations for 990 hospital beds. Average dispensing frequency per hospital bed per day was 0.9 (range 0.4–2.3).

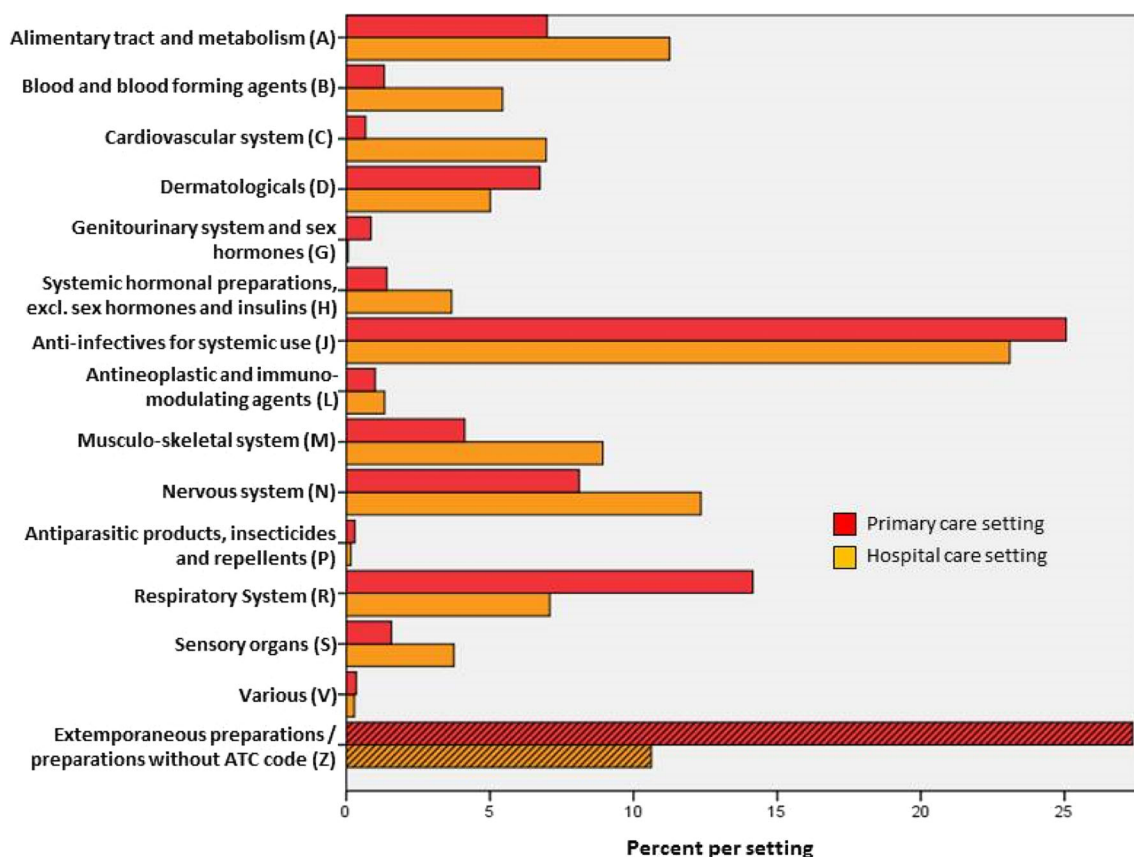
### Prescription patterns by anatomical class (ATC level 1)

Figure 1 shows most frequently prescribed drug groups on ATC level 1, comparing primary care and hospital care settings. In the primary care setting, the highest frequencies were seen for anti-infective drugs (J) (accounting for 25% of all prescriptions), followed by medicines for the respiratory (R) (14%), nervous system (N) (13%), and alimentary system (A) (12%). Dermatological agents (D) and medicines for the musculoskeletal system (M) ranged between 5 and 10%. In the hospital setting, anti-infective drugs were also the most frequently prescribed class for children and adolescents (24%), followed by preparations of anatomical class N (nervous system) and A (alimentary tract and metabolism) with 13 and 12%, respectively. Drugs of the blood and blood-forming system (B) and dermatological (D), musculoskeletal (M), and respiratory (R) system medicines showed relative prescription frequencies between 5 and 10%. Extemporaneous preparations and preparations without ATC code (Z) accounted for 27 and 11% of all prescriptions in primary and hospital care settings, respectively.

Anti-infectives (25 versus 23%), drugs for the respiratory system (14 versus 7%) and genitourinary system (0.9 versus 0.1%), and dermatologicals (7 versus 5%) were more frequently prescribed in primary care than in hospital care, as per percentage of overall prescriptions per setting. Medicines of all other anatomical groups showed higher relative prescription frequencies in the hospital than in the primary care setting, particularly cardiovascular medicines (7 versus 0.7%) (Fig. 1). Differences between primary care and hospital care settings overall and for all group-wise comparisons were highly significant ( $p < 0.001$ ) because of the large number of individual prescriptions.

### Prescription patterns by therapeutic class (ATC level 2)

Figure 2 depicts the ten most frequently used therapeutic classes for each primary care and hospital care setting. These top 10 therapeutic classes covered 54% (primary care) and 56% (hospital care) of total prescriptions in the respective setting. Six of these therapeutic classes were overlapping between both settings (41 and 42% of total prescriptions), namely anti-bacterials for systemic use (J01), anti-inflammatory/anti-rheumatic agents (M01), analgesics (N02), psychoanaleptics



**Fig. 1** Frequency of prescriptions by medicine groups (ATC level 1), comparing primary care and hospital care settings. Differences between primary care and hospital care settings overall and for all group-wise comparisons were significant ( $p < 0.001$ )

(N06), drugs for obstructive airway diseases (R03), and nasal preparations (R01). Relative to overall prescriptions per setting, prescriptions of pain medication (M01, N02) were more frequent in hospitals, while prescriptions of anti-bacterials and medicines for obstructive airway diseases (R03) were more frequent in primary care.

Table 1 lists the top 10 therapeutic classes (ATC level 2) by age group (primary care setting). Anti-bacterials for systemic use were the most frequent prescriptions in all three age groups, with highest frequencies in children aged 3 to 9 years. Similarly, medications for respiratory diseases, i.e., medication against obstructive airway diseases (R03), cough and cold preparations (R05), nasal preparations (R01), and anti-histamins (R06), were used most often in children between 3 and 9 years of age.

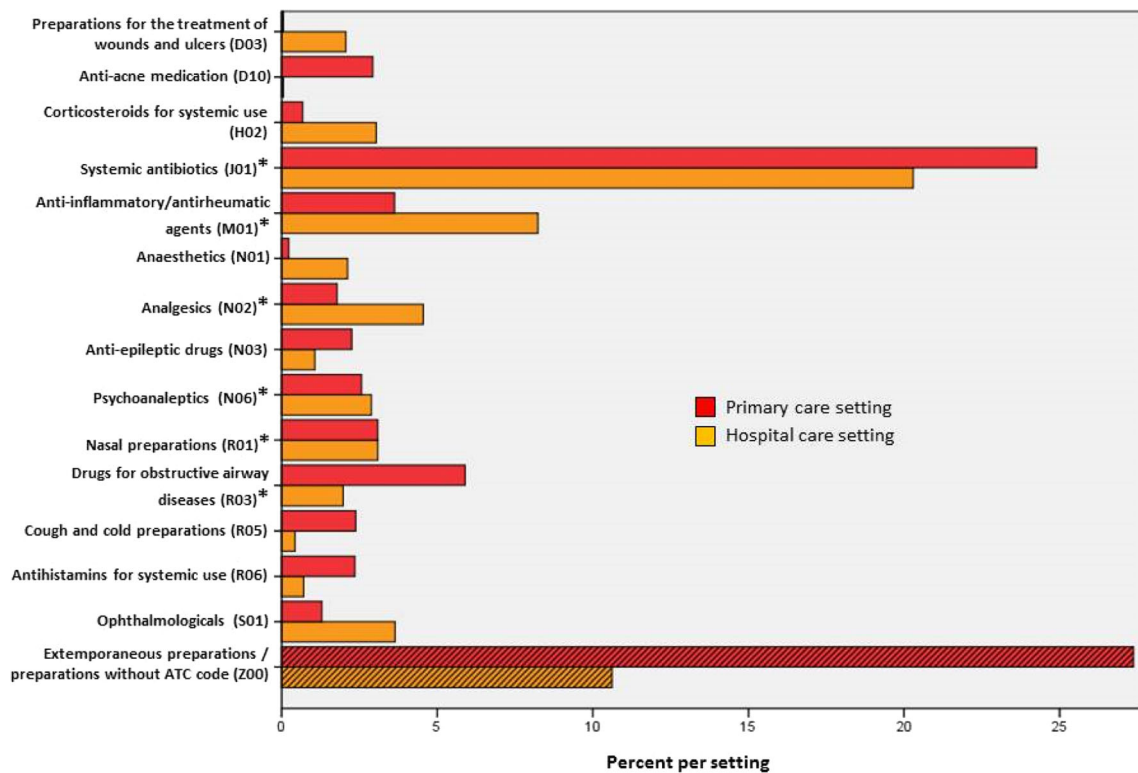
Prescription of anti-inflammatory/anti-rheumatic products increased with age, and anti-acne drugs and psychoanaleptics were hardly present in children below 10 years of age. In contrast, analgesics (N02) were most frequently used in the youngest age group. The top 10 therapeutic classes accounted for 42, 52, and 59% of all prescriptions in children aged 0–2, 3–9, and 10–19, respectively. A display of frequencies per age group for all anatomical classes in the primary care setting is also provided in Fig. 3 of the electronic supplement (ESM 1).

### Prescription patterns by chemical substance (ATC level 5)

The ten most frequently prescribed medicines are shown in Table 2. Eight of the ten most frequently used drugs were either pain medication/anti-pyretics (ibuprofen, paracetamol, mefenamic acid) or systemic anti-bacterials (broad-spectrum penicillins, cefaclor, clarithromycin, and phenoxymethylpenicillin). The top 80% prescribed chemical substances are listed in the electronic supplement (ESM 2). These comprise 66 and 114 medicines for primary and hospital care settings, respectively, with 30 overlapping between both settings, 150 substances overall, which we used to define a hit list of pediatric medicines for Austria.

### Discussion

This survey evaluated medicine use in children and adolescents in Austria over a 1-year period (2014). To our knowledge, it is the first survey comprising pediatric medicine use in both primary and hospital care settings. The survey provides an overview and insight into pediatric medicine use in Austria.



**Fig. 2** Top 10 most frequently prescribed therapeutic classes (ATC level 2) in primary and hospital care settings. Differences between primary care and hospital care settings overall and for all group-wise comparisons were

significant ( $p < 0.001$ ). Asterisks denote the top 10 therapeutic classes in both care settings.

It allows comparing prescription patterns in Austria to those in other (European) countries. Moreover, the results serve as basis to investigate temporal trends in prescription patterns in the future, particularly to study the effect of measures aiming to improve the information base and rational use of pediatric medicines in Austria.

Currently, there exists no nationwide database in Austria linking patient demographics, disease data, and treatment data. Within the limitations of the systems, the data sources used in this survey were the best available to obtain representative and valid information on medicine use in children and adolescents in Austria. Although data were collected retrospectively, the potential for selection bias is small. For the primary care setting, the data cover prescriptions by pediatricians as well as general practitioners and specialists caring for children (ear-nose-throat, gynecologists, etc.). Hospital data in this survey cover about 50% of pediatric hospitals in Austria and have a good range from small pediatric departments in provincial towns to large university departments covering all Austrian federal provinces. We contacted 100% of Austrian hospital pharmacies but some hospital administrations did not allow disclosure of information. For the hospitals providing data, the data fully cover all pediatric inpatient wards in the respective institution. We can reasonably extrapolate the results obtained

from this analysis to all hospitals in Austria. All prescription data in both settings were collected over a 1-year period; hence, seasonal variation is not an issue.

The survey has some methodological limitations, mainly the lack of individual patient data, disease information, and indication for medicine use. In the primary care setting, another limitation relates to some missing data. Privately paid medicine prescriptions are not contained in the insurance reimbursement database. This applies to all medicines that are generally not paid by health insurance and to medicines at a price lower than the prescription fee. This data gap probably results in underrepresentation of certain analgesics/antipyretics like paracetamol or ibuprofen, as well as antibiotics like amoxicillin or phenoxymethylpenicillin in our primary care data. Data concerning over-the-counter medication, most vaccines, and oral contraceptives are not included in our database. Moreover, the data provided for extemporaneous preparations did not contain information on active ingredients; therefore some substances, e.g., topical corticosteroids supplied as ointment mixtures, might not be captured. Another point of caution for interpretation is that reimbursement and dispensing data are only a proxy for medicine use and imply some imprecision. In hospitals, since we have no information on the amount of medicine given to an individual patient, our data are at best semi-quantitative.

**Table 1** Top 10 most frequently prescribed therapeutic classes (ATC level 2) in the primary care setting, stratified by age group

Therapeutic class (ATC level 2)	Prescriptions per 1000 children (% of total prescriptions in this age group)
0–2 years	
Anti-bacterials for systemic use (J01)	750 (20.8)
Drugs for obstructive airway diseases (R03)	168 (4.7)
Anti-diarrheals, intestinal anti-inflammatory/anti-infective agents (A07)	98 (2.8)
Analgesics (N02)	84 (2.3)
Stomatological preparations (A01)	80 (2.2)
Nasal preparations (R01)	77 (2.1)
Anti-fungals for dermatological use (D01)	70 (2.0)
Cough and cold preparations (R05)	64 (1.8)
Other dermatological preparations (D11)	63 (1.7)
Anti-inflammatory and anti-rheumatic agents (M01)	63 (1.7)
Total	1517 (42.1)
3–9 years	
Anti-bacterials for systemic use (J01)	818 (27.8)
Drugs for obstructive airway diseases (R03)	194 (6.6)
Cough and cold preparations (R05)	95 (3.2)
Nasal preparations (R01)	90 (3.1)
Anti-inflammatory and anti-rheumatic agents (M01)	86 (2.9)
Anti-histamins for systemic use (R06)	76 (2.6)
Anti-epileptics (N03)	58 (2.0)
Anti-diarrheals, intestinal anti-inflammatory/anti-infective agents (A07)	45 (1.5)
Analgesics (N02)	40 (1.4)
Ophthalmological agents (S01)	36 (1.2)
Total	1538 (52.3)
10–19 years	
Anti-bacterials for systemic use (J01)	555 (22.6)
Anti-acne preparations (D10)	155 (6.3)
Drugs for obstructive airway diseases (R03)	142 (5.8)
Anti-inflammatory and anti-rheumatic agents (M01)	120 (4.9)
Psychoanaleptics (N06)	117 (4.8)
Nasal preparations (R01)	85 (3.5)
Anti-epileptics (N03)	78 (3.2)
Anti-histamins for systemic use (R06)	68 (2.8)
Drugs for acid-related disorders (A02)	63 (2.6)
Psycholeptics (N05)	52 (2.1)
Total	1435 (58.6)

In concordance with surveys performed in other countries [4, 21, 25], we observed anti-infectives, drugs for the respiratory system, and pain medication to be most often prescribed to children and adolescents in the primary care setting. These medicines are used commonly across all ages.

In hospitals, highest prescription frequencies occurred for anti-infectives (mainly systemic antibiotics) and drugs for the nervous system (analgesics, anesthetics) and alimentary tract (mainly antacids, anti-emetics). These data are comparable

with the results of surveys performed in Switzerland [8], Finland [18], and the USA [13, 16]. Analysis by therapeutic class (ATC level 2) confirms that anti-bacterials for systemic use, anti-inflammatory agents, analgesics, and anesthetics comprise more than one third of all drugs used for children and adolescents in hospitals. The comparison of results between primary care and hospital settings needs to be interpreted with caution due to differences between database structures.

**Table 2** The ten most frequently prescribed medicines (ATC level 5) in primary and/or hospital care settings, in Austria

ATC code level 5	Substance	Primary care percentage of all prescriptions	Hospital care percentage of all prescriptions
J01CR02	Amoxicillin and beta-lactamase inhibitor	6.0	1.8
M01AE01	Ibuprofen	0.7	5.1
N02BE01	Paracetamol	1.5	3.8
J01DC04	Cefaclor	4.2	0.2
J01CA01	Ampicillin	0	3.9
J01FA09	Clarithromycin	2.3	0.7
M01AG01	Mefenamic acid	1.5	1.2
N06BC01	Caffeine	0	2.5
J01CE10	Benzathine phenoxymethylpenicillin	2.2	0.2
H02AB06	Prednisolone	0.5	1.8

The top 10 prescribed classes covered 54% of total prescriptions in primary care. This rate is much lower in Austria than in a study from Italy where the ten most commonly prescribed classes covered more than 80% of prescriptions [4]. Although differences in the study populations and methodology have to be considered, this difference may indicate that prescriptions are more dispersed among different classes for children in Austria.

Compared to amoxicillin and phenoxymethylpenicillin, we observed a rather high prescription frequency of broad-spectrum penicillins like amoxicillin with beta-lactamase inhibitor. Also, second-generation cephalosporins and macrolides were quite frequently prescribed which has also been described in Germany [11].

Use of anti-inflammatory/anti-rheumatic drugs and analgesics is highly common in both primary care and hospital settings. Among these substances, we primarily found non-steroidal anti-inflammatory drugs (e.g., ibuprofen, mefenamic acid, ketoprofen), paracetamol, and metamizole sodium. The age cutoffs for recommended use differ in the corresponding Summaries of Product Characteristics, and the choice of the appropriate medicine needs to be made carefully. Especially in neonates and infants, overdosing is an issue, whereas older children may be at risk of underdosing [15]. Ibuprofen, licensed for children from 3 months of age, was found to be the substance most frequently used in hospital, followed by paracetamol (approved for children with a body weight of more than 3 kg). Despite a relatively good safety profile, there are concerns regarding the tolerability of NSAIDs, particularly the increased risk of gastrointestinal bleeding and impaired renal function [9]. Results of a retrospective multicenter study in Italy showed that 69% of children referred to emergency room for suspected gastrointestinal bleeding after NSAID intake had been treated with ibuprofen [3] and 47% had been treated at inappropriate dose, duration, and age. Given that actual ibuprofen use in children is even more widespread than documented in literature reports and our results, we must be wary of a rather high frequency of inappropriate use. Moreover, the frequent use of ibuprofen is not consistent with

guidelines recommending paracetamol as analgesic and anti-pyretic drug of first choice [7]. However, this may be the result of a paper on the use of anti-pyretics in children which considered paracetamol and ibuprofen more or less comparable regarding safety and effectiveness [26].

Another remarkable finding is the high prevalence of pantoprazole prescriptions, both in primary care and in hospitals. Among medicines for alimentary tract and metabolism, pantoprazole was the most prevalent substance in both care settings. We did not find similar reports in comparable studies [21, 22, 25]. Pantoprazole is recommended in adolescents aged 12 years and above for the symptomatic and long-term treatment as well as for relapse prevention of gastroesophageal reflux disease. For treatment of gastric or duodenal ulcer, pantoprazole is only licensed for adults. Janett et al. found a potential association of long-term use of proton-pump inhibitors and hypomagnesemia in adults [14]. Therefore, the potential risk for children and adolescents being treated with pantoprazole must be born in mind. Identifying the reasons for the frequent use of pantoprazole would be an interesting subject of further investigations on medicine use in children in Austria.

Having established prescription patterns for children and adolescents in Austria, we are faced with the question what evidence this treatment is based on [1]. Ideally, pharmacotherapy in children should be based on medicines specifically developed for children with systematic evaluation of age-appropriate doses, efficacy, and safety in clinical trials. In recent years, several initiatives have been launched to generate more solid evidence for pediatric medicines [10, 27]. However, much of the current pediatric use of medicines is still based on observational data from the academic literature or practical experience only. There is a need to collect this heterogeneous information on pediatric medicines, critically appraise it, and make it readily available for practicing clinicians, as for example in the Dutch Kinderformularium or the British National Formulary for Children [23, 28]. The present survey is part of a project to develop an information platform for pediatric medicines for Austria. The hit list of 150

medicines identified in the survey will be the basis for working up their evidence base and developing an Internet-based information platform. This tool is intended to support practicing physicians and other health care professionals to improve the quality and minimize the risks of pharmacotherapy in children and adolescents in Austria.

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**Authors' contributions** E. Rauch contributed to the conception and design of the study, data collection, data analysis, interpretation of findings, drafting the article, revising the article, and final approval of the version submitted. H. Herkner and F. Lagler contributed to study conception, data analysis, interpretation of findings, critical revision of the article, and final approval of the version submitted. R. Saueremann and S. Hetz contributed to collection of data, critical revision of the article, and final approval of the version submitted. W. Gall contributed to data processing and data analysis, critical revision of the article, and final approval of the version submitted. C. Male contributed to conception and design of the study, had final responsibility for the study, contributed to data analysis and interpretation, revised the manuscript, and approved the final manuscript as submitted.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors. The survey did not study any individual patient data but assessed summary data on prescription frequencies. Therefore, no ethical approval was obtained and informed consent was not applicable.

## References

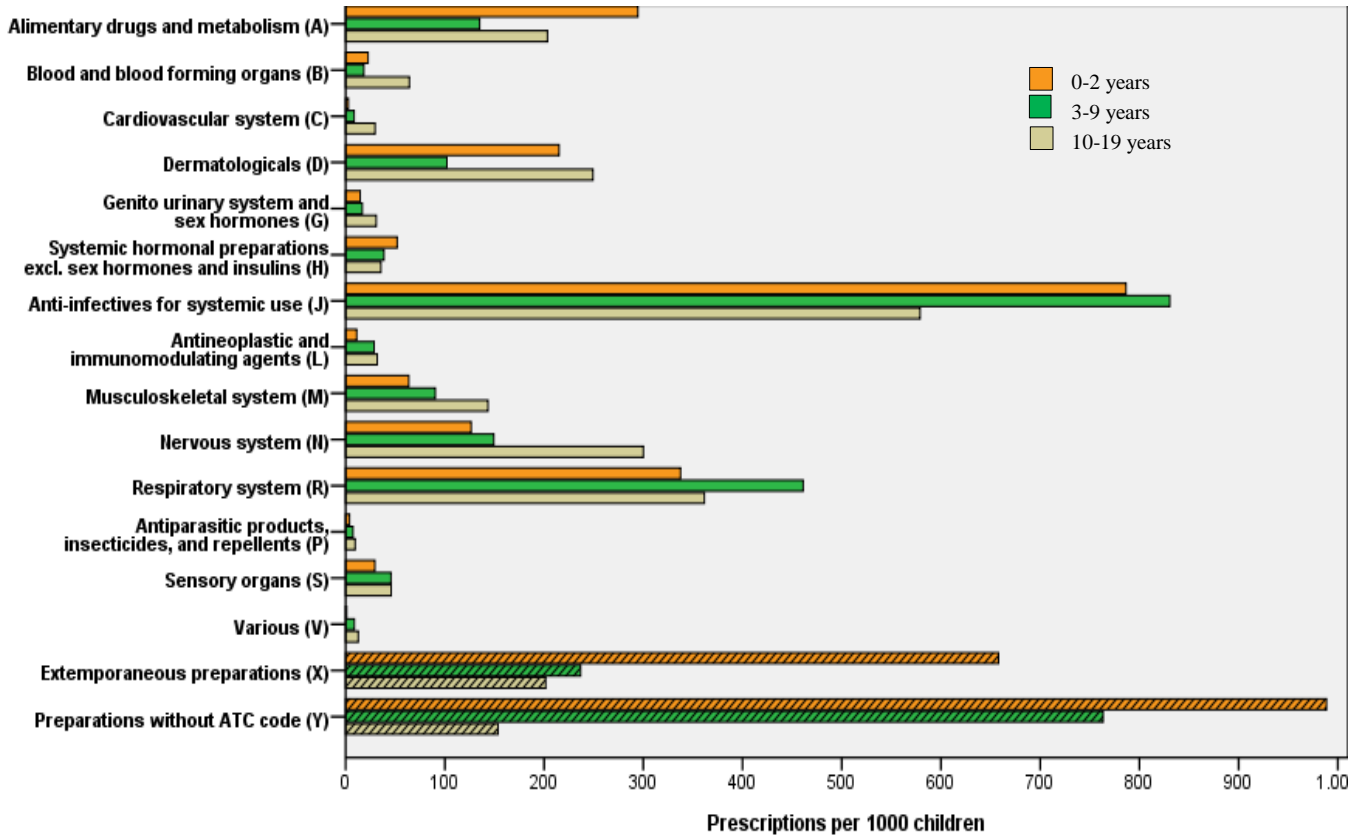
- Bonati M, Pandolfini C (2011) Off-label drug use in children should be rational. *Arch Dis Child* 96(9):870–871
- Bonati M, Jacqz-Aigrain E, Choonara I (2017) Licensed medicines, off-label use or evidence-based. Which is most important? *Arch Dis Child* 102(1):53–54
- Cardile S, Martinelli M, Barabino A, Gandullia P, Oliva S, di Nardo G, Dall'Oglio L, Rea F, de'Angelis GL, Bizzari B, Guariso G, Masci E, Staiano A, Miele E, Romano C (2016) Italian survey on non-steroidal anti-inflammatory drugs and gastrointestinal bleeding in children. *World J Gastroenterol* 22(5):1877–1883
- Cazzato T, Pandolfini C, Campi R, Bonati M, ACP Puglia-Basilicata Working Group (2001) Drug prescribing in out-patient children in Southern Italy. *Eur J Clin Pharmacol* 57(8):611–616
- Clavenna A, Bonati M (2009) Drug prescriptions to outpatient children: a review of the literature. *Eur J Clin Pharm* 65:749–755
- Czarniak P, Bint L, Faviè L, Parsons R, Hughes J, Sunderland B (2015) Clinical setting influences off-label and unlicensed prescribing in a paediatric teaching hospital. *PLoS One* 10(3):e0120630
- De Martino M, Chiarugi A (2015) Recent advances in pediatric use of oral paracetamol in fever and pain management. *Pain Ther* 4: 149–168
- Di Paolo E, Stoetter H, Cotting J, Frey P, Gehri M, Beck-Popovic M, Tolsa JF, Fanconi S, Pannatier A (2006) Unlicensed and off-label drug use in a Swiss paediatric university hospital. *Swiss Med Wkly* 136:218–222
- Dills R, Anderson LA, Pierce CA (2012) The role of nonsteroidal anti-inflammatory drugs in pediatric patients. *Pharmacol Res* 65(1):5–8
- European Commission (2006) Regulation (EC) No1901/2006 and 1902/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use. *Official J Eur Communities*, 18: L378/1 and L/20
- Holstiege J, Enders D, Schink T, Innocenti F, Oteri A, Bezemer I, Kagueidou F, Molokhia M, Poluzzi E, Puccini A, Ulrichsen SP, Sturkenboom MC, Trifiro G, Garbe E (2015) Trends in paediatric macrolide use in five European countries—a population based study. *Eur J Clin Pharmacol* 71:991–999
- Horen B, Montastruc JL, Lapeyre-Mestre M (2002) Adverse drug reactions and off-label drug use in paediatric outpatients. *Br J Clin Pharmacol* 54(6):665–670
- Hsu B, Brazelton T (2009) Off-label medication use in an academic hospital pediatric critical care unit. *WMJ* 108(7):343–348
- Janett S, Camozzi P, Peeters G, Lava S, Simonetti G, Simonetti B, Bianchetti M, Milani G (2015) Hypomagnesemia induced by long-term treatment with proton-pump inhibitors. *Gastroenterol Res Pract* 951768
- Kazouini A, Mohammed BS, Simpson CR, Helms PJ, McLay JS (2011) Paracetamol prescribing in primary care: too little and too much? *Br J Clin Pharmacol* 72(3):500–504
- Lasky T, Ernst FR, Greenspan J, Wang S, Gonzalez L (2011) Estimating pediatric inpatient medication use in the United States. *Pharmacoepidemiol Drug Saf* 20(1):76–82
- Lass J, Irs A, Pisarev H, Leinemann T, Lutsar I (2011) Off label use of prescription medicines in children in outpatient setting in Estonia is common. *Pharmacoepidemiol Drug Saf* 20(5):474–481
- Lindell-Osuagwu L, Korhonen MJ, Saano S, Helin-Tanninen M, Naaranlahti T, Kokki H (2009) Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. *J Clin Pharm Ther* 34(3):277–287
- Mason J, Pirmohamed M, Nunn T (2012) Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature. *Eur J Clin Pharmacol* 68:21–28
- Neubert A, Dormann H, Weiss J, Egger T, Criegee-Rieck M, Rascher W, Brune K, Hinz B (2004) The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. *Drug Saf* 27(13):1059–1067
- Olsson J, Kimland E, Pettersson S, Odland V (2011) Paediatric drug use with focus on off-label prescriptions in Swedish outpatient care—a nationwide study. *Acta Paediatr* 100(9):1272–1275
- Palmaro A, Bissuel R, Renaud N, Durrieu G, Escourrou B, Oustric S, Montastruc JL, Lapeyre-Mestre M (2015) Off-label prescribing in pediatric outpatients. *Pediatrics* 135(1):49–58
- Pharmaceutical Press (2016) *British National Formulary for Children*
- Rashed AN, Wong IC, Wilton L, Tomlin S, Neubert A (2015) Drug utilisation patterns in children admitted to a paediatric



- general medical ward in five countries. *Drugs Real World Outcomes* 2(4):397–410
25. Sturkenboom MC, Verhamme KM, Nicolosi A et al (2008) Drug use in children: cohort study in three European countries. *BMJ* 337: a2245. <https://doi.org/10.1136/bmj.a2245>
  26. Sullivan JE, Farrar HC (2011) Fever and antipyretic use in children. *Pediatrics* 127:580–587
  27. US Food and Drug Administration (2007) Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA) 2007 <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf> (accessed 2017-09)
  28. Van der Zanden TM, de Wildt SN, Liem Y, Offringa M, de Hoog M et al (2017) Developing a paediatric drug formulary for the Netherlands. *Arch Dis Child* 102(4):357–361. <https://doi.org/10.1136/archdischild-2016-311674>

Electronic supplementary material (ESM 1)

Figure 3: Prescription frequencies in primary care of medicine groups (ATC level 1) stratified by age cohorts



**Electronic supplementary material (ESM 2)**

**Table 3: Eighty percent most frequently prescribed chemical substances (ATC level 5) used in primary and hospital care (n=150)**

ATC Code level 5	Name	Primary care percentage of all prescriptions (%)	Hospital care percentage of all prescriptions (%)	License status for use in children (0-18 years)
J01CR02	Amoxicillin & beta-lactamase inhibitor	6.0	1.8	complete
M01AE01	Ibuprofen	0.7	5.1	partial
N02BE01	Paracetamol	1.5	3.8	complete
J01DC04	Cefaclor	4.2	0.2	complete
J01CA01	Ampicillin	*	3.9	complete
J01FA09	Clarithromycin	2.3	0.7	complete
M01AG01	Mefenamic acid	1.5	1.2	partial
N06BC01	Caffeine	*	2.5	complete
J01CE10	Benzathine Phenoxymethylpenicillin	2.2	0.2	complete
H02AB06	Prednisolone	0.5	1.8	partial
J01FA10	Azithromycin	2.2	*	complete
R03AC02	Salbutamol	1.2	0.9	partial
D03AX03	Dexpanthenol	*	2.0	complete
J01DC02	Cefuroxime	*	1.9	complete
J01XA01	Vancomycin	*	1.8	complete
R03DC03	Montelukast	1.8	*	complete
A02BC02	Pantoprazole	0.6	1.1	partial
S01XA02	Retinol	*	1.7	no
J01CA04	Amoxicillin	1.6	*	complete
R01AA05	Oxymetazoline	0.3	1.2	complete
B02BA01	Phytomenadione	*	1.4	complete
R03BA05	Fluticasone	1.1	0.2	complete
D10BA01	Isotretinoin	1.3	*	partial
R01AA	Sympathomimetics, plain	1.0	0.2	complete
M01AE14	Dexibuprofen	0.4	0.8	partial
J01FF01	Clindamycin	0.4	0.7	partial
J01GB03	Gentamicin	*	1.1	complete
N06BA04	Methylphenidate	1.1	*	partial
R06AX27	Desloratadine	1.1	*	complete
M01AB05	Diclofenac	0.4	0.7	partial
B05AA01	Albumin	*	1.0	complete
J01XX01	Fosfomycin	*	0.9	complete
J01DH02	Meropenem	*	0.9	partial
N03AG01	Valproic acid	0.7	0.2	complete
C02AC01	Clonidine	*	0.9	no
J01CE02	Phenoxymethylpenicillin	0.9	*	complete

ATC Code level 5	Name	Primary care percentage of all prescriptions (%)	Hospital care percentage of all prescriptions (%)	License status for use in children (0-18 years)
A06AD65	Macrogol, combinations	0.4	0.5	partial
R05DA04	Codeine	0.8	*	no
B01AB05	Enoxaparin	0.6	0.3	no
A04AA01	Ondansetron	*	0.8	partial
J01DD13	Cefpodoxime	0.8	*	complete
D01AA01	Nystatin	0.3	0.4	complete
A10AB05	Insulin aspart	0.6	0.1	complete
R03BA02	Budesonide	0.4	0.2	complete
D11AX	Other dermatologicals	0.6	*	complete
N01BB20	Combinations	*	0.6	complete
A02BC05	Esomeprazole	0.3	0.3	partial
J01DD02	Ceftazidime	*	0.6	complete
D05AA	Tars	*	0.6	no
B01AB01	Heparin	*	0.6	partial
R01AA07	Xylometazoline	*	0.6	partial
R01AD09	Mometasone	0.6	*	partial
A11CC05	Colecalciferol	0.3	0.3	complete
J01FA07	Josamycin	0.6	*	complete
N03AX14	Levetiracetam	0.3	0.3	partial
A01AB09	Miconazole	0.4	0.2	complete
A12CC03	Magnesium gluconate	*	0.6	no
J01XD01	Metronidazole	*	0.6	complete
J01AA02	Doxycycline	0.3	0.3	partial
A01AD02	Benzylamine	*)	0.6	partial
A07CA	Oral rehydration salt formulations	0.6	*)	complete
N05CC01	Chloral hydrate	*	0.5	no
A03AX13	Silicones	*	0.5	complete
J01CR04	Sultamicillin	*	0.5	partial
A12AA20	Calcium (different salts in combination)	*	0.5	complete
R05CB06	Ambroxol	0.5	*	complete
D07AC14	Methylprednisolone aceponate	0.3	0.2	partial
R06AE07	Cetirizine	0.5	*	partial
J01DB01	Cefalexin	0.5	*	complete
A07FA01	Lactic acid producing organisms	0.5	*	complete
N06AB06	Sertraline	0.5	*	partial
J01MA02	Ciprofloxacin	0.3	0.2	complete
A09AA02	Multienzymes	*	0.5	complete
J01DD01	Cefotaxime	*	0.5	complete
J02AC01	Fluconazole	*	0.5	complete
R06AE09	Levocetirizine	0.3	0.2	partial
R03AK06	Salmeterol and fluticasone	0.5	*	partial

ATC Code level 5	Name	Primary care percentage of all prescriptions (%)	Hospital care percentage of all prescriptions (%)	License status for use in children (0-18 years)
M01AE02	Naproxen	0.5	*	complete
J05AB01	Aciclovir	*	0.5	complete
C07AB03	Atenolol	*	0.5	no
L03AX	Other immunostimulants	0.4	*	complete
R07AA02	Natural phospholipids	*	0.4	complete
C01CA24	Epinephrine	*	0.4	complete
J01CR01	Ampicillin and beta-lactamase inhibitor	*	0.4	complete
C01CA04	Dopamine	*	0.4	no
S01AA11	Gentamicin	*	0.4	complete
J01DD08	Cefixime	0.4	*	complete
J01GB01	Tobramycin	*	0.4	complete
D10AF01	Clindamycin	0.4	*	partial
J01AA08	Minocycline	0.4	*	partial
D06AX	Other antibiotics for topical use	*	0.4	complete
A07AA02	Nystatin	*	0.4	complete
N03AX09	Lamotrigine	0.4	*	partial
S01XA20	Artificial tears and other indifferent preparations	*	0.4	no
H02AB09	Hydrocortisone	*	0.4	complete
N05BA01	Diazepam	*	0.4	partial
J06BA02	Immunglobulins, normal human, for intravascular adm.	*	0.4	complete
J01CE01	Benzylpenicillin	*	0.4	complete
D10AX03	Azelaic acid	0.4	*	partial
N01AH01	Fentanyl	*	0.4	partial
D10AD03	Adapalene	0.3	*	partial
A03FA03	Domperidone	0.3	*	complete
D01AC01	Clotrimazole	*	0.3	partial
R01AX10	Various nasal preparations	*	0.3	partial
S01GX02	Levocabastine	0.3	*	partial
H02AB02	Dexamethasone	*	0.3	complete
N03AA02	Phenobarbital	*	0.3	no
R01AX30	Combinations (Other nasal preparations)	*	0.3	partial
R05CB10	Combinations	0.3	*	partial
V01AA02	Grass pollen	0.3	*	partial
R05CB01	Acetylcysteine	0.3	*	partial
H02AB04	Methylprednisolone	*	0.3	complete
N06BA09	Atomoxetine	0.3	*	partial
J01EE03	Sulfametrole and trimethoprim	*	0.3	partial
R01AD12	Fluticasone furoate	0.3	*	partial
S01FB01	Phenylephrine	*	0.3	no
R02AB	Antibiotics	0.3	*	partial

ATC Code level 5	Name	Primary care percentage of all prescriptions (%)	Hospital care percentage of all prescriptions (%)	License status for use in children (0-18 years)
M01AE03	Ketoprofen	*	0.3	no
N02BB02	Metamizole sodium	*	0.3	partial
B03XA01	Erythropoietin	*	0.3	partial
N05AX08	Risperidone	0.3	*	partial
J01CR05	Piperacillin and beta-lactamase inhibitor	*	0.3	partial
S01AX18	Povidone-Iodine	*	0.3	no
J02AA01	Amphotericin B	*	0.3	partial
A01AD11	Other agents for local oral treatment	*	0.3	complete
N05BA06	Lorazepam	*	0.2	partial
J01XX08	Linezolid	*	0.2	no
A03BB01	Butylscopolamine	*	0.2	partial
H03AA01	Levothyroxine sodium	*	0.2	complete
L04AB02	Infliximab	*	0.2	partial
N01BB02	Lidocaine	*	0.2	partial
B02BD02	Coagulation factor VIII	*	0.2	complete
N01AX14	Esketamine	*	0.2	complete
B05AA02	Other plasma protein fractions	*	0.2	no
A03BA01	Atropine	*	0.2	complete
C03DA01	Spirolactone	*	0.2	partial
D04AA13	Dimetindene	*	0.2	complete
J01DD04	Ceftriaxone	*	0.2	complete
J05AB06	Ganciclovir	*	0.2	partial
M03AC09	Recuronium bromide	*	0.2	complete
N01AX10	Propofol	*	0.2	partial
R01AB01	Phenylephrine	*	0.2	partial
R03CC03	Terbutaline	*	0.2	no
C01CA03	Norepinephrine	*	0.2	no
B01AB02	Antithrombin III	*	0.2	complete
R06AB03	Dimetindene	*	0.2	partial
R06AA02	Diphenhydramine	*	0.2	partial
B01AC09	Epoprostenol	*	0.1	no
L04AC02	Basiliximab	*	0.1	partial
N02AF02	Nalbuphine	*	0.1	complete

Medicines belonging to the top 80% in both settings are marked in red (n=30), to top 80% in primary care only are marked in green (n=36), to top 80% in hospital care only are marked in blue (n=84). Age was used as single criterion to define licence status for use in children, based on the approved age in the summary of product characteristics of medicines in the respective chemical substance group (ATC level 5). The Austria Codex was used as reference.

\*) not among 80% of most frequently prescribed substances in the corresponding care setting