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Research paper

Paediatric outpatient prescriptions in France between 2010 and 2019: A nationwide population-based study
Paediatric outpatient prescriptions in France, 2010 to 2019

Marion Taine[a,b,*], Lucile Offredo[a,b], Rosemary Dray-Spira[b], Alain Weill[b], Martin Chalumeau[a,c], Mahmoud Zureik[b,d]

[a] Obstetrical, Perinatal and Pediatric Epidemiology Research Team, Centre of Research in Epidemiology and StatisticS, U1153 Inserm, Université de Paris, F-75004 Paris, France
[b] EPI-PHARE (French National Agency for Medicines and Health Products Safety -ANSM- and French National Health Insurance -CNAM-), Saint-Denis, France
[c] Department of General Paediatrics and Paediatric Infectious Diseases, Necker-Enfants Malades Hospital, AP-HP, Université de Paris, Paris, France
[d] Université Paris-Saclay, Université Versailles Saint-Quentin-en-Yvelines, Université Paris-Sud, Inserm, Anti-infective evasion and pharmacoepidemiology, CESP, 78180, Montigny-le-Bretonneux, France

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ABSTRACT

Background: Paediatric outpatient prescription (POP) monitoring is pivotal to identify inadequate prescriptions and optimize drug use. We aimed at describing recent trends in POPs in France.
Methods: All reimbursed dispensations of outpatient prescribed drugs (excluding vaccines) were prospectively collected for the paediatric population (<18 years old) in the French national health database in 2010–2011 and 2018–2019 (mean 117,356,938/year). POP prevalence (proportion of children receiving ≥1 drug prescriptions/year) was calculated by age groups and compared by prevalence rate ratios (PRRs). Given the large sample size, 95% confidence intervals of POP prevalences and PRRs did not differ from estimates.
Findings: Among the 14,510,023 children resident in France in 2018–2019, mean POP prevalence was 857‰ children. Most prescribed therapeutic classes were analgesics (643‰), antibiotics (405‰), nasal corticosteroids (328‰), nonsteroidal anti-inflammatory drugs (NSAIDs) (244‰), antihistamines (246‰) and systemic corticosteroids (210‰). POPs decreased with age from 976‰ for infants to 782‰ for adolescents. Children <6 years old were notably more exposed to inhaled corticosteroids (PRR=3.06), non-penicillin beta-lactam antibacterial agents (PRR=3.05) and systemic corticosteroids (PRR=2.11) than older ones. The POP prevalence was slightly higher (PRR=1.04) during 2018–2019 than 2010–2011, with marked increases for anti-emetics (PRR=1.84), vitamin D (PRR=1.49), proton pump inhibitors (PRR=1.42), systemic contraceptives (PRR=1.24) and nasal corticosteroids (PRR=1.21) and decreases for propulsive/prokinetic agents (PRR=0.09), NSAIDs (PRR=0.73) and systemic antibiotics (PRR=0.88).
Interpretation: POP remained highly prevalent in France throughout the 2010s, especially for children <6 years old, with only a few improvements for selected therapeutic classes. These findings should prompt clinical guidance campaigns and/or regulatory policies.
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1. Introduction

The paediatric population and especially the youngest children are particularly vulnerable to short- and long-term adverse drug effects because of their physiological and developmental immaturity [1,2]. Paradoxically, paediatric medicine development has been neglected for decades [3], leading to highly frequent use of drugs not or insufficiently evaluated for this specific age group [3,4]. Severe drug adverse events and massive off-label prescribing in the paediatric population [5-7] paved the way for legislation ensuring access to evidence-based use of drugs in children [8]. These regulations mainly allowed for a better assessment of frequent short-term adverse effects [9], with rare and/or long-term adverse effects of drugs in the paediatric population often remaining unknown. Such a gap in knowledge should prompt avoiding inappropriate and unnecessary prescriptions in the paediatric population. Thus, the monitoring of

* Corresponding author at: EPI-PHARE – 143/147 Boulevard Anatole France – 93285 Saint-Denis CEDEX - FRANCE
E-mail address: marion.taine@inserm.fr (M. Taine).

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Research in Context

Evidence before this study

The monitoring of paediatric outpatient prescriptions (POPs) at the population level is of paramount importance to identify chronic or emerging areas of inappropriate prescriptions and prepare corrective actions such as clinical guidance or regulatory decisions.

In France, the only available study dates from 2011 and reported concerning findings, with the world's highest prevalence of drug dispensation for paediatric patients before age 2 years (97% of infants had been exposed to ≥1 drug over the year). This over-prescription included drugs with high risk of adverse events such as antibiotics and systemic corticosteroids or drugs without a demonstrated benefit but with safety concerns. Since then, several regulations came into force in France and POPs may have significantly changed.

Added value of this study

This comprehensive study of the French paediatric prescription database — including a mean of 117,356,938 prescriptions/year — showed up-to-date POP prevalences and the last decade trends by age groups. POPs remained highly prevalent in France throughout the 2010s and consistently by sex and different age groups including neonates, with only few improvements in selected therapeutic classes. This study especially highlighted a persistent high POP prevalence for children <6 years old (971‰), for systemic corticosteroids (210‰) and antibiotics (405‰). Some regulatory decisions and safety warnings probably contributed to a decrease in some POP trends (eg. antibiotics, NSAIDs). Other decisions led to a substitution of drugs with additional safety concerns.

Implication of all the available evidence

The French POP level is amongst the highest amongst countries with advanced economies and is rather due to an inadequate positive attitude of physicians and the public toward drug use in children than to epidemiological differences of disease prevalences between countries. These findings should prompt new clinical guidance campaigns and/or regulatory decisions such as drug reimbursement cessation or incentives to optimize practices, also taking into account the risk of drug substitution. Priority targets should probably be corticosteroids and antibiotics, given their adverse side effects and their high level of POPs. Finally, determinants of the very high POP prevalence need to be explored to better target prescribers and populations at risk of high drug prescription. Regular assessments of POP trends are needed to evaluate the impact of corrective actions and detect the emergence of inappropriate POPs.

paediatric outpatient prescriptions (POPs) at the population level is of paramount importance to identify chronic or emerging areas of inappropriate prescriptions and prepare corrective actions such as clinical guidance or regulatory decisions [4,10-12].

POPs should be monitored regularly, but few population-based studies have been performed in the last decade in countries with advanced economies. In 2009, Clavenna et al. reported that the prevalence of children exposed to ≥1 drug over a year ranged from 510‰ in Denmark to 70‰ in Greenland and the median number of different drugs used per child over a year ranged from 0·8 in Norway to 3·2 in the United States [4]. In this last country, Hales et al. showed an overall decrease in drug prescription in children between 1999 and 2014, in particular for antibiotics, anti-histamines and anti-cough medications, but an increasse in the prescription of anti-asthmatic drugs and stimulants for attention-deficit disorders [13]. In New Zealand, Tomlin et al. also showed a decrease in antibiotic prescription between 2010 and 2015, with a slight increase in prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and antihistamines and striking increase in anti-emetic agents [14]. In France, the only available study reported concerning findings [15], with the world's highest prevalence of drug dispensation for paediatric patients before age 2 years: 97% of infants had been exposed to ≥1 drug over the year 2011, with a median of 9 drugs per infant per year. This over-prescription included drugs with high risk of adverse events such as antibiotics [16] and systemic corticosteroids [17] or drugs without a demonstrated benefit but with safety concerns (nasal decongestants [18], cough drugs [19] and propulsive/prokinetic agents [20]). This high prevalence of dispensation is probably related, amongst other explanations, to the positive attitude toward drugs by physicians and public because 90% of consultations end with a prescription in France [21,22].

Since this publication, several regulations came into force in France and included the cessation of the reimbursement of nasal decongestants [23], the removal of cough drugs from the market for the youngest children [24], warnings related to the safety of NSAIDs [25], and recommendations promoting the better use of antibiotics for upper respiratory tract infection [26], with the latter leading to significant change in prescription patterns . In this context, POPs may have significantly changed. Our objective was to investigate recent POPs in France and to compare them with those in 2010−2011, at the national level.

2. Methods

2.1. General methodology

We conducted a national administrative database analysis and followed the RECORD-PE guidelines to report the results [27]. The French National Health Data System (Système national de données de santé [SNDS]) covers 98•8% of the French population and includes reimbursement data for ambulatory care (the health insurance claims database, or Datamart de Consommation Inter-Régime [DCIR]) for all children covered by the Universal Public Health Insurance in France [28-30]. Every user (or parent user for children) of the French Public Health Insurance is informed of his/her opposition right regarding the use of their data for research purposes. The EPI-PHARE scientific group has regulatory permanent access to the SNDS database (French Decree no. 2016−1871 from December 26, 2016).

In this study, the term "prescriptions" refers to prescribed and dispensed reimbursed drugs in outpatient settings and excludes vaccines and not-reimbursed over-the-counter (OTC) drugs. Vaccines were excluded because free-of-charge (non-reimbursed) vaccinations are performed in dispensaries and account for as much as 5% of vaccinations in children <6 years old, thereby preventing a population-based exhaustive evaluation with the DCIR database. In France, some drugs available as OTCs are also reimbursed when prescribed because they are included on the list of reimbursable pharmaceutical specialities (e.g., paracetamol, NSAIDs). They are then evaluable in the DCIR. However, drugs not included in this list (e.g., homoeopathy, phytotherapy, carbocysteine) or purchased as OTCs without a prescription were not evaluable in the DCIR.

2.2. Inclusion criteria, cohort constitution and data extracted

The eligible participants were children <18 years old present in the DCIR between January 1, 2010 and December 31, 2011 and/or between January 1, 2018 and December 31, 2019. Each child was historically followed from the beginning of the study period if they belonged to the DCIR or from the date of their inclusion if it occurred during the

study period. The follow-up ended with the occurrence of one of the following events: end of the study period, 18-year birthday or death.

Two open cohorts of 2 years each were constituted at a 6-year interval. A 2-year period was chosen for each cohort to allow for modulating annual fluctuations in prescriptions related to the variable intensity of viral epidemics. The 2018–2019 cohort allowed for studying current prescriptions, and comparisons with the 2010–2011 cohort allowed for identifying trends, assuming their monotony.

For each participant, we collected data on sex, all reimbursed dispensed drugs classified according to the Anatomical Therapeutic Chemical (ATC) classification [31], and age at dispensation.

2.3. Statistical analyses

To describe the general characteristics of the study population in 2010–2011 and 2018–2019, we calculated the total distribution of person-years by sex and age groups over these 2 periods. Then, we calculated the median (interquartile range [IQR]) number of drugs prescribed by year, for the overall paediatric population then by age groups adapted from those suggested by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals [1] (≤ 6 weeks of life, 0–23 months, 2–5 years, 6–11 years, 12–17 years). Because the DCIR database is not exhaustively updated each year for children without any drug prescription, we approximated the total number of person-years spent in an age category by averaging the number of children residing in France on January 1 of the investigated year and the following year by using the census figures provided by the National Institute of Statistics and Economical studies [32,33].

For the 2 periods (2010–2011 and 2018–2019), we estimated the POP prevalence (i.e., the mean annual prevalence of ≥1 prescription) by dividing the total number of children with at least one drug prescription over a calendar year by the total number of person-years for this year [10]. For neonates and infants ≤6 weeks old, the POP prevalence was similarly estimated except that the total number of infants born in a year with at least one drug prescription during the first 6 weeks of life was divided by the total number of live births the same year. These POP prevalences were calculated for the overall paediatric population and by age groups, sex and drug anatomical classes (level 1 ATC classification) and therapeutic classes (levels 2 to 4 ATC classification) and, for the most prescribed drugs, by active substances (level 5 ATC classification). In addition, yearly prevalence of prescription of at least 2 drugs of the same therapeutic class were calculated overall and by age groups to have an indicator of repeated prescription over the year mixing repeated acute prescriptions and chronic prescriptions. The therapeutic classes (ATC levels 2 to 4) and ATC level 5 drugs at high POP (i.e., prescribed to >100‰ of the paediatric population per year) [12], were described. Crude prevalence rate ratios (PRRs) were used to evaluate ratios in POP prevalence by the 2 studied periods and sex. We described the main increasing and decreasing trends of POP prevalence by therapeutic classes from 2010 to 2011 to 2018–2019. To prepare key messages for future targeted corrective actions, we compared PRRs between the age groups < 6 versus ≥ 6 years old during 2018–2019. Indeed, many consultations are due to self-limited diseases amongst children < 6 years old and result in potentially avoidable prescriptions [34,35]. In contrast, amongst older children, the consultation rate is lower [34] and adherence to the follow-up and treatment may be less optimal in some chronic diseases [36,37]. Given the very large sample size, 95% confidence intervals (CI) of POP prevalence and PRR were reported only when their values with 2 decimals differed from estimates.

2.4. Role of funding source

Not applicable as there was no external funding for this study.

3. Results

3.1. Overall drug prescriptions

During the 2018–2019 period, the 14,510,023 French paediatric residents received a mean of 117,356,938 prescriptions/year, with a median of 5 [IQR 3–8] different drugs/child/year; 12,431,002 paediatric patients received ≥1 outpatient prescription/year, for a POP prevalence of 857‰/year (Table 1 and Supplementary Table S1). POP prevalences were 976‰, 969‰, 828‰, and 782 ‰ for paediatric patients <2, 2–5, 6–11 and 12–17 years old, respectively (Table 1). The POP prevalence was similar for girls (863‰) and boys (851‰; PPR=1•01), except during adolescence, when it was higher for girls (PRR=1•06) (Table 1).

3.2. Main drug prescriptions

The most commonly prescribed ATC level 1 drugs were for the nervous system (672‰), the alimentary tract and metabolism (516‰), and respiratory system (499‰) as well as anti-infective agents for systemic use (412‰) (Fig. 1). The prevalence rates of prescribing for some ATC level 1 drugs were mainly due to a unique therapeutic class or one specific drug (e.g., prevalence for paracetamol was 641‰; after excluding paracetamol, the prevalence for nervous system drugs decreased from 672‰ to 165‰; Supplementary Figure S1). Children <6 years old had the highest prescription prevalence for most ATC levels, except for sex hormones and musculoskeletal products, which were more often prescribed to adolescents.

For 14 therapeutic classes, the POP prevalence was >100‰: analgesics (643‰), antibiotics (405‰), nasal corticosteroids (328‰), vitamin D (304‰), antihistamines (246‰), NSAIDs (244‰), systemic corticosteroids (210‰), cough suppressants (172‰), antiseptics (155‰), drugs for functional gastrointestinal disorders (142‰), antidiarrheal agents (119‰), anti-emetic agents (113‰), topical anaesthetics (113‰) and short-acting β2-agonists (111‰) (Table 2 with the corresponding ATC level 5 agents in Supplementary Table S2). The most repeatedly prescribed therapeutic classes over a year also corresponded to the 7 therapeutic classes with the highest POP prevalence: 371‰ for children receiving at least 2 prescriptions/year for analgesics, 180‰ for antibiotics, 125‰ for nasal corticosteroids, 102‰ for vitamin D, 80‰ for antihistamines, 70‰ for NSAIDs, and 64‰ for systemic corticosteroids (Table 3).

3.3. Age sub-groups

As compared with older children, those <6 years old more frequently received POPs for systemic corticosteroids (PRR=2·11), non-penicillin beta-lactam antibacterial agents (PRR=3·05), inhaled corticosteroids (PRR=3·06), topical anaesthetics (PRR= 3·46) and ophthalmological anti-infectives (PRR=5·06; Supplementary Figure S2). Children > 6 and <6 years old had similar POP prevalences for proton pump inhibitors (PPIs; PRR=0·98 [95% CI 0·97; 0·99]), NSAIDs (PRR=0·96) and cough suppressants (PRR=0·99). Systemic contraceptives (104‰ for adolescent girls) and anti-acne drugs (78‰ topical and 31‰ systemic) were mainly prescribed to adolescents (Table 2).

In neonates and infants ≤6 weeks old, the therapeutic classes (ATC levels 2–4) with high POP prevalence (Table 4) were vitamin D (404‰), antiseptics (279‰), vitamin K (260‰) and analgesics (215‰).

3.4. Drug prescription trends

The POP prevalence increased from 825‰ to 857‰ from 2010 to 2011 to 2018–2019 (PRR=1·04; Table 1). The main increasing trends of POP prevalence involved alimentary tract drugs with anti-emetics, vitamin D, and PPIs (PRR=1·84, 1·49 and 1·42, respectively),

Table 1
Distribution by sex and age group (years) of drug prescriptions during 2010–2011 and 2018–2019.

	2010–2011						2018–2019					
	All ages n = 14,446,249	≤6 weeks n = 897,151	<2 years n = 1600,769	2–5 years n = 3234,444	6–11 years n = 4876,185	12–17 years n = 4734,851	All ages n = 14,510,023	≤6 weeks n = 754,398	<2 years n = 1434,707	2–5 years n = 3085,950	6–11 years n = 4990,884	12–17 years n = 4998,483
≥1 prescription/year/child												
N	11,923,309	384,466	1,453,807	3,044,437	3,893,127	3,531,940	12,431,002	443,522	1,399,577	2,990,384	4,130,945	3,910,096
Prevalence (‰)	825	429	908	941	798	746	857	588	976	969	828	782
All												
Boys	818	431	910	945	796	723	851	590	978	974	828	762
Girls	833	426	907	937	801	770	863	585	968	960	829	807
No of drugs/year/child												
Median (IQR)	6 (3–9)	3 (2–4)	8 (5–12)	8 (5–12)	5 (3–8)	5 (3–8)	5 (3–8)	2(1–3)	6 (4–9)	7(4–10)	4 (3–7)	4 (2–7)
0, n	2,522,940	512,685	146,963	190,007	983,058	1,202,913	2,079,021	310,876	35,130	95,566	859,939	1,088,387
(%)	(17%)	(57%)	(9%)	(6%)	(20%)	(25%)	(14%)	(41%)	(2%)	(3%)	(17%)	(22%)
1–4, n	4,450,196	338,411	367,047	677,451	1,743,626	1,649,898	5,622,908	392,398	473,233	915,646	2,133,087	2,019,764
(%)	(31%)	(38%)	(23%)	(21%)	(36%)	(35%)	(39%)	(52%)	(33%)	(30%)	(43%)	(40%)
≥5, n	7,485,289	46,056	1,086,760	2,366,987	2,149,502	1,882,041	6,889,273	51,124	926,345	2,074,738	1997,859	1890,332
(%)	(52%)	(5%)	(68%)	(73%)	(44%)	(40%)	(47%)	(7%)	(65%)	(67%)	(40%)	(38%)

respiratory drugs with nasal corticosteroids, short-acting β2-agonists and inhaled corticosteroids (PRR=1·21, 1·17, and 1·10, respectively), and systemic contraceptives (PRR=1·24; Table 2). The main decreasing trends were for alimentary tract drugs with the propulsive/prokinetics agents (PRR=0·09), respiratory drugs with some nasal preparations, systemic antihistamines, leukotriene receptor antagonists, and cough suppressants (PRR= 0·00, 0·75, 0·80 and 0·85, respectively), antalgics with opioids (PRR=0·66), anti-inflammatory drugs with NSAIDs and topical products for muscle pain (PRR=0·73, and 0·75, respectively), and antibiotics (PRR=0·88). The POP prevalence significantly decreased for the main broad-spectrum antibiotics such as amoxicillin clavulanate (PRR=0·70), josamycin (PRR=0·61), cefpodoxime (PRR=0·42) and clarithromycin (PRR=0·35) but increased for amoxicillin (PRR=1·28; Supplementary Table S2).

POP prevalence in neonates and infants ≤6 weeks old increased from 429‰ to 588‰ from 2010 to 2011 to 2018–2019 (PRR=1·37) (Table 1). Amongst therapeutic classes with high POP prevalence in this age group, the prevalence significantly increased for vitamin D and analgesics (PRR=1·62 [95%CI: 1·61;1·63] and 1·95 [1·94;1·96]) (Table 4). Amongst the other therapeutic classes, the highest increasing trends of POP prevalence concerned PPIs (PRR=4·82 [95%CI: 4·78;4·86]), other drugs for gastrooesophageal reflux disease (alginic acid, PRR=3·22 [95%CI: 3·20;3·24]), antifungal drugs such as nystatin (PRR=3·91 [95%CI: 3·88;3·94]), amphotericin B (PRR=2·70 [2·67;2·73]) and topic econazole (PRR=3·69 [95%CI: 3·66;3·72]), topic anaesthetics (PRR=3·07 [95%CI: 3·05;3·09]), iron preparations (PRR=2·31 [95%CI: 2·28;2·34]), ophthalmological antibiotics (PRR=1·65 [95%CI: 1·63;1·67]), and nasal corticosteroids (PRR=1·59 [95%CI: 1·56;1·62]) (Tables 4 and Supplementary 3).

4. Discussion

4.1. Main results and interpretation

In this first comprehensive analysis of the national paediatric prescription database in France, one of the largest in the world, the current overall POPs (prevalence of 857‰) was the highest as compared with other countries or regions with similar economies, such as New Zealand (731‰) [14], British Columbia (Canada) (550‰) [38], Denmark (508‰) [39], and Italy (491‰) [40]. The high POPs was observed consistently by sex and different age groups including neonates, the most vulnerable group, but also amongst most therapeutic classes. These high levels of POP are not explained by a different epidemiology of diseases in France versus neighbouring countries [41] but more probably by French specificities in prescribing and reimbursing drugs for the paediatric population [21,22,42,43]. In France, prescriptions of drugs also available as OTCs represent a significant proportion of the total reimbursement for the ambulatory paediatric population [22,44]. Indeed, the French health insurance widely reimburses prophylactic drugs (e.g., vitamin D) or antalgics/antipyretics (e.g. paracetamol), and also numerous “old” drugs [45] with questionable benefit-risk ratio [19,46,47][67]. However, some prescription-only therapeutic classes, such as systemic antibiotics, corticosteroids or PPIs, have high levels of prescribing, which suggests substantial overprescribing.

In our study, French children were 5- and 20-fold more likely than American and Norwegian children, respectively, to receive POPs for systemic corticosteroids [48,49]. Amongst French children <6 years old, this ratio was increased to 33-fold as compared with Norwegian peers [49]. Systemic corticosteroids are responsible for well-known serious adverse effects [50] such as increased risk of infections [17]. Furthermore, systemic corticosteroid POPs decreased by only 3% during this 10-year period in France. Nasal corticosteroids, which carry some of the risks of systemic ones, were also widely prescribed in France as compared with several other countries [14,39,40,49]. The POP prevalence for nasal corticosteroids was 273‰, whereas that of

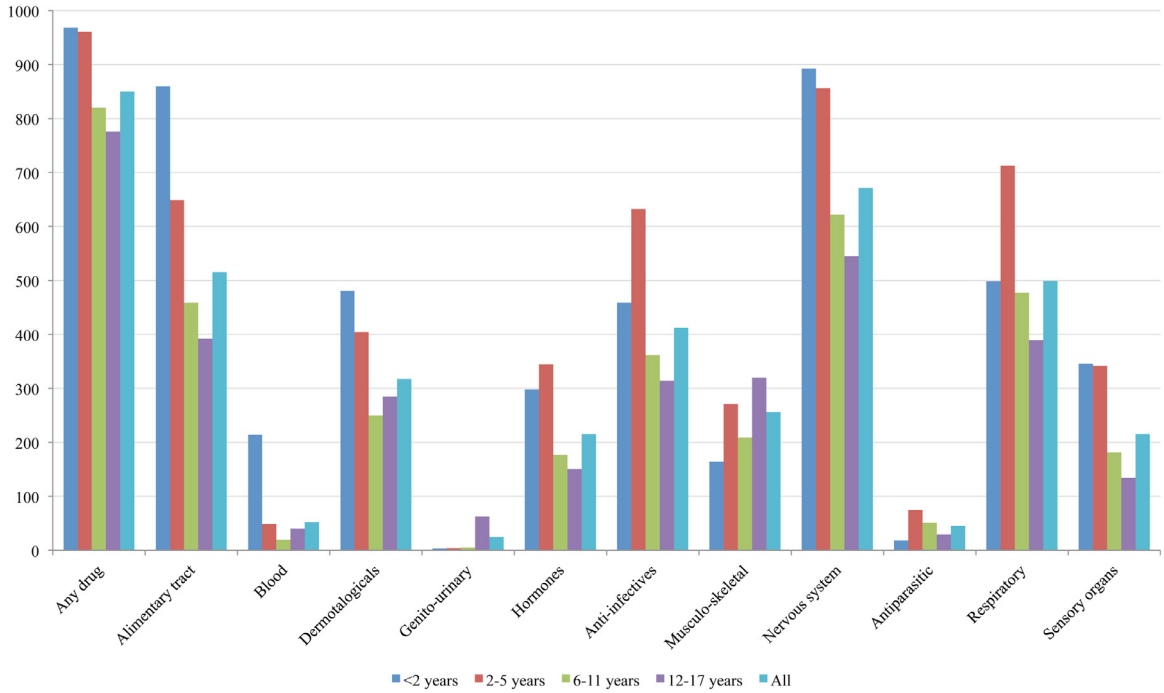

Fig. 1. Prevalence of paediatric outpatient prescriptions in France in 2018–2019 (expressed as the frequency of children receiving ≥1 prescription(s) per 1000 children-years) by age groups and anatomical classes.

its main indication, allergic rhinitis, ranges from 38‰ to 80‰ in the paediatric population in western Europe [51]. The POP prevalence for nasal corticosteroids showed an increasing trend during the study period, with an increase of 21% in the overall paediatric population and 59% amongst neonates, although nasal corticosteroids are not labelled for this vulnerable population [47,52]. These increasing trends coincided with the reimbursement cessation of some nasal decongestants in 2011 [23]. In contrast, children and adolescents were 3-fold less likely to receive a POP for inhaled corticosteroids than were preschoolers and infants. This low level of asthma drugs, especially in adolescents (with a POP prevalence for short-acting β2-agonists and inhaled corticosteroids of 75‰ and 62‰, respectively) contrasts with the 12.7% asthma prevalence amongst this age group [53] and international guidelines encouraging the maintenance of controller drugs [54]. Asthma seems undertreated amongst French adolescents as in other countries [53,55].

The POP prevalence for PPIs was also very high in France, especially amongst infants (61‰), as compared with New Zealand (38‰) [14] or Denmark (5‰) [56]. During the study period, the POP prevalence was increased by 42% for the overall paediatric population and by 382% for neonates and infants ≤6 weeks old. During the same period, recent alerts pointed to the association of PPIs with bone fractures, community-acquired pneumonia and bacterial diarrhoea [57]. Furthermore, the PPI efficiency for reflux symptoms is not demonstrated amongst infants [58]. This prompted the re-affirmation of clinical guidelines for the judicious and limited use of PPIs in paediatric patients [59,60]. Similarly, POPs for metopimazine increased by 84% over the 10 years despite the potential neurological and cardiologic side effects of this anti-emetic [46]. These trends are likely due to drug replacement after cessation of the licensing of major propulsives/prokinetics [20]. Such drug replacement was not intended by drug regulatory agencies [20], no prescription being required for gastrooesophageal reflux [59,60] or emesis [46].

Some improvements regarding POP over-prescription were observed over the 10-year period, for example in the field of antibiotics, NSAIDs and cough suppressants. Some of these improvements perhaps followed the publication of clinical guidance and/or regulatory decisions. Indeed, Trinh et al. [26] highlighted a significant impact of French guidelines promoting a better use of antibiotics for upper respiratory tract infections, which led to a decrease by 33% in antibiotics prescription rates per 1000 paediatric inhabitants/year. Our results allowed to show that although slightly fewer children received antibiotics prescriptions per year (decrease by 12%; Table 2), these prescriptions were especially less often repeated in the same year (decrease by 23%; Table 3). Also, for the overall paediatric population, the structure of prescribed antibiotics has evolved toward a decrease of broad-spectrum antibiotics in favour of amoxicillin. However, French children were still 5.3-fold more likely than Dutch children to receive antibiotics.[68] Antibiotics are still mainly prescribed for viral infections [61] and strongly contribute to the increase in antibiotic resistance [26,61].

Although some improvements in POPs were identified in our study in higher prescription of prophylactic agents such as vitamin D (+49% over 10 years in the overall paediatric population) [62], this high level of POPs in the outpatient paediatric settings is worrisome. Reforms in public health such as drug reimbursement cessation [20,23], incentives for preventive practices [63], or guidelines [26] showed beneficial changes in POP trends [24,26], but may also have negative consequences [64]. The replacement of drugs with safety concerns by others with similar concerns supports the existence of obstacles impeding changes in prescribing behaviours [65]. Therefore, it is crucial to anticipate and prevent the increase in prescribing replacement drugs when this type of regulation comes into force.

4.2. Strengths and limitations

This is the first analysis of POPs in France including in-depth analyses by therapeutic classes and ATC level 5 drugs as well as 10-year trends. This time interval allowed for observing the potential impact of some clinical guidelines or regulatory decisions that occurred during this period. The SNDS database is optimal for drug prescription monitoring owing to its exhaustive population coverage including for example 14,510,023 children in the 2018–2019 period.

Table 2
Prevalence of most commonly prescribed therapeutic classes in outpatient pediatrics by age groups (expressed as the frequency of children receiving ≥1 prescription per 1000 children-years) and prevalence rate ratios (PRRs) between 2018–2019 and 2010–2011.

ATC level 1	ATC level 2, 3 or 4 drugs	< 2 years		2–5 years		6–11 years		12–17 years		All		
		2010–2011	2018–2019	2010–2011	2018–2019	2010–2011	2018–2019	2010–2011	2018–2019	2010–2011	2018–2019	PRR
A	Caries prophylactic agents	424	177	96	46	41	40	74	79	106	68	0.64
A	Drugs for GORD	96	123	23	21	17	20	38	53	34	42	1.24
A	Proton pump inhibitors	36	61	14	15	11	14	31	45	21	30	1.42
A	Drugs for FGD	133	23	174	131	187	172	157	154	168	142	0.85
A	Propulsives	192	9	194	16	111	9	83	13	130	12	0.09
A	Antiemetics/antinausea agents	55	108	95	175	60	111	43	77	61	113	1.84
A	Drugs for constipation	43	46	67	73	41	45	26	28	42	45	1.08
A	Antidiarrhea agents (others)	234	251	211	219	83	93	43	46	115	119	1.04
A	Vitamin D	521	739	338	428	138	245	74	160	204	304	1.49
B	Vitamin K/hemostatics	203	147	1	1	0	0	0	0	23	15	0.65
B	Iron preparations	43	38	35	22	13	10	18	19	23	18	0.81
D	Antifungals (topic)	150	140	85	71	50	47	64	65	74	67	0.92
D	Emollients and protectives	222	86	113	65	47	38	29	25	76	44	0.58
D	Antibiotics (topic)	55	58	85	85	54	53	42	43	57	57	0.99
D	Corticosteroids	124	135	134	138	87	92	68	70	95	99	1.03
D	Antiseptics/disinfectants	285	279	229	234	118	116	108	109	158	155	0.98
D	Anti-acne agents (topic)	1	0	1	1	8	5	102	78	37	29	0.79
D	Anti-acne agents (systemic)	0	0	0	0	1	1	31	31	11	11	1.04
G	Contraceptives (systemic)	2	2	1	1	0	0	44	52	15	19	1.24
H	Corticosteroids (systemic)	283	298	366	343	177	169	129	143	215	210	0.97
J	Antibacterial agents (systemic)	444	434	691	627	413	357	350	307	458	405	0.88
J	Tetracyclines	0	0	0	0	1	1	54	45	18	16	0.88
J	β-lactam antibiotics, penicillin	312	384	490	541	272	290	193	206	299	324	1.08
J	Other β-lactam antibiotics	268	125	395	183	157	69	86	39	199	88	0.44
J	Macrolides, streptogramins	65	40	151	91	85	50	77	51	95	58	0.61
J	Direct-acting antiviral drugs	6	7	14	14	7	8	9	10	9	10	1.08
M	NSAIDs	277	164	434	271	296	201	333	295	337	244	0.73
M	Products for muscular pain	1	0	4	1	30	16	93	74	41	31	0.75
N	Anesthetics (topic)	371	420	182	130	87	90	28	38	121	113	0.94
N	Opioids	16	1	40	9	19	9	46	47	32	21	0.66
N	Analgesics and antipyretics	778	863	807	843	558	589	463	510	607	643	1.06
N	Anxiolytic agents	6	4	18	12	12	10	24	23	16	14	0.87
P	Antinematodal agents	12	13	66	69	46	48	20	24	38	40	1.06
R	Nasal corticosteroids	377	386	449	510	220	298	169	227	272	328	1.21
R	Other nasal preparations	260	0	260	0	80	0	32	0	125	0	0.00
R	β–2-agonists (inhaled)	138	182	140	167	81	91	64	75	95	111	1.17
R	Adrenergics+corticosteroids (inhaled)	4	3	19	18	34	30	32	31	27	25	0.95
R	Corticosteroids (inhaled)	114	131	125	140	53	59	26	31	67	74	1.10
R	Leukotriene receptor antagonist	9	9	24	23	25	19	19	14	21	17	0.80
R	Cough suppressants	72	10	289	246	195	187	166	157	193	172	0.89
R	Antihistamines (systemic)	175	104	460	386	293	249	210	197	290	246	0.85
S oph	Anti-infectives	257	280	185	191	52	56	36	31	99	98	0.99
S oph	Anti-inflammatory + anti-infective agents	15	10	26	21	20	18	22	17	22	17	0.81
S oph	Decongestants/antiallergics	6	5	22	20	40	41	40	43	32	34	1.04
S oto	Anti-infective agents	36	40	56	65	24	32	13	19	29	35	1.23
S oto	Corticosteroids + anti-infective agents	53	41	82	72	47	48	30	35	50	48	0.96

A: alimentary tract and metabolism, B: blood and blood forming organs, D: dermatologicals, G: genito-urinary system and sex hormones, H: systemic hormonal preparations, J: anti-infective agents for systemic use, M: musculoskeletal products, N: nervous system, R: respiratory system, S oph: sensory organs, ophthalmological, S oto: sensory organs, otological; NSAID: non-steroidal anti-inflammatory drugs; FGD: functional gastrointestinal disorders; GORD: gastroesophageal reflux disease.

Table 3
Prevalence of most common therapeutic classes prescribed at least twice per year in outpatient pediatrics by age groups (expressed as the frequency of children receiving ≥2 prescriptions per 1000 children-years) and prevalence rate ratios (PRRs) between 2018–2019 and 2010–2011.

ATC level 1	ATC level 2, 3 or 4 drugs	< 2 years		2–5 years		6–11 years		12–17 years		All		
		2010–2011	2018–2019	2010–2011	2018–2019	2010 2011	2018–2019	2010–2011	2018–2019	2010–2011	2018–2019	PRR
A	Caries prophylactic agents	247	76	28	8	4	4	11	11	39	15	0.37
A	Drugs for GORD	38	53	7	6	4	4	8	11	9	12	1.23
A	Proton pump inhibitors	17	30	5	4	3	3	6	9	6	8	1.34
A	Drugs for FGD	32	2	35	23	40	35	35	34	36	29	0.79
A	Propulsives	47	1	31	1	12	0	11	1	20	1	0.04
A	Antiemetics/antinausea agents	7	17	11	28	5	13	4	9	6	15	2.47
A	Drugs for constipation	10	11	19	21	8	10	5	5	10	11	1.14
A	Antidiarrhea agents (others)	64	67	38	40	7	9	3	4	19	19	1.01
A	Vitamin D	297	439	95	145	18	49	9	30	63	102	1.60
B	Vitamin K/hemostatics	74	3	0	0	0	0	0	0	8	0	0.05
B	Iron preparations	8	9	4	3	1	1	3	4	3	3	0.98
D	Antifungals (topic)	34	29	14	11	6	6	10	11	12	11	0.89
D	Emollients and protectives	72	21	28	14	8	7	5	4	18	9	0.48
D	Antibiotics (topic)	7	7	10	10	5	5	4	5	6	6	1.02
D	Corticosteroids	29	32	25	27	13	14	11	12	17	18	1.07
D	Antiseptics/disinfectants	36	35	40	40	17	17	20	21	25	25	1.00
D	Anti-acne agents (topic)	0	0	0	0	1	1	29	21	10	7	0.76
D	Anti-acne agents (systemic)	0	0	0	0	0	0	12	12	4	4	1.06
G	Contraceptives (systemic)	0	0	0	0	0	0	24	30	8	10	1.28
H	Corticosteroids (systemic)	109	112	143	131	45	43	27	30	68	64	0.94
J	Antibacterial agents (systemic)	262	235	436	351	172	130	136	107	234	180	0.77
J	Tetracyclines	0	0	0	0	0	0	20	17	7	6	0.86
J	β-lactam antibiotics, penicillin	132	181	216	256	78	85	44	48	103	118	1.14
J	Other β-lactam antibiotics	110	36	157	52	36	12	14	5	64	21	0.32
J	Macrolides, streptogramins	12	7	36	19	15	8	12	7	18	10	0.53
J	Direct-acting antiviral drugs	0	0	1	1	1	1	1	1	1	1	0.92
M	NSAIDs	113	50	177	80	90	47	118	94	121	70	0.58
M	Products for muscular pain	0	0	0	0	2	1	13	9	5	3	0.7
N	Anesthetics (topic)	238	279	49	28	14	13	4	7	43	40	0.93
N	Opioids	1	0	3	0	2	1	6	6	4	2	0.71
N	Analgesics and antipyretics	580	660	564	606	263	289	197	224	344	371	1.08
N	Anxiolytic agents	1	0	2	1	2	2	5	6	3	3	1.02
P	Antinematodal agents	1	1	9	10	6	6	3	3	5	5	1.10
R	Nasal corticosteroids	179	180	205	249	63	98	42	61	101	125	1.24
R	Other nasal preparations	100	0	86	0	12	0	3	0	35	0	0.00
R	β–2-agonists (inhaled)	49	69	51	69	29	36	21	27	34	43	1.29
R	Adrenergics+corticosteroids (inhaled)	1	1	9	8	16	15	13	14	12	12	1.00
R	Corticosteroids (inhaled)	44	55	47	59	16	18	6	6	23	26	1.17
R	Leukotriene receptor antagonist	3	4	9	10	12	10	9	7	9	8	0.87
R	Cough suppressants	16	1	96	79	46	44	35	31	50	43	0.85
R	Antihistamines (systemic)	51	20	196	133	105	81	67	62	107	80	0.75
S oph	Anti-infectives	81	89	40	42	6	7	4	3	21	21	1.01
S oph	Anti-inflammatory + anti-infective agents	2	2	4	3	2	2	3	2	3	2	0.83
S oph	Decongestants/antiallergics	1	0	3	3	7	7	6	6	5	5	1.04
S oto	Anti-infective agents	8	9	10	12	3	4	1	2	5	5	1.16
S oto	Corticosteroids + anti-infective agents	12	8	14	12	5	6	3	4	7	7	0.92

A: alimentary tract and metabolism, B: blood and blood forming organs, D: dermatologicals, G: genito-urinary system and sex hormones, H: systemic hormonal preparations, J: anti-infective agents for systemic use, M: musculo-skeletal products, N: nervous system, R: respiratory system, S oph: sensory organs, ophthalmological, S oto: sensory organs, otological; NSAID: non-steroidal anti-inflammatory drugs; FGD: functional gastrointestinal disorders; GORD: gastroesophageal reflux disease.

Table 4
Prevalence of most common therapeutic classes prescribed to outpatient infants ≤ 6 weeks old (expressed as the frequency of infants receiving ≥1 prescription per 1000 infants) and prevalence rate ratios (PRRs) between 2018–2019 and 2010–2011.

ATC	ATC level 3 or 4 label	2010–2011	2018–2019	PRR [95% CI]
A01AA	Caries prophylactic agents	68	4	0.06 [0.03;0.09]
A01AB	Anti-infective/antiseptic agents (topic)	11	8	0.74 [0.71;0.77]
A02B	Drugs for GORD	19	59	3.16 [3.14;3.18]
A02BC	Proton pump inhibitors	4	21	4.82 [4.78;4.86]
A02BX	Other drugs for GORD	15	48	3.22 [3.2;3.24]
A03A	Drugs for FGD	41	18	0.45 [0.43;0.47]
A03F	Propulsives	19	1	0.05 [0.00;0.12]
A07AA	Intestinal antibiotics	6	22	3.91 [3.88;3.94]
A11CC	Vitamin D	249	404	1.62 [1.61;1.63]
B02BA	Vitamin K	248	260	1.05 [1.04;1.06]
B03A	Iron preparations	7	16	2.31 [2.28;2.34]
B05X	Solution additive	4	13	3.01 [2.97;3.05]
D01A	Antifungals (topic)	13	30	2.37 [2.35;2.39]
D02A	Emollients and protectives	66	20	0.30 [0.28;0.32]
D08A	Antiseptics/disinfectants	276	279	1.01 [1.00;1.02]
J02AA	Amphotericin B	10	28	2.70 [2.67;2.73]
N01B	Anesthetics (topic)	27	82	3.07 [3.05;3.09]
N02B	Other analgesics and antipyretics	110	215	1.95 [1.94;1.96]
R01A	Decongestants (topic)	19	20	1.07 [1.05;1.09]
R01AD	Nasal corticosteroids	12	18	1.59 [1.56;1.62]
S01A	Anti-infective agents (ophthalmological)	55	78	1.43 [1.42;1.44]
S01AA	Antibiotics (ophthalmological)	33	54	1.65 [1.63;1.67]
S01AX	Other anti-infective agents (ophthalmological)	34	40	1.19 [1.17;1.21]

FGD: functional gastrointestinal disorders; GORD: gastroesophageal reflux disease; PRR: prevalence rate ratio; 95% CI; 95% confidence interval.

Our study has limitations. First, the national pharmaceutical claims database does not collect information on the indications for drug prescriptions, which precludes any analysis of the appropriateness of drug prescriptions. Second, as in many other studies, dispensed prescriptions were used as a proxy for drug prescription [14,15]. Third, prescribing and reimbursement of drugs also available as OTCs appears to represent an important share of the total POP [22], contrary to most countries with advanced economies [22,29,30]. For instance in our study, amongst the 14 most-prescribed paediatric outpatient drugs, 5 were drugs also available as OTCs (helicidin, metopimazine, phloroglucinol, racecadotril, tixocortol). Fourth, we studied dispensed POPs but not those administered, knowing the adherence rate ranges from 5% to 50% in other countries with advanced economies [66]. Fifth, our statistical approach did not allow for exploring POPs corresponding to less frequent diseases (such as attention deficit hyperactivity disorder, childhood depression, type I diabetes). Sixth, if the since the date of birth was not available, we used POPs before ≤6 weeks of life to approach POPs for neonates (who should be defined as at < 28 days of life) [1]. Seventh, the choice of the 6-year old threshold for comparing POP between age groups is relatively arbitrary but allows for providing preliminary key messages for two populations that differ by their consultation rate [34].

4.3. Implications

POPs remained highly prevalent in France throughout the 2010s, especially in children <6 years old, with only few improvements in selected therapeutic classes. These findings should prompt clinical guidance campaigns and/or regulatory decisions such as drug reimbursement cessation [23] or incentives to optimize practices [63]. Priority targets should probably be corticosteroids, PPIs, anti-emetic drugs and antibiotics, given their adverse side effects and their high level of POPs. These interventions must also take into account the risk of drug replacement observed in our study. Finally, determinants of the very high POP prevalence need to be explored to better target prescribers and populations at risk of high drug prescription. Regular assessments of POP trends are needed to evaluate the impact of corrective actions and detect the emergence of inappropriate POPs.

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Authors' contributions

Conceptualization/design: Marion Taine, Martin Chalumeau, Rosemary Dray-Spira, Alain Weill, Mahmoud Zureik; Data collection: Lucile Offredo, Marion Taine; Statistical analysis: Lucile Offredo, Marion Taine; Drafting the initial manuscript: Marion Taine; Review or editing the manuscript: Martin Chalumeau, Lucile Offredo, Rosemary Dray-Spira, Alain Weill, Mahmoud Zureik; Supervision: Martin Chalumeau, Rosemary Dray-Spira, Alain Weill, Mahmoud Zureik

Data statement

The procedures carried out with the French data privacy authority (CNIL, Commission nationale de l'informatique et des libertés) do not provide for the transmission of the database. Consultation by the editorial board or interested researchers may nevertheless be considered, subject to prior determination of the terms and conditions of such consultation and in respect for compliance with the applicable regulations. All requests for access must be submitted to the Health data hub. Further information to do this request is available on these websites:

- https://www.snds.gouv.fr/SNDS/Processus-D-acces-aux-donnees
- https://documentation-snds.health-data-hub.fr/introduction/03-acces-snds.html#les-acces-sur-projet

Declaration of Interests

M Chalumeau has received honoraria for expert consultation from Merck Serono outside the submitted work. All remaining authors declare no competing interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanepe.2021.100129.

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