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

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
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 increase 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., homeopathy, 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 follow-up 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 in 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%/0, 969%/8, 828%/0, and 782%/0 for paediatric patients <2, 2–5, 6–11 and 12–17 years old, respectively (Table 1). The POP prevalence was similar for girls (863%/0) and boys (851%/0; PRR=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%/0), the alimentary tract and metabolism (516%/0), and respiratory system (499%/0) as well as anti-infective agents for systemic use (412%/0) (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%/0; after excluding paracetamol, the prevalence for nervous system drugs decreased from 672%/0 to 165%/0; 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%/0: analgesics (643%/0); antibiotics (405%/0), nasal corticosteroids (328%/0), vitamin D (304%/0), antihistamines (246%/0), NSAIDs (244%/0), systemic corticosteroids (210%/0), cough suppressants (172%/0), antiseptics (153%/0), drugs for functional gastrointestinal disorders (142%/0), anti-diarrheal agents (119%/0), anti-emetic agents (113%/0), topical anaesthetics (113%/0) and short-acting β2-agonists (111%/0) (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%/0 for children receiving at least 2 prescriptions/year for analgesics, 180%/0 for antibiotics, 125%/0 for nasal corticosteroids, 102%/0 for vitamin D, 80%/0 for antihistamines, 70%/0 for NSAIDs, and 64%/0 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%/0 for adolescent girls) and anti-acne drugs (78%/0 topical and 31%/0 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%/0), antiseptics (279%/0), vitamin K (260%/0) and analgesics (215%/0).

3.4. Drug prescription trends

The POP prevalence increased from 825%/0 to 857%/0 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),
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), cepodoxime (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 gastroesophageal 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], and nasal corticosteroids (PRR=1.21, 1.17, and 1.10, respectively). The POP prevalence for nasal corticosteroids was 273%, whereas that of...
its main indication, allergic rhinitis, ranges from 38% 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 schoolers and infants. This low level of asthma drugs, especially in adolescents (with a POP prevalence for short-acting /2-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%) or Denmark (5%) [56]. During the study period, the POP prevalence 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 gastroesophageal 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] 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.
| ATC level 1 | ATC level 2, 3 or 4 drugs | < 2 years | 2 – 5 years | 6 – 11 years | 12 – 17 years | All |
|------------|--------------------------|----------|------------|-------------|-------------|-----|
| 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          | Anti-diarrhea 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/termers | 203 147 1 | 1 | 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 | 6 4 | 52 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 | 31 31 11 | 11 1.04 |
| J          | β-lactam antibiotics, penicillin | 312 384 490 541 | 272 290 193 | 206 299 324 | 1.08 |
| J          | Other β-lactam antibiotics | 268 135 359 183 | 157 69 86 | 39 199 88 | 0.44 |
| J          | Macrolides, streptomycins | 65 40 151 91 | 85 50 77 | 51 95 58 | 0.61 |
| J          | Antibacterial agents (systemic) | 0 0 | 0 0 | 1 1 | 31 31 11 | 11 1.04 |
| J          | Tetracyclines | 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          | Analgesics (topic) | 371 420 182 130 | 87 90 28 | 38 121 113 | 0.94 |
| N          | Anti-infectives | 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 | 10 12 | 24 23 16 | 14 0.87 |
| N          | Antihypertensives | 377 386 449 | 510 | 220 298 169 | 227 272 328 | 1.28 |
| R          | Nasal corticosteroids | 12 13 | 66 69 | 46 48 | 20 24 38 | 40 1.06 |
| R          | Other nasal preparations | 260 0 | 249 | 0 | 220 169 | 227 272 328 | 1.28 |
| 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 | 14 21 17 | 0.80 |
| R          | Cough suppressants | 72 10 | 289 246 | 195 187 | 166 157 193 | 172 0.89 |
| S oph      | Anti-infectives | 175 104 460 386 | 293 249 210 197 | 290 246 0.85 |
| S oph      | Anti-inflammatory + anti-infective agents | 257 280 186 191 | 52 56 36 | 31 59 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 / antihistamines | 6 5 | 22 | 20 | 40 41 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, 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 |
| A Carries prophylactic agents        | 247       | 76        | 28         | 8           | 4   |
| A Drugs for GORD                    | 38        | 53        | 7          | 6           | 4   |
| A Proton pump inhibitors             | 17        | 30        | 5          | 4           | 3   |
| A Drugs for FGD                     | 32        | 2         | 35         | 23          | 40  |
| A Propulsins                        | 47        | 1         | 31         | 1           | 12  |
| A Antimetetics/antiin saving agents  | 7         | 17        | 11         | 28          | 5   |
| A Drugs for constipation             | 10        | 11        | 19         | 21          | 8   |
| A Antidiabetic agents (others)       | 64        | 67        | 38         | 40          | 7   |
| A Vitamin D                          | 257       | 439       | 95         | 145         | 18  |
| B Vitamin K/hemostatics             | 74        | 3         | 0          | 0           | 0   |
| B Iron preparations                  | 8         | 9         | 4          | 3           | 1   |
| C Antifungals (topic)                | 34        | 29        | 14         | 11          | 6   |
| C Emollients and protectives         | 72        | 21        | 28         | 14          | 8   |
| C Antibiotics (topic)                | 7         | 7         | 10         | 10          | 5   |
| C Corticosteroids                    | 29        | 32        | 25         | 27          | 13  |
| C Antiseptics/disinfectants          | 36        | 35        | 40         | 40          | 17  |
| D Anti-anaesthetic agents (topic)     | 0         | 0         | 0          | 0           | 1   |
| D Anti-anaesthetic agents (systemic) | 0         | 0         | 0          | 0           | 0   |
| G Contraceptives (systemic)          | 109       | 112       | 143        | 131         | 45  |
| H Corticosteroids (systemic)         | 262       | 235       | 436        | 351         | 172 |
| J Antibacterial agents (systemic)    | 0         | 0         | 0          | 0           | 29  |
| J Tetracyclines                      | 0         | 0         | 0          | 0           | 20  |
| J β-lactam antibiotics, penicillin   | 132       | 181       | 216        | 256         | 78  |
| J Other β-lactam antibiotics         | 110       | 36        | 157        | 52          | 36  |
| J Macrolides, streptogramins         | 12        | 7         | 36         | 19          | 15  |
| J Direct-acting antiviral drugs       | 0         | 0         | 1          | 1           | 1   |
| J Other nasal preparations           | 580       | 660       | 564        | 606         | 263 |
| K NSAIDs                              | 113       | 50        | 177        | 80          | 90  |
| L Products for muscular pain         | 0         | 0         | 0          | 0           | 2   |
| N Opioids                            | 238       | 279       | 49         | 28          | 14  |
| N Anesthetics (topic)                | 1         | 0         | 3          | 0           | 2   |
| N Analgesics and antipyretics        | 580       | 660       | 564        | 606         | 263 |
| N Anxiolytic agents                  | 1         | 0         | 2          | 1           | 2   |
| N Antimembran agents                 | 1         | 1         | 9          | 10          | 6   |
| O Nasal corticosteroids              | 179       | 180       | 205        | 249         | 63  |
| O Other nasal preparations           | 100       | 0         | 85         | 0           | 12  |
| P β-2–agonists (inhaled)             | 49        | 69        | 51         | 69          | 29  |
| P Adrenergics+corticosteroids (inhaled)| 1        | 1         | 9          | 8           | 16  |
| P Corticosteroids (inhaled)          | 44        | 55        | 47         | 59          | 16  |
| P Leukotriene receptor antagonist    | 3         | 4         | 9          | 10          | 12  |
| Q Cough suppressants                 | 16        | 1         | 96         | 79          | 46  |
| Q Antihistamines (systemic)          | 51        | 20        | 196        | 133         | 105 |
| R Anti-infectives                    | 81        | 89        | 40         | 42          | 6   |
| R Anti-inflammatory + anti-infective agents | 2   | 2       | 4         | 3           | 2   |
| R Decongestants/antiallergics        | 1         | 0         | 3          | 3           | 7   |
| R Anti-infective agents              | 8         | 9         | 10         | 12          | 5   |
| S oto Corticosteroids + anti-infective agents | 12  | 8       | 14         | 12          | 5   |

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.
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 (belifcidin, 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 1 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.

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 protective | 66 | 20 | 0.30 [0.28;0.32] |
| D08A | Antiseptics/disinfectants | 276 | 279 | 1.01 [1.00;1.02] |
| J02AA | Amphoteratin 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.

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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-a-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.
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