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Original Research

Prescriptions of respiratory medications in children aged 0–10 years: A longitudinal drug utilization study in the POMME database

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ABSTRACT

Introduction: Respiratory tract disorders are common in children. However, there is no available data on the prescription of respiratory medications for children in France. This study aimed to provide an overview of medications for obstructive airway diseases prescriptions for children during the initial ten years of their lives within POMME, a French population-based cohort of children.

Material and methods: This longitudinal, population-based study used data from the French POMME birth cohort, comprising children born in Haute Garonne between July 2010 and June 2011. Anonymous medical information, including medication reimbursement data, was collected between ages 0 and 10 years. Exposure was defined as at least one prescription for respiratory medications (ATC code R03*), focusing on specific subclasses. Data were analyzed by age, season, and prescribing physicians' specialties.

Results: Out of 5956 children, 4951 (83.1 %) received respiratory medication prescriptions. Inhaled corticosteroids (ICSs) were the most prescribed (95.3 %), followed by short-acting β 2-agonists (68.8 %). The number of prescriptions increased with age, except for ICSs alone, which peaked between 6 months and 2 years. The average number of prescriptions per child was relatively low.

Discussion: This study highlighted high prescription rates of respiratory medications in children under 10 years, with ICSs being the most prevalent. While these medications are primarily intended for asthma management, the findings suggested a significant proportion of off-label prescriptions, especially in young children. Further research and clinical guidance are warranted to ensure appropriate medication use in the pediatric population.

1. Introduction

Drug utilization studies in pediatrics are relatively scarce. Two European studies have shed light on the prevalence of respiratory medications (Anatomical Therapeutic Chemical (ATC) code R03*: Medications for obstructive airway diseases) as the second most prescribed ATC class among children aged two and older, after medications for the nervous system [1,2].

Asthma stands out as the most prevalent condition necessitating the use of medications for obstructive airway diseases in pediatrics. According to a French study conducted between 2005 and 2006 on children around five years of age, the estimated prevalence of asthma was 9.8 % [3]. In 2022, the Global Initiative for Asthma (GINA) issued

comprehensive recommendations for the management of asthma in children, structured into four stages [4]. GINA's recommendations emphasize tailoring asthma management based on age and symptom frequency. The initial line of therapy involves inhaled corticosteroids (ICSs). As a second-line approach, a second category of medications may complement ICSs: long-acting β 2-agonists (LABAs) for children over five years of age or leukotriene receptor antagonists (LTRAs) for children under five. Short-acting β 2-agonists (SABAs) can be used as needed at each stage. Furthermore, in 2009, the French National Authority for Health (HAS) recommended escalating doses of ICSs, possibly in combination with LABAs, for managing asthma in children under 36 months of age [5]. Remarkably, prescription patterns exhibit considerable diversity across countries, despite uniform international recommendations issued by GINA. For instance, one study showed that LTRAs and

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Abbreviations

ATC	Anatomical Therapeutic Chemical
ENT	Ear Nose and Throat
GINA	Global Initiative for Asthma
HAS	Haute Autorité de Santé (French National Authority for Health)
ICS	Inhaled Corticosteroid
LABA	Long-Acting β 2-Agonists
LAMA	Long-Acting Muscarinic Antagonist, LTRA Leukotriene Receptor Antagonists
SABA	Short-Acting β 2-Agonists

LABAs were the most frequently prescribed medications in Japan [6], while ICSs and SABAs predominated in Europe. Even within Europe, disparities emerged, with SABAs being the preferred choice in some countries like the UK and the Netherlands, whereas ICSs were more prevalent in southern countries such as Italy [7].

Studies carried out in Europe and Asia examining respiratory medication prescriptions in the pediatric population revealed a noteworthy proportion of off-label prescriptions for upper and lower respiratory tract infections [8–10]. In France, the HAS issued recommendations in 2019, which discourage the use of bronchodilators or corticosteroids in the treatment of bronchiolitis in children under 12 months of age due to demonstrated ineffectiveness [11]. However, as of today, there is no available data on the prescription of respiratory medications for children in France. Instead of examining the use of respiratory drugs in a cohort of children with asthma, this current study aimed to provide an overview of medications for obstructive airway diseases prescriptions for all children during the initial ten years of their lives.

This study's objective was to describe the patterns of respiratory medication prescriptions in children aged 0–10 years within POMME, a French population-based birth cohort of children.

2. Materials and methods

2.1. Study design

The study design was a longitudinal, population-based drug utilization study examining prescription patterns of respiratory medications in children included in the POMME cohort.

2.2. Data source

We utilized the French POMME cohort, described in a previous article, to conduct this study [12]. POMME is a French birth cohort comprising 8372 children born in Haute Garonne between July 1, 2010, and June 30, 2011, and covered by the general health insurance scheme. POMME collects anonymous medical information, including data on medications and healthcare reimbursed for mothers during pregnancy and for children from conception. Children are followed until death or relocation outside the area. For the present study, data were available until June 2021, which corresponded to the children's 10th year. The anonymous data are derived from two different sources.

Firstly, the French Health Insurance System annually provides all data on prescribed and reimbursed medicines and medical care for children. This system, covering approximately 80 % of the population, is universal and handles healthcare reimbursements for individuals affiliated with a health insurance scheme in France, complemented by mutual funds or private insurance companies. Most medication expenses, except those contributing minimally to health, are either partially or fully covered by the health insurance system. The French list of reimbursable medicines is available on the French Health Insurance

System's website [13]. All ATC class R03 medications authorized for market in France are reimbursed by social security regardless of age. Therefore, it is not possible for some medications to be prescribed but not reimbursed. Information about medications includes ATC Classification System codes [14], prescription dates, dispensing dates, the number of packages dispensed, and the prescribing physician's specialty.

Secondly, the Maternal and Child Protection Service provides data from children's certificates completed during mandatory medical examinations at birth, 9 months, and 24 months of age. These examinations are conducted by general practitioners or pediatricians using standardized questionnaires to compile the certificates. Subsequently, parents send these certificates in a confidential manner to the Mother and Child Protection Centre. These certificates contain various types of information, including administrative details about the mother, father, and child, as well as medical information about the mother, pregnancy, and the child.

2.3. Study population

The eligible study population was drawn from the POMME cohort, with the following exclusion criteria applied: (i) discontinuation of follow-up (defined as no reimbursement for healthcare or medication for a period of at least one continuous year) between 0 and 10 years, and (ii) no prescription and reimbursement for a respiratory drug (ATC code R03*) between 0 and 10 years of age.

2.4. Drug exposure

Children were considered exposed if they received at least one reimbursement for a medication for obstructive airway diseases (ATC code R03). Within the R03 ATC class, we focused on four ATC subclasses: (I) inhaled corticosteroids (ICSs) (ATC code R03BA); (II) long-acting β 2-agonists (LABAs) (ATC code R03AC, excluding salbutamol, terbutaline, pirbuterol, indacaterol, and bambuterol); (III) leukotriene receptor antagonists (LTRAs) (ATC code R03DC); (IV) long-acting muscarinic antagonist (LAMA) (ATC code R03BB), and (V) short-acting β 2-agonists (SABAs) (ATC code R03AC, including salbutamol, terbutaline, pirbuterol, indacaterol, and bambuterol).

Additionally, we examined the following combinations: (I) ICSs plus LABAs (ATC codes R03BA* plus R03AC* or ATC code R03AK*); (II) ICSs plus LTRAs (ATC codes R03BA* plus R03DC*); (III) ICSs plus LAMA (ATC codes R03BA* plus R03BB* or ATC code R03AL*); (IV) LABAs plus LTRAs (ATC codes R03BA* plus R03AC* or ATC code R03DC*); (V) ICSs plus LABAs plus LTRAs (ATC codes R03BA* plus R03AC* plus R03DC* or ATC code R03AK* plus R03DC*), and (VI) ICSs plus LTRAs LAMA (ATC codes R03BA* plus R03DC* plus R03BB*).

For constructing a Sankey diagram, we took into account the duration of ICS prescriptions, defining long-term prescriptions as at least 3 continuous ICS deliveries over the relevant age period. Continuous prescription was defined by a 45-day interval between each delivery (1 month plus a 15-day grace period). All other ICS prescriptions not meeting this criterion were considered short-term.

2.5. Statistical analysis

Respiratory medications prescribed and delivered to children were described using prevalence rates. Qualitative variables were presented as absolute numbers and percentages and continuous variables were presented as means (\pm standard deviation). The average number of prescriptions per child was calculated by averaging the sum of prescriptions of all medications belonging to the considered class during the follow-up period (0–10 years).

Prescriptions were also described according to child age using the following categories: <6 months, [6 months–2 years[, [2–4 years[, and \geq 5 years of age. We described average ages of prescriptions for all the

prescription in one hand and for the first prescription, for each child, of the medication belonging to the considered class on the other hand.

The number of prescriptions for drugs containing ICS or LABA was described, and percentages were calculated based on the total number of ICS or LABA prescriptions.

Finally, prescribing physicians' specialties were categorized as general practitioners, pediatricians, pulmonologists, Ear Nose and Throat (ENT) doctors, and others.

All analyses were conducted using SAS Enterprise Guide® 7.1 (SAS Institute Inc., Cary, NC, USA). The Sankey diagram was produced using sankeyMATIC (<https://sankeymatic.com/build/>).

3. Results

Of the 8372 children in the POMME cohort, 2426 (30.0 %) were excluded due to a discontinuation of follow-up (Fig. 1). Among the 5956 children who were not lost to follow-up, 4951 (83.1 %) received at least one reimbursement for medication for obstructive airway diseases between the age of 0 and 10 years.

Table 1 presents the number and percentages of children exposed to medication for obstructive airway diseases according to the ATC subclasses. Almost all children received at least one prescription for ICSs (95.3 % of children prescribed medication for obstructive airway diseases). The second most prescribed drug subclass was SABAs (N = 3,407, 68.8 %), followed by LTRAs (N = 704, 14.2 %) and LABAs (N = 675, 13.6 %). ICSs alone accounted for the majority of ICS prescriptions (N = 4,677, 94.5 %). The most common combination was ICSs plus LABAs (N = 634, 12.8 %), followed by ICSs plus LTRAs (N = 373, 7.5 %), and ICSs plus LABAs plus LTRAs (N = 125, 2.5 % of children). Children received an average of 8.1 (± 9.4) medication for obstructive airway diseases prescriptions between the age of 0 and 10 years. ICS and SABAs were the subclasses for which the average number of prescriptions per child were the highest (6.7 ± 6.5 and 5.0 ± 6.0 respectively), followed by SABAs (5.0 ± 6.0). The medication combination with the highest average number of prescriptions per child was ICS plus LABA plus SABA ($3.5 \pm$

Table 1

Prescription of respiratory medications among the study population (N = 4951).

	Children receiving at least one prescription (N = 4951) n (%)	Average number of prescriptions per child Mean \pm SD [min-max]	Average age of first prescription Mean \pm SD [min-max]
ICS	4718 (95.3)	6.7 ± 7.5 [1–97]	1.7 ± 1.8 [0–10.4]
ICS alone	4677 (94.5)	6.0 ± 6.5 [1–74]	1.7 ± 1.7 [0–10.6]
ICS plus LABA	634 (12.8)	3.0 ± 3.4 [1–24]	5.4 ± 2.5 [0.2–10.6]
ICS plus LTRA	373 (7.5)	2.3 ± 2.5 [1–20]	3.1 ± 2.0 [0.4–10.5]
ICS plus LABA	10 (0.2)	1.0 ± 0 [1–1]	3.1 ± 2.0 [0.4–7.4]
ICS plus LABA plus LTRA	125 (2.5)	3.5 ± 4.2 [1–23]	5.2 ± 2.4 [0.5–10.4]
ICS plus LTRA plus LABA	3 (0.1)	1.3 ± 0.6 [1,2]	0.8 ± 0.4 [0.5–1.2]
LABA	675 (13.6)	3.5 ± 4.3 [1–33]	5.3 ± 2.5 [0.2–10.6]
LABA alone	4 (0.1)	1.0 ± 0.0 [1–1]	5.5 ± 2.2 [2.3–7.0]
LABA plus LTRA	1 (0.0)	1.0	9.6
LTRA	704 (14.2)	3.4 ± 4.5 [1–38]	3.6 ± 2.3 [0.4–10.8]
LTRA alone	480 (9.7)	2.3 ± 2.5 [1–23]	3.9 ± 2.3 [0.4–10.8]
LAMA	17 (0.3)	1.2 ± 0.6 [1–3]	2.7 ± 1.9 [0.4–7.4]
LAMA alone	5 (0.1)	1.4 ± 0.5 [1,2]	3.3 ± 1.1 [2.1–5.0]
SABA	3407 (68.8)	5.0 ± 6.0 [1–81]	2.3 ± 2.2 [0.1–10.5]
Others	7 (0.1)	1.3 ± 0.8 [1–3]	5.0 ± 2.3 [2.8–10.1]
All R03	4951 (100)	8.1 ± 9.4 [1–106]	1.6 ± 1.7 [0–10.5]

4.2). The mean age of the first prescription was lower for ICS alone (1.7 ± 1.7) and higher for LABA (5.3 ± 2.5) prescribed alone or in combination (mean age of first prescription over five years in both cases) as compared with other subclasses. The mean age of the first LTRA prescription was $3.6 (\pm 4.5)$.

Fig. 2 illustrates the number of prescriptions of medication for obstructive airway diseases subclasses by child's age. Before the age of 6 months, children mainly received ICS alone (N = 967, 19.5 %) and SABA (N = 379, 7.7 %). After 6 months of age, the percentage of children exposed at least once to ICSs alone increased and remained relatively constant across age categories (N = 3,108, 62.8 % for the category [6 months–2 years], N = 2,891, 58.4 % for the category [2–4 years], and N = 2,886, 58.3 % for the category ≥ 4 years). The percentage of children exposed to SABAs was highest in the [6 months–2 years] category (N = 1,660, 33.5 %) and then gradually decreased. In the [6 months–2 years] category, the most commonly prescribed medications after ICSs and SABAs were the combination of ICSs plus LTRAs (N = 127, 2.6 %), followed by LTRAs alone (N = 111, 2.2 %). In the [2–4 years] category, the most commonly prescribed medications after ICSs and SABAs were LTRAs alone (N = 162, 3.3 %), followed by the combination of ICSs plus LABAs (N = 149, 3.0 %), and the combination of ICSs plus LTRAs (N = 138, 2.8 %). In the ≥ 4 years age category, the medication most prescribed after ICSs and SABAs was the combination of ICSs plus LABA (N = 434, 8.8 %), followed by LTRA alone (N = 205, 4.1 %), and the combination of ICSs plus LTRA (N = 104, 2.1 %).

Table 2 presents the number of prescriptions for drugs containing ICS

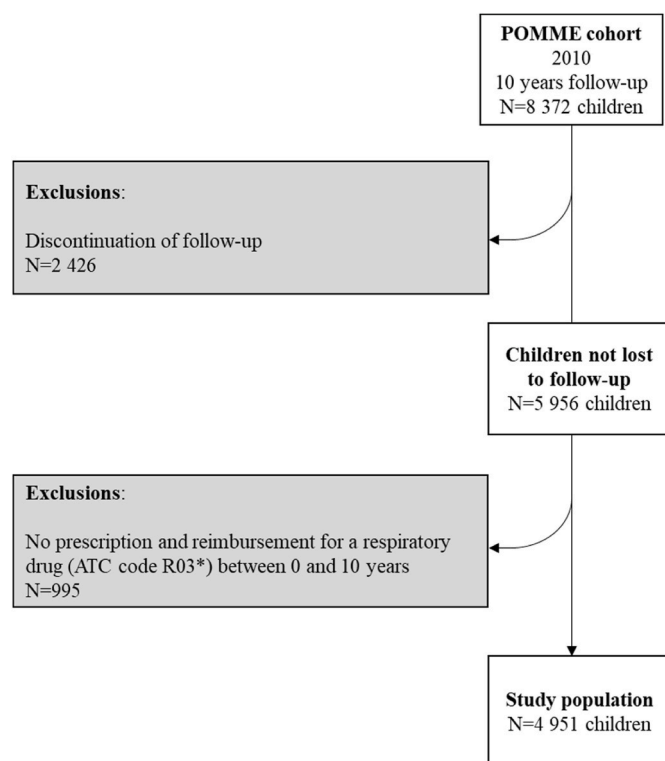


Fig. 1. Flow-chart of the study population.

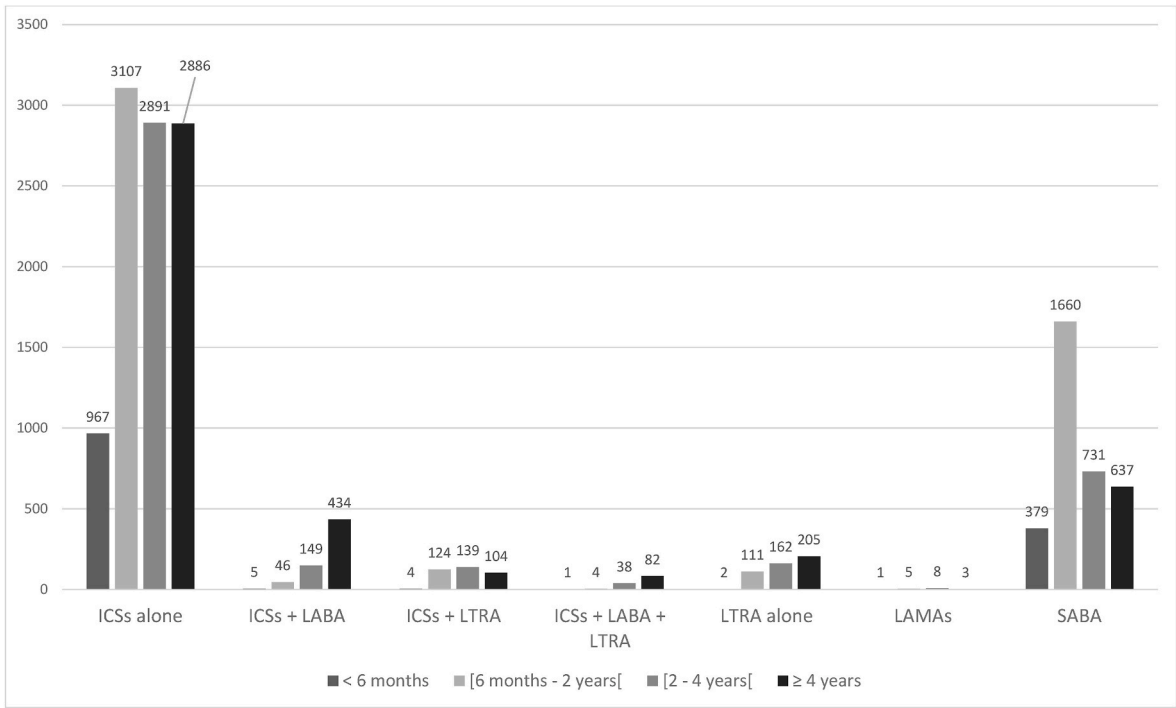


Fig. 2. Number of prescriptions of respiratory medication subclasses according to the child age.

Table 2
Medications containing ICS or LABA prescribed during the study period.

Ranking	Medications containing ICS	N (%)	Ranking	Medications containing LABA	N (%)
1	Fluticasone	12712 (36.0 %)	1	Salmeterol and fluticasone	3447 (93.8 %)
2	Budesonide	11204 (31.8 %)	2	Formotérol and budesonide	222 (6.0 %)
3	Béclométasone	7687 (21.8 %)	3	Fenoterol and ipratropium bromide	3(0.1 %)
4	Salmeterol and fluticasone	3447 (9.8 %)	4	Formoterol	1(0.0 %)
5	Formotérol and budesonide	222(0.6 %)			
	Total	35,272		Total	3673

or LABA. The most frequently prescribed ICS were fluticasone (12712 prescriptions, 36.0 % of the ICS prescriptions) and budesonide (11204 prescriptions, 31.8 % of the ICS prescriptions), and the most frequently prescribed LABA were salmeterol (3447 prescriptions (in combination with fluticasone), 93.8 % of the LABA prescriptions) and formoterol (222 prescriptions (in combination with budesonide), 6.0 % of the LABA prescriptions).

A Sankey diagram showing the evolution of treatments among children by age category is presented in Fig. 3. The proportion of children receiving SABA alone was very low across all age groups, despite these medications being indicated alone as the first line for intermittent asthma. More short-term ICS prescriptions than long-term (at least 3 consecutive months) were observed, whether alone or with SABA. Various prescription strategies were numerous, and a large proportion of children receiving ICS before 6 months or between 6 months and 2 years no longer received them as they grew. However, three groups of children stood out for the stability of their treatments across age categories from 2 to 10 years: (1) children treated with ICS for short durations, (2)

children treated with SABA and ICS for short durations, and (3) children treated with SABA and ICS for long durations.

A total of 58,017 prescriptions were recorded. The majority of prescriptions were made by general practitioners (n = 36,551 prescriptions, 63.0 %), regardless of age group. Other prescribers included pediatricians (n = 18,565, 32.0 % of prescriptions), pulmonologists (n = 1,160, 2.0 %), ENT specialists (n = 1,161, 2.0 %), and other specialists (n = 580, 1.0 %).

4. Discussion

This study showed that over 80 % of children in the POMME cohort received prescriptions for medication for obstructive airway diseases at least once during their first 10 years of life. In particular, ICSs alone and in combination were the most commonly prescribed medications (94.5 % of exposed children), aligning with recommendations from the GINA and the French HAS.

In the present study, the most frequently prescribed medication was ICSs, with 95.3 % of children receiving at least one prescription, followed by the combination of ICS plus LABA (12.8 %). As children aged, the number of medication for obstructive airway diseases prescriptions generally increased, except for ICSs prescribed alone, which peaked in children aged between 6 months and 2 years. LTRAs were predominantly prescribed to children between 6 months and 4 years of age, after which their prescription decreased. This trend can be attributed to the indication of LTRAs for children with asthma aged 6 months and above, often in combination with ICSs. Notably, LABAs had a mean age at first prescription exceeding 5 years, as these medications lack marketing authorization before the age of 4, making the prescriptions in younger children off-label. Our results align with international and French recommendations for the management of asthma in children, which favor ICSs as the first-line treatment and suggest combinations with LTRAs for children under 5 or LABAs for children over 5 as a second-line treatment [4]. However, it is noteworthy that the number of children exposed to LTRA alone increased with age, with a significant number of children exposed after 5 years. This use of LTRA alone is not in line with recommendations and should be considered in light of the adverse effect

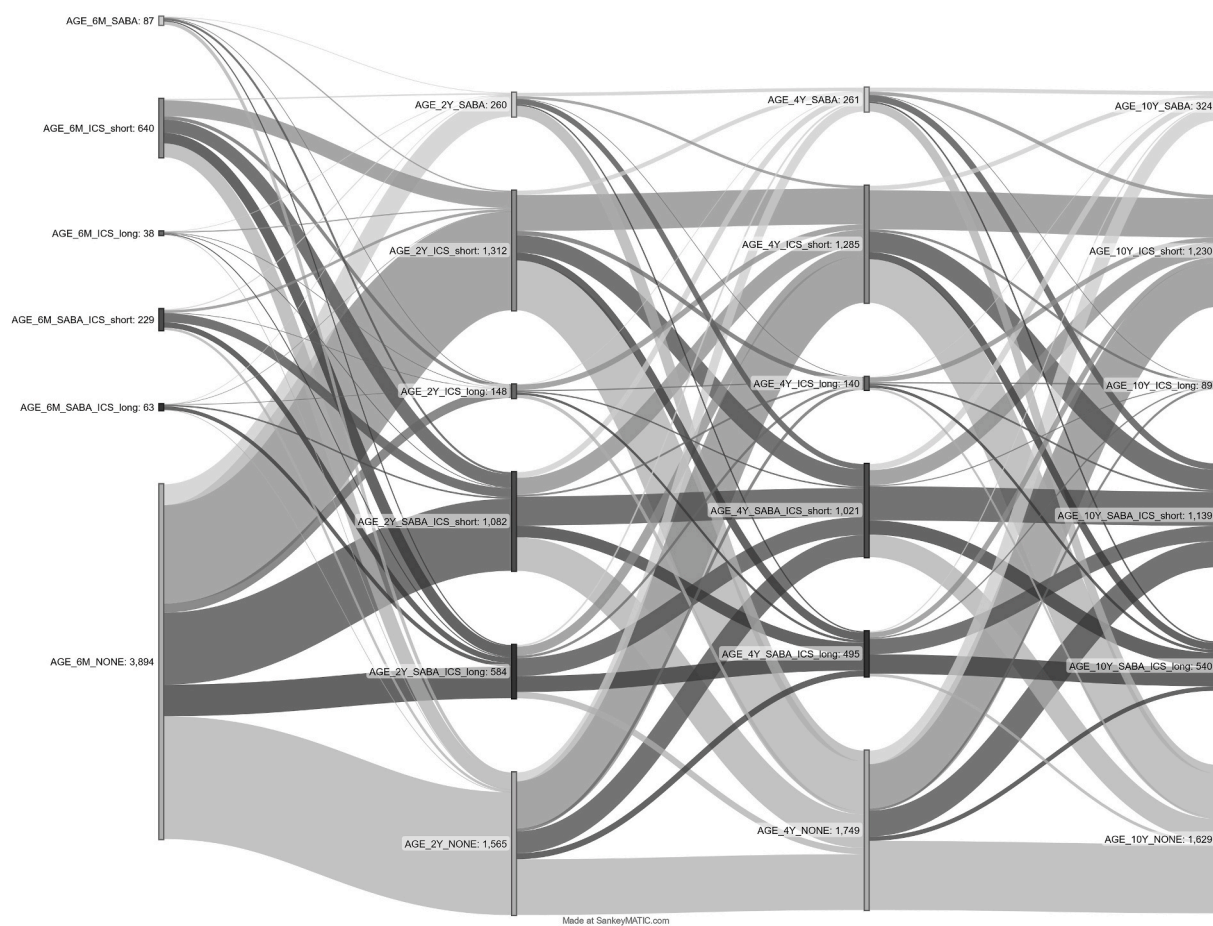


Fig. 3. Evolution in the number of children receiving R03 medication prescriptions by age. AGE_6M: age category <6 months, AGE_2Y: age category [6 months-2 years], AGE_4Y: age category [2-4 years], and AGE_10Y: age category ≥ 5 years of age; ICS_short: short-term ICS prescriptions, ICS_long: long-term ICS prescriptions, SABA_ICS_short: SABA plus short-term ICS prescriptions, SABA_ICS_long: SABA plus long-term ICS prescriptions, NONE: no R03 prescription.

profile of LTRA. Indeed, montelukast has been associated with potentially serious neuropsychiatric adverse effects, including suicide, leading to the inclusion of the drug in the Food and Drug Administration's "black box warning" [15,16].

Despite the long follow-up duration, the average number of prescriptions per child was relatively low if medications were prescribed for asthma indications. ICSs alone were prescribed an average of six times per child between ages 0 and 10, while all other medications, either alone or in combination, averaged fewer than 4 prescriptions per child. This suggests that these medications are more likely to be prescribed on an as-needed basis, warranting further investigation into actual prescription durations using more complex statistical model, as done in some other studies [17].

While medications within the ATC class R03 are typically indicated for asthma management in children, our study observed different usage patterns among the children included. The discrepancy between the percentage of children exposed to R03 (83.3 %) and the estimated asthma prevalence in the general population (9.8 %), coupled with the high proportion of children only exposed before age four, the low number of long-term ICS prescriptions, and the relatively low number of prescriptions per child, suggested that a significant proportion of prescriptions may not be related to asthma management but rather for occasional respiratory infections common in young children. This is inconsistent with HAS recommendations, which discourage the use of bronchodilators or corticosteroids in the treatment of bronchiolitis in children under 12 months of age due to demonstrated ineffectiveness [11]. Consequently, a notable proportion of medication for obstructive airway diseases prescriptions were off-label, raising concerns about

off-label prescriptions in children. Asthma cannot be diagnosed in such a young child. The reasons for the observed discordance between guidelines and prescription practices in our study are multiple: (1) prescribing habits of doctors, (2) doctors' desire to treat patients by prescribing medication, (3) parental pressure for doctors to prescribe medication for their child, and (4) confusion between the diagnosis of viral infection and asthma. This phenomenon of off-label prescriptions in pediatrics is widespread globally. For instance, a 2015 Canadian study highlighted off-label drug use rates in children ranging from 33.2 % to 46.5 % for inpatients and from 3.3 % to 13.5 % for outpatients [18]. This phenomenon is largely attributed to the scarcity of clinical trials in pediatric populations and is associated with an increased risk of adverse effects and the potential for inappropriate dosing based on body weight [19, 20]. One strategy to reduce the misuse of ICS in young children could be to renew information campaigns for healthcare professionals regarding the use of ICS in children under 36 months. A study showed that health agency recommendations are effective in reducing medication misuse but need to be regularly renewed [21]. Conducting studies highlighting the number of avoidable adverse effects of ICS in children could also provide arguments for less frequent use of these medications in young children.

This study has several limitations. Firstly, we excluded children with interrupted follow-up, making it challenging to distinguish between those who relocated outside the department and those who had limited utilization of medical care. It is possible that some children were wrongly excluded because they resided in Haute-Garonne and had no medication or care reimbursement for an entire year, but if that is the case, the number of children concerned was low due to the frequent use

of the healthcare system by children. Additionally, this limited exposure bias by not considering unexposed children who moved out of Haute-Garonne.

Secondly, since our study relied on reimbursement data, we lacked information on the specific indications for these prescriptions, necessitating further research to assess prescription relevance in relation to clinical guidelines and situations. We do not have data on the diagnoses made for the children and were unable to correlate medication prescription data for obstructive airway diseases with asthma diagnoses in the children. It is therefore important to be cautious when interpreting the results, particularly regarding the off-label use of ICS in children under 12 months old."

Lastly, the POMME cohort is limited to the Haute Garonne area, and prescribing practices may vary across different areas in France.

Despite these limitations, this study boasts several notable strengths. To begin with, it is the first descriptive study dedicated explicitly to medication for obstructive airway diseases. While previous investigations have primarily focused on cohorts of children diagnosed with asthma, our research breaks new ground by examining the prescription patterns of medications indicated for asthma, devoid of preconceived diagnostic assumptions. Furthermore, a key strength of this study is that it was carried out on almost 5000 children who were continuously followed-up from birth to the age of 10 years. The data on drug exposure were sourced from reimbursement records, providing a distinct advantage over databases reliant on medical records or questionnaires. This approach mitigated the potential for recall bias, enhancing the reliability of our findings. Another noteworthy aspect is the representativeness of the POMME cohort in relation to French live births, as evidenced by the similarity in children's characteristics to those documented in the French national perinatal survey published in 2010 [22].

In conclusion, this large-scale drug-utilization study provides valuable insights into the prescription patterns of medication for obstructive airway diseases in children. While these medications are primarily indicated for asthma management, our findings suggested a significant proportion of prescriptions may be related to occasional respiratory infections, particularly in children under 4 years, where asthma diagnosis is more challenging. Many of these prescriptions appear to be off-label, underscoring the need for further research and clinical guidance to ensure appropriate medication use in pediatric populations.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by CNIL (Commission Nationale de l'Informatique et des Libertés), DR-2013-060. This study was performed on anonymized patient data. The mothers of the child included in POMME were informed of their inclusion and of the potential use of their anonymized data for research purposes. They can oppose the use of their data at any time.

Consent for publication

The women included in the POMME database know that their collected and anonymized data can be used for medical research purposes and can thus be published.

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Data statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so the research data is confidential.

Generative AI was used to improve language and readability, with caution.

CRediT authorship contribution statement

Justine Benevent: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Conceptualization. **Inès Bensadallah:** Writing – original draft, Software. **Anthony Caillet:** Validation, Software, Data curation. **Marine Michelet:** Writing – review & editing, Conceptualization. **Anna-Belle Beau:** Writing – review & editing, Methodology. **Isabelle Lacroix:** Writing – review & editing, Conceptualization. **Christine Damase-Michel:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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