Evaluation of Drug Deliveries and Refunds for Obstructive Airway Diseases in France between 2012 and 2017

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Short title: Drug deliveries for obstructive airways diseases

Abbreviations: ATC, Anatomical Therapeutic Classification; COPD, Chronic Obstructive Pulmonary Disease; GINA, Global Initiative for Asthma; ICS, Inhaled Corticosteroids; LABA, Long-Acting Beta2-Agonists; SABA short-acting beta2-agonists; SNDS, French national health data system.

ABSTRACT

Background. – The aim of this survey was to investigate variations of drugs for obstructive airway diseases delivery rates and refunds at a national level which are rarely reported.

Methods. - The French national health data system (56 million, 87% of the population) was used to identify insurance beneficiaries with at least one drug delivery (Anatomical Therapeutic Classification R03) per year between 2012 and 2017.

Results. - At least one drug delivery in 2017 was identified for 7.5 million people (12.9%). High proportions of people with at least one, two or three drug deliveries were observed between the ages of 0 to 2 years (22%, 10%, 5.5%), then decreased between the ages of 18 and 40 years (9.3%, 3.8%, 2.3%) and increased again in people 75 years and older (17.8%, 11.9% 9.9%), with strong variations between years. In 2017, the proportions of people with at least one delivery, either alone or in combination with other drugs, were 68% for inhaled corticosteroids (ICS) (median 1; IQR 1-4), 59% for short-acting beta2-agonists (SABA) (1; 1-3), 42% for long-acting beta2-agonists (LABA) (2; 1-6), 11% for leukotriene receptor antagonists (3; 1-9), and 12% for inhaled anticholinergics (4; 1-10). Younger patients more often received SABAs (0-2 years: 84%) and leukotriene receptor antagonists (3-6 years: 14%) and people 75 years and older more often received LABAs (59%) and ICS, either alone or in combination with other drugs (28%).The mean annual refund reimbursed per person decreased from €136 in 2012 to €118 in 2017.

Conclusion. - This study suggests a low level of use for drug classes associated with low delivery rates, suggesting inappropriate prescriptions and poor follow-up. These results highlight the difficulty of identifying these problems if delivery rates variations over several years are not taken into account.

Key Words. - Asthma, COPD, Drugs, Epidemiology, Observational study

1. Introduction

Asthma affects about 340 million people worldwide and this number is expected to increase over the years to come [1]. Higher prevalences are reported in industrialized countries (15-20%), in children, especially boys, and young adults [1-3]. The prevalence of chronic obstructive pulmonary disease (COPD) increases after the age of 40 [4]. An estimated 174 million people are affected worldwide, with a prevalence of about 15% in the Americas [4, 5]. An overlap of these two diseases is observed in 10 to 15% of cases [6].

Prevalence and incidence data available for these diseases are usually derived from cross-sectional general population studies using various inclusion criteria, based on self-report with or without confirmation by clinical examinations, but also specific cohorts with variable sample sizes, and variable projection calculations [2, 3, 7-14]. Depending on their primary objective, cross-sectional studies are repeated in the long term at variable intervals [2], which limits regular updated data. An alternative consists of the use of dispensed drug refund claims data that are rapidly and regularly available for large population [12, 15-22]. People treated for obstructive airway diseases, can be identified by the delivery of certain drug classes. However, the frequencies and amplitudes of refund periods used to select cases are often defined in advance. Thus, global distributions in treated populations according to various drug consumption criteria are rarely reported.

Since the 2000s, the development and improvement of various inhaler devices and the growing number of molecules and combinations available contributed to increased reimbursement refund [23]. Drugs account for more than one-half of the direct costs related to asthma and about 20% of the direct costs related to COPD [24-26]. Poor compliance with treatment guidelines [27-29] also leads to over-prescription and poor adherence, contributing to increased health care utilization [30-33].

This study, based on a large population and using the French national health data system (SNDS), evaluated delivery rates, combinations, costs and variations over time (2012-2017) of the various drug classes indicated for the treatment obstructive airways diseases.

2. Methods

2.1. Data

The SNDS collects the individual socio-demographic characteristics of the beneficiaries of the various French health insurance schemes, together with the prescriptions and procedures performed on an outpatient basis or in hospitals, resulting in individualized reimbursement [34]. The SNDS does not record office medicine diagnoses or the results of clinical examinations and investigations, but there is a long term chronic disease status eligible for 100% reimbursement. Identification of prescribed and reimbursed drugs is based on Anatomical Therapeutic Classification (ATC) codes.

2.2. Population

French national health insurance general scheme or local mutualist section beneficiaries were selected (2012-2017), which represents 87% of the French population. Then, people with at least one reimbursed health care utilization, whatever it is, in each year of the study were included: 57.5 million in 2017 (Table A.1.).

2.3. Drugs of interest

Among the drugs of the ATC group R03, called "drugs for obstructive airway diseases", the following subgroups were taken into account and detailed: R03A (adrenergics, inhalants, alone or in combination, either short-acting beta2-agonists (SABA) or long-acting beta2-agonists (LABA), including inhalation solutions); R03B (Other drugs for obstructive airway diseases, inhalants, such as inhaled corticosteroids (ICS), anticholinergics and cromones); R03C (Adrenergics for systemic use); R03D (Other systemic drugs for obstructive airway diseases, such as xanthines, leukotriene receptor antagonists and omalizumab). In subgroup R03D, mepolizumab was marketed in France in 2018, later than in other European countries. During the same year, deliveries were considered independently, whether or not they were prescribed at the same time. ATC R03 drugs combined in the same dosage form were considered separately. Drug combinations were considered by the presence of at least one delivery during the year for each of the drug groups selected.

2.4. Analyses

The annual delivery rates evolution corresponded to the number of people with at least one delivery of an ATC R03 drug during each year over the total number of people in the study population. The proportions of people with at least 1, 2, 3, 6, 9 or 12 deliveries per year were described. The variation of the treatment initiation rate in 2017 was studied according to the duration of the previous period without ATC R03 delivery (1 to 5 years before 2017). The medians and interquartile ranges (IQR) of annual deliveries of the various therapeutic subgroups studied were reported for people with at least one delivery of subgroup considered during the year. Finally, a 5-year longitudinal follow-up (2012-2017) presented the annual variations of deliveries for a cohort of people (age calculated in 2012) with at least one delivery in 2012 and who were still alive in 2017, according to the number of deliveries, and the ATC R03 subgroups considered. Sankey diagrams were plotted to illustrate the variations and annual flows between groups.

The total refund reimbursed (euros) by French national health insurance for ATC R03 subgroups, the age distribution of this refund and the mean refund per person with at least one delivery of the subgroup considered, were estimated between 2012 and 2017. Total refunds were reported according to specific ATC subgroup, as several subgroups may be combined in the same packaging with a single price.

CNAM (National health insurance fund) has permanent access to the SNDS by decree and authorized by the CNIL (French data protection authority). SAS software was used (version 7.13, SAS Institute Inc., Cary, NC, USA) for statistical analysis and R (3.4.3.) was used for Sankey diagrams.

3. RESULTS

3.1. Annual delivery

At least one of the selected ATC R03 drugs delivery during the year was identified for 7.1 million people from 2012 to 2014, 7.3 million in 2015 and 7.5 million in 2017. In 2012, 51% of the people with at least one delivery were over the age of 40 versus 55% in 2017. In 2017, 55% of these people

were women with a lower proportion (20%) of people under the age of 18 years compared to the proportion observed in men (32%) (Table A.1.).

The overall proportion of people with at least one delivery during the year (Fig. 1A.) was relatively stable (12.8% in 2012 and 12.9% in 2017). This proportion was higher in the extreme age-groups, as in 2017: 22.0% of 0-2-year-olds, 18.7% of 3-6-year-olds, 16.1% of 65-74-year-olds and 17.8% of people 75 years and older (Fig. 1A.).

The proportion of people treated decreased as the annual number of deliveries increased (Fig. 1B.). In 2017, 12.9% of people received at least one reimbursement, 0.9% received at least 12. The proportion of people in 2017 with at least one, two or three deliveries according to age (Fig. 2A.) was high between 0 and 2 years (22%, 10% and 5.5%, respectively), and after a decrease steadily increased until the age of 75 and older (17.8%, 11.9% and 9.9%).

ATC group R03 drugs were not dispensed to a variable proportion of those people with at least one delivery in 2017 according to the number of previous years considered (Fig. 2B.). For example, the proportion of people aged 18 to 40 with at least one delivery in 2017 (9.3%) decreased according to the amplitude of the previous periods with no drug delivery: 2016 (4.9%), 2015-2016 (3.9%) and 2012-2016 (2.8%).

3.2. Delivery of the various classes

Among those people with at least one delivery in 2017, regardless of age (Table 1), 68% had at least one delivery of ICS, either alone or in combination, and, among these people, ICS were dispensed once during the year to 50% and 4 or more times to 25% (median 1; IQR 1-4), 59% received SABA (1; 1-3), 42% received LABA (2; 1-6), 11% received leukotriene receptor antagonists (3; 1-8), and 12% received inhaled anticholinergics, either alone or in combination (4; 1-10). Younger people more often received SABA (0-2 years: 84%) and leukotriene receptor antagonists (3-6 years: 14%, 7-17 years: 17%), while people aged 40 and older mainly received LABA (75 and older: 59%) and inhaled anticholinergics, either alone or in combination (75 and older: 28%) and, to a lesser extent, xanthines (75 years and older: 1%) and oral beta2-agonists (75 and older: 0.9%). The median number

of deliveries was generally higher among older people, but with broad IQRs. A low delivery rate (0.2%) was observed for omalizumab with a peak of 0.3% in 2017 for people aged 41-64.

In 2017, 15% of patients with at least one delivery only received ICS. This proportion was 65% for 0-2-year-olds and 73% for people aged 75 and older. Twenty-two percent of patients only received SABA (34% of 0-2-year-olds, 10% of people aged 75 and older) (Table 1). The frequency of at least one annual delivery of each of these two classes alone was 12%, and was higher among very young people (44% between 0-2 years). Twelve percent of patients received at least one delivery of an ICS and a SABA. This proportion was 44% among 0-2-year-olds. Twenty percent of patients received at least one delivery of an ICS, a LABA, and a leukotriene receptor antagonist or anticholinergic.

3.3. Evolution of people treated in 2012

The 5-year variation in the proportions of people according to their number of deliveries or combination treatments is described by a Sankey diagram (Fig. 3A, 3B). In 2012, a single delivery was identified for 49% of people; 2-3 for 24%; 4-6 for 11%; 7-10 for 8% and 11 or more for 8%. Five years later, these drugs were no longer dispensed to 53% of these people and the proportion of people with one delivery (13%) or 2 to 3 deliveries (10%) had decreased. Cessation of delivery in the first year after 2012 according to treatment modality mainly concerned people with delivery of ICS or SABA alone, followed by ICS and SABA combinations. An early decrease in delivery rates was also observed for the group of people treated with ICS and maintenance treatment without SABA. These changes varied according to the person's age (Fig. A1.). The proportion of children aged 0- to 2 years and 3 to 6 years who were no longer treated after 5 years was 74% and 67%, respectively. The proportion of older people no longer treated after 5 years was also higher (41-64 years: 48%, 75 and older: 40%).

3.4. Reimbursed drug refund

Total refund in 2012 was €974 million for 7.1 million people with at least one reimbursement of ATC group R03 drugs. Total refund then decreased between 2013 (€917 million) and 2017 (€887 million), while the number of people treated increased (7.1 to 7.5 million people) (Table 2). In 2017,

80% of the €887 million reimbursed for drug refund concerned people 41 years and older. Only the proportion of 65-74-year-olds accounting for total refund increased from 18.2% in 2012 to 22% in 2017, while the proportion of people 75 years and older remained stable. The mean annual refund per person decreased, from €136 in 2012 to €118 in 2017, and for each age-group. In 2017, the mean refund was €272 for people aged 0 to 2 years and €218 for people 75 years and older.

The decrease in total refund between 2012 and 2017 was observed for most classes of drugs, but was more pronounced for leukotriene receptor antagonists (€111 million in 2012, €50 million in 2017), ICSs (€127 million in 2012 vs. €97 million in 2017) and LABAs (€117 million in 2012 vs. €97 million in 2017). Total refund only increased for omalizumab (€77 million in 2012 and €122 million in 2017) with a mean annual refund per person of just over €10,000 in 2017. In 2017, the class of ICS-LABA fixed combinations accounted for 47% of total refund and omalizumab accounted for 14%.

4. Discussion

In France, due to the small number of population-based epidemiological surveys, studies have been conducted on the SNDS database, mainly based on drug reimbursements (1 to 4 reimbursements or over a period of two years), which can also be used to study severity, persistence and misuse [20-22]. Furthermore, diagnoses established in the emergency room or at office consultations are not recorded in the SNDS. Hospital discharge diagnoses can be used, but they are relatively rare, especially for asthma. Identification of patients with obstructive airway diseases based on drug reimbursements may be overestimated by the more or less isolated use of these drugs for acute illnesses. However, exclusion of these people from the analysis could result in exclusion of patients with intermittent or mild clinical forms. This phenomenon can be assessed in terms of the annual treatment recurrence rate, but also the delivery of certain drug classes that are more often used to treat chronic disease or more severe forms. Few drugs of the ATC group R03 are specific to asthma or COPD. In view of their epidemiological characteristics, they are often distinguished by using a cut-off between 35 and 45 years of age, although these two diseases can coexist after this age [17, 18]. Other information can be used, such as disease severity or intensity of treatment [12,

15-18], but they also present similar limitations or performances for the identification of COPD patients.

Prevalence rates of drug delivery can be compared with population-based prevalence rates to estimate their degree of consistency. In this study, at least one delivery per year was identified in 2017 (12.9%), with the following distribution according to age-group: 0-2 years (22.0%), 3-6 years (18.7%), 7-17 years (11.1%). For comparison, studies on young schoolchildren in France have reported a lifetime prevalence of asthma or asthma treatment during the previous 12 months of 9.8% in 2005-2006 and 11% in 2012-13 [7, 8], similar to the rate observed for 2 reimbursements per year. Among young adolescents in 2005-2006, the prevalence of treated asthma during the previous 12 months was 8.6%, while, in our study, the prevalence was slightly lower, at 6% for two reimbursements per year, but for a larger age-group (7-17 years) also bearing in mind that the prevalence of asthma at puberty decreased. Our study observed a higher proportion of boys, as already reported [7, 8].

Among people 15 years and older, the self-reported prevalence of ongoing asthma in 2012 was 7.4% (9.6% for 15-24-year-olds, then decreased to 5.6% for 55-64-year-olds and 8.9% for people 65 years and older) [9]. In the present study, 9.3% of 18-40year-olds had at least one reimbursement per year and 3.8% two reimbursements. This analysis did not distinguish between asthma and COPD. The prevalence of COPD in France is reported to be 3.8% for people 40 years and older and 7.5% for workers 45 years and older based on spirometry [14]. In this study, after the age of 40 years, 14.4% of people had at least one reimbursement during the year and 8.4% had two reimbursements.

Estimation of temporal changes in prevalence and incidence or treatment initiation is also limited by the lack of regular population-based data. A periodic cross-sectional self-report study reported an increased lifetime prevalence of asthma in young children (2005-2006: 9.8% vs 2012-2013: 11.0%) [8]. In the present study, reimbursement rates per age-group remained globally stable over a 5-year period, but with a slight increase among people 40 years and older, which could be

related to increased exposure to specific risk factors over previous years. Thus, COPD prevalence estimates suggest a growing number of cases and a growing prevalence [13, 14].

Among RO3 drugs, SABA are prescribed in more than half of the population. Surprisingly, one quarter to one third of the population <40-yrs received only SABA, without ICS. This could reflect intermittent, undertreated or undiagnosed asthma, which is a source of concern in view of the GINA 2020 guidelines [35], since it has been shown that the use of high doses of SABA alone is associated with excess asthma mortality. However, delivery of SABA alone appeared to fluctuate between 2012 and 2017, which may also correspond to isolated episodes, such as one-time prescriptions related to viral respiratory infection. The number of SABA deliveries per se is a poor reflect of asthma control, due to intermittent use and shelf life of the inhalator.

The long-term goals of asthma treatment are to control symptoms and decrease the risk of exacerbations, deterioration of pulmonary function and adverse drug reactions. According to the Global Initiative for Asthma (GINA) and guidelines published prior to 2019, all asthma patients should receive treatment for acute asthma attacks (SABA) combined with maintenance treatment with ICS [27-29, 35]. These guidelines did not appear to have been rigorously applied in this study, as SABA, alone or in combination, were not dispensed during the year to about one-quarter of people, especially in adolescents and young adults. This absence of delivery may be due to absence of prescription or a low rate of utilization of SABA. On the other hand, almost one-quarter to one-third of people only received SABA, which may indicate intermittent, undertreated or undiagnosed asthma. This high proportion of patients treated by SABA alone is a source of concern in view of the GINA 2020 guidelines [35], as it has been shown that the use of high doses of SABA alone is associated with excess mortality due to asthma. However, delivery of SABA alone appeared to fluctuate between 2012 and 2017, which may correspond to isolated episodes.

Slightly less than two-thirds of adolescents and young adults received ICS in this study. About 15% of people received ICS at least once and this proportion was relatively stable by age-group and from year to year, but with a low persistence rate, which may correspond to an initial prescription for

indications other than asthma, or treatments that were subsequently discontinued. On the other hand, it cannot be ruled out that treatment may have been intensified in some patients, but the persistence rates for all treatments and combinations studied tend to suggest that treatments were discontinued, for whatever reason (lost to follow-up or poor persistence).

Omalizumab is a marker of improved recognition of the management of severe asthma [11]. Nevertheless, the annual reimbursement rate remained stable, but with a peak for people aged 41 to 64. In 2015, omalizumab was approved in France for the treatment of chronic urticaria after failure of first-line treatment and a small proportion may have been wrongly included.

As recommended according to clinical stage, ICS, LABA, leukotriene receptor antagonists, or anticholinergics with or without SABA were dispensed to a large proportion (nearly two-thirds) of people 40 years and older, who probably comprised a higher proportion of patients with COPD.

The health care refund reimbursed by French national health insurance for patients with obstructive pulmonary diseases (asthma, COPD, chronic bronchitis, emphysema and bronchiectasis, excluding cystic fibrosis) accounted for 2.9% of total refund for the overall population, i.e. €3.5 billion for all refund combined, including €1.1 million for drugs (31%) [18]. This study, which exclusively focused on ATC group R03 drugs and 87% of the population, found a total refund of €887 million, lower than that observed in 2012 (€974 million), while the number of people with at least one reimbursement per year increased. This decreased refund was more marked for certain drug classes such as leukotriene receptor antagonists. These variations may be related to changes in drug prices, the availability of generic drugs for certain classes, variations in delivery intensity or the frequency of drug combinations. The great majority of global refund (80%) concerned people 41 years and older, who had a higher annual number of deliveries and who received multiple drug classes, including the most expensive drugs, indicated in persistent asthma or COPD, such as leukotriene receptor antagonists, xanthines and omalizumab.

4. Limitations

This study is devoted to asthma and COPD, whereas chronic obstructive diseases include other diseases with lower prevalence. In 2017, in France, 3.63 million of individuals (5.6% of the whole French population) were identified with a respiratory chronic disease excepting cystic fibrosis. They were mainly identified by at least three refunds of ATC R03 group drugs in 2017 only (69%); short stay hospital diagnosis (ICD codes J40 to J47, J96 and J98) during the preceding five years only (10%); a long term disease diagnosis codes in 2017 only (2%) (data not shown). For his study on 87% of the French population (58 million), 2.8% had at least three refunds giving 3.2 million extrapolating to whole population.

This observational study was based on comprehensive office medicine reimbursement data for these drugs in a very large population. During acute exacerbations, emergency medicines can be dispensed directly by pharmacists, without the need for a prescription. However, direct delivery may be limited by the fact that some drugs are registered on the official list of drugs that may directly or indirectly present a health risk, for which a prescription and delivery for the specified duration are required. This is the case, for example, for medications containing theophylline. Moreover, some patients may have stockpiled their dispensed medication and may or may not have used them subsequently during follow-up.

Combinations of different drug classes dispensed concomitantly from the same prescription were not analysed in the study of treatment modalities because the rates of consumption and delivery may differ according to these various drug classes with variations induced by the prescriber and by the patient. Treatment switches during the same year may also have been considered to be combination treatments.

5. Conclusion

This study, with a follow-up of five years, confirms a high rate of ATC group R03 drugs treatment discontinuation with significant flows between low annual reimbursement rates, especially for treatments of acute episodes, mainly affecting the youngest patients and may be related to isolated prescription for acute asthma or another acute bronchial disease, poor adherence or persistence, as

often reported in these diseases, or inappropriate prescriptions or treatment with respect to asthma management guidelines. With constant fields and definitions, data from administrative databases can be used as indicators of growth curves and consumption in the absence of specific population surveys.

Supplementary data

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Disclosure of interest

The authors declare that they have no competing interest.

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Table 1. Among those people with at least one annual delivery of an ATC group R03 drug between 2012 and 2017, percentages of people with at least one delivery by therapeutic group and treatment modality, and by age (for 2017)

	2012	2013	2014	2015	2016	2017	2017						
Age (years)	Total	Total	Total	Total	Total	Total	0-2	3-6	7-17	18-40	41-64	65-74	75 et +
N (Million)	7.1	7.1	7.1	7.3	7.5	7.5	0.46	0.54	0.88	1.5	2.3	0.95	0.90
	%	%	%	%	%	%	%	%	%	%	%	%	%
Classes (alone or in combination)													
Inhaled corticosteroids	69.9	69.7	68.8	68.5	68.1	67.9	64.6	69.7	59.2	63.5	70.1	73.0	73.5
Median (IQR)*	1 (1-4)	1 (1-4)	1 (1-4)	1 (1-4)	1 (1-4)	1 (1-4)	1 (1-2)	1 (1-3)	1 (1-3)	1 (1-2)	1 (1-4)	2(1-6)	3 (1-7)
SABA	56.2	56.1	57.9	58.0	58.6	58.6	84.0	78.5	76.5	64.0	51.3	43.1	41.9
Median (IQR)	1 (1-2)	1 (1-2)	1 (1-3)	1 (1-3)	1 (1-3)	1(1-3)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	1(1-3)	2 (1-4)	2 (1-4)
LABA	42.0	42.1	42.4	42.3	42.6	42.3	2.3	13.0	30.2	40.0	50.6	57.7	59.2
Median (IQR)	2 (1-6)	2 (1-6)	2 (1-6)	2 (1-6)	2 (1-6)	2 (1-6)	1 (1-2)	2 (1-4)	2 (1-4)	1(1-3)	2 (1-6)	4 (1-9)	5 (1-10)
Leukotriene receptor antagonists	13.7	13.1	12.7	11.8	11.3	10.9	6.0	14.3	16.7	10.5	10.5	9.8	8.7
Median (IQR)	2 (1-7)	2 (1-7)	2 (1-8)	3 (1-8)	3 (1-8)	3 (1-9)	2 (1-3)	2 (1-4)	2 (1-6)	2 (1-6)	1 (4-10)	7 (1-12)	9 (2-12)
Inhaled anticholinergics alone or in combination	9.4	9.5	10.0	10.9	11.3	11.8	0.4	0.4	0.6	3.1	14.8	24.9	28.5
Median (IQR)	4 (1-10)	4 (1-10)	4 (1-10)	4 (1-10)	4 (1-10)	4 (1-10)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)	3 (1-9)	6 (2-11)	5 (2-11)
Xanthines	0.7	0.7	0.6	0.5	0.5	0.4	0.0	0.1	0.0	0.1	0.4	0.7	1.0
Median (IQR)	6 (1-12)	6 (1-12)	7 (1-12)	6 (1-12)	6 (1-12)	7 (1-12)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-3)	6 (1-11)	9 (2-12)	9 (2-12)
Oral beta2-agonists	0.8	0.7	0.5	0.4	0.3	0.3	0.0	0.0	0.0	0.1	0.3	0.5	0.9
Median (IQR)	5 (1-11)	6 (1-11)	7 (1-12)	7 (1-12)	8 (2-12)	7 (1-12)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-5)	6 (1-11)	8 (2-12)	9 (2-12)
Parenteral beta2-agonists	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.1	0.1	0.1
Median (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)
Omalizumab	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.2	0.3	0.2	0.1
Median (IQR)	10 (5-13)	10 (5-13)	10 (5-13)	10 (5-12)	10 (5-12)	10 (5-12)	1 (1-1)	5 (2-11)	11 (6-13)	8 (4-12)	10 (5-12)	11 (6-13)	11 (6-13)
Treatment modalities**													
SABA alone	20.4	20.6	21.5	22.0	22.4	22.4	34.3	26.7	34.3	30.6	18.5	11.5	9.8
ICS alone	15.4	15.7	14.4	14.8	14.7	15.4	14.3	15.0	10.8	15.7	16.9	16.5	14.9
ICS and SABA alone	12.5	12.1	12.3	12.1	12.0	11.6	43.6	35.2	15.7	8.0	6.1	4.7	4.6
ICS and (LABA or leukotriene receptor antagonists or anticholinergics) without SABA	21.5	21.4	21.0	20.6	20.2	19.6	0.9	4.1	9.2	16.7	24.1	29.5	31.7
ICS and (LABA or leukotriene receptor antagonists or anticholinergic) and SABA	20.5	20.4	21.1	20.9	21.2	21.3	5.8	15.4	23.6	23.1	23.0	22.3	22.3
Other modalities:	9.8	9.7	9.7	9.6	9.6	9.7	1.1	3.6	6.4	5.9	11.4	15.5	16.7
Anticholinergics only	1.4	1.6	1.5	1.5	1.4	2.1	0.0	0.0	0.0	0.3	1.9	3.2	3.5
Leukotriene receptor antagonists only	2.9	2.7	2.6	2.4	2.2	1.5	0.7	2.4	3.1	2.4	2.0	1.8	1.6
LABA only	1.8	1.8	1.7	1.5	1.4	1.3	0.0	0.0	0.2	0.6	1.6	2.3	2.7
LABA and anticholinergics only	0.4	0.5	0.6	1.0	1.2	1.4	0.0	0.0	0.0	0.2	1.9	3.3	3.1
SABA and anticholinergics only	1.0	1.0	1.0	1.1	1.1	1.1	0.0	0.0	0.1	0.6	1.4	1.9	2.7
SABA and leukotriene receptor antagonists only	1.1	1.1	1.1	1.0	0.9	0.9	0.3	1.1	2.6	1.2	0.6	0.4	0.3
Other	1.2	1.0	1.2	1.1	1.4	1.4	0.1	0.1	0.4	0.6	2.0	2.6	2.8

* Median and interquartile range of the number of deliveries for people with at least one delivery, ** people with at least one delivery of each class in 2017

IQR: interquartile range, ICS: inhaled corticosteroids, SABA: short-acting beta2-agonist. LABA: long-acting beta2-agonist

Table 2. Annual growth of total and mean refund per person of ATC group R03 drugs reimbursed by French national health insurance according to age and drug class

	2012	**2013**	**2014**	**2015**	**2016**	**2017**
N (million)	7.1	7.1	7.1	7.3	7.5	7.5
Total refund (€ million)						
All ages	974.1	917.0	904.8	910.4	904.0	886.8
	%	%	%	%	%	%
0-2 years	1.4	1.3	1.3	1.2	1.2	1.2
3-6 years	2.7	2.5	2.3	2.2	2.1	2.1
7-17 years	6.8	6.4	6.2	6.0	5.8	5.8
18-40 years	12.2	11.6	11.5	11.1	11.2	11.1
41-64 years	36.3	36.5	36.3	36.3	36.0	35.6
65-74 years	18.2	19.1	19.8	20.7	21.5	22.1
≥ 75 years	22.3	22.7	22.7	22.5	22.2	22.2
Mean refund (€)*						
0-2 years	136.5	129.1	127.8	124.0	120.7	118.1
3-6 years	28.2	26.2	24.5	22.8	22.8	22.4
7-17 years	46.8	41.7	38.1	36.2	34.3	34.2
18-40 years	73.3	65.8	64.0	61.9	58.3	58.3
41-64 years	76.2	70.6	69.3	68.0	65.6	64.9
65-74 years	166.9	154.6	155.1	148.6	145.0	139.3
≥ 75 years	252.2	236.8	234.0	222.3	215.8	206.0
0-2 years	272.1	257.0	253.9	236.7	231.0	218.4
Global refund (€ million)						
Selective beta-2-adrenoreceptor agonists (inhalant)	116.8	116.7	116.7	110.6	104.1	96.7
Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics	429.3	405.5	397.0	406.6	409.9	415.2
ICS	127.1	120.5	109.3	103.9	102.6	97.2
Anticholinergics	108.6	111.9	117.7	116.5	114.8	103.2
Selective beta-2-adrenoreceptor agonists (systemic)	2.7	2.4	1.9	1.7	1.5	1.3
Xanthines	1.4	1.2	1.1	1.0	0.9	0.7
Leukotriene receptor antagonists	111.1	70.3	59.1	56.8	51.6	50.5
Omalizumab	77.0	88.6	101.9	113.2	118.7	122.0
Mean refund (€)*						
Selective beta-2-adrenoreceptor agonists (inhaled)	27.4	27.5	26.9	24.8	22.7	21.3
Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics	161.2	153.1	148.6	143.4	138.5	139.9
ICS	45.2	43.5	41.1	37.8	37.7	34.9
Anticholinergics	187.2	189.3	187.4	179.6	179.0	162.4
Selective beta-2-adrenoreceptor agonists (systemic)	42.4	42.5	49.6	50.3	50.3	48.6
Xanthines	26.2	26.6	27.0	26.8	26.6	25.5
Leukotriene receptor antagonists	113.4	75.4	65.7	65.4	60.6	61.6
Omalizumab	12287.7	12635.9	13026.7	12893.6	11451.4	10154.0

ICS: inhaled corticosteroids,

*At least one refund of each drug class

Note: refunds were reported according to ATC subgroup, as several subgroups may be combined in the same packaging taken into account in this classification with a single price

Figure caption

Fig. 1. Annual trend of the percentage of people with at least one annual dispensing of ATC group R03 drugs by age (A) and by annual number of deliveries (B)

Fig. 2. Percentages of people according to their annual number of deliveries of ATC group R03 drugs in 2017, by age-group (A). Percentages of people with at least one dispensing in 2017 according to the duration of the previous period with no delivery, by age-group (B)

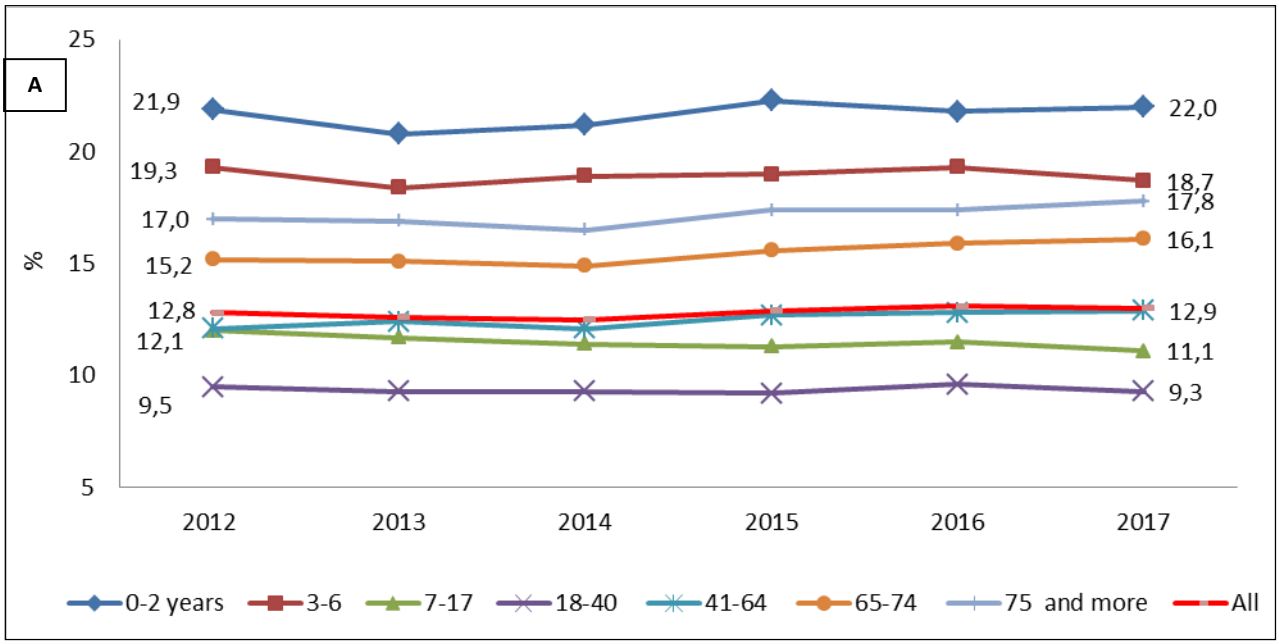
Fig. 3. Among people with at least one dispensing of an ATC group R03 drug in 2012, evolution from 2012 to 2017 of the proportion of people according to the number of dispensing (A) and the drug classes dispensed (B)

Supplementary material

Table A.1 Age of people with at least one dispensing of ATC group R03 drugs by year and by gender

Fig. A. 1. Among people with at least one dispensing of an ATC group R03 drug in 2012, evolution from 2012 to 2017 of the proportion of people according to the number of dispensing (A) and the drug classes dispensed (B)

Fig. 1. Annual trend of the percentage of people with at least one annual dispensing of ATC group R03 drugs by age (A) and by annual number of deliveries (B)



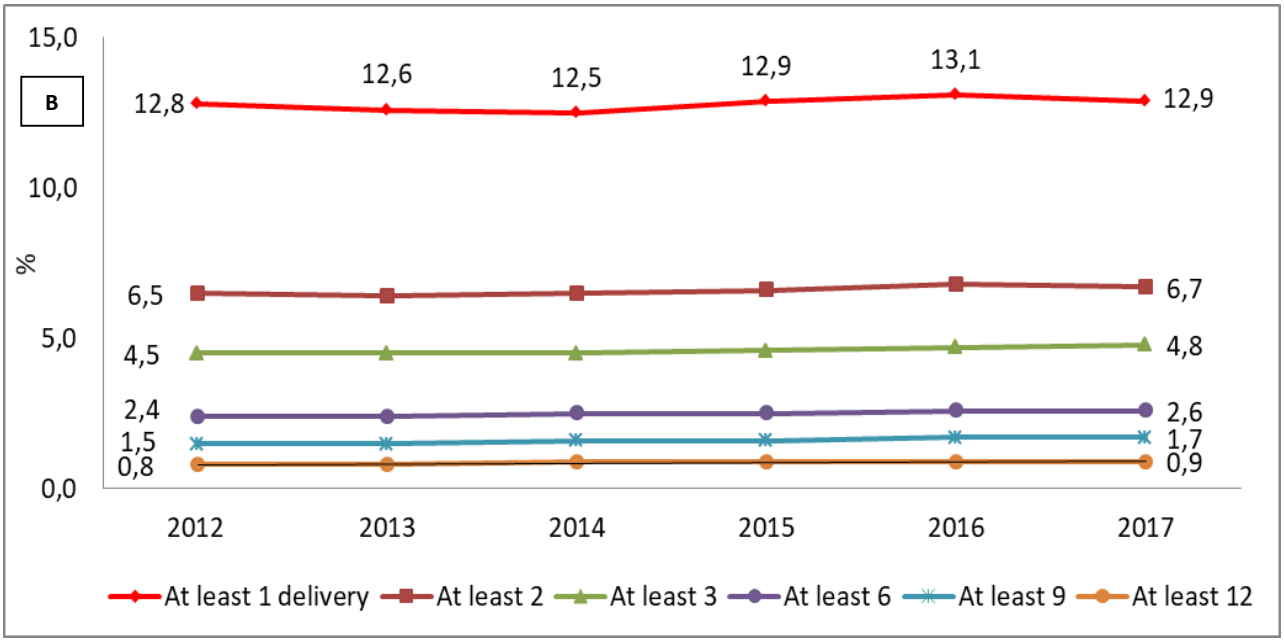
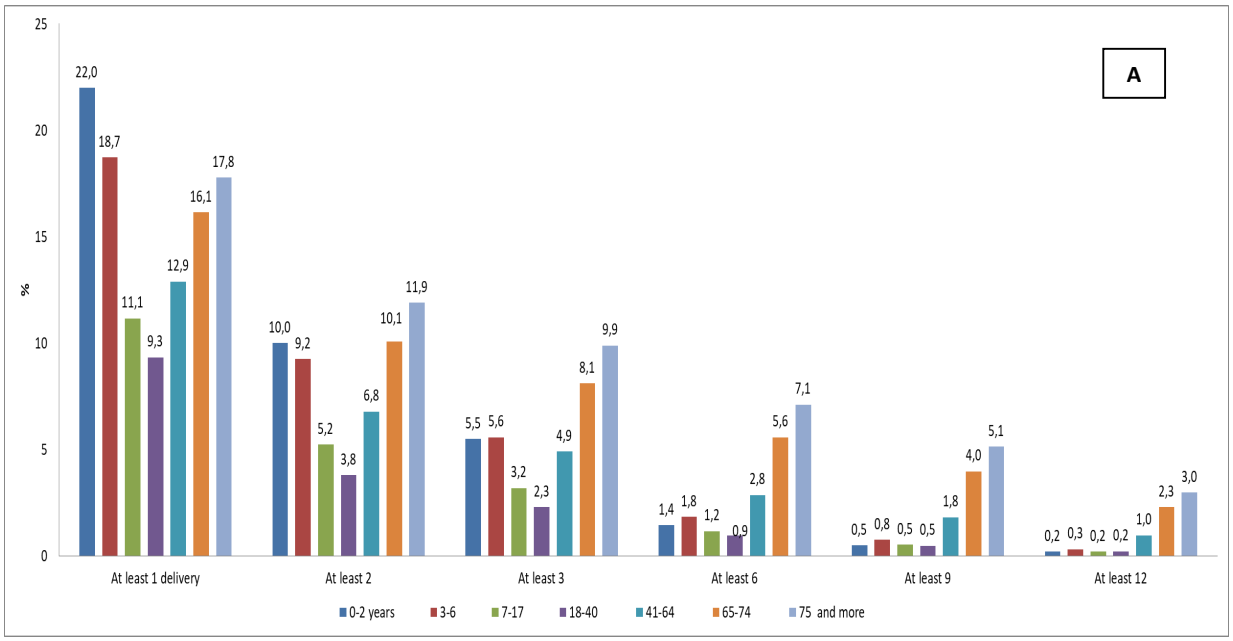
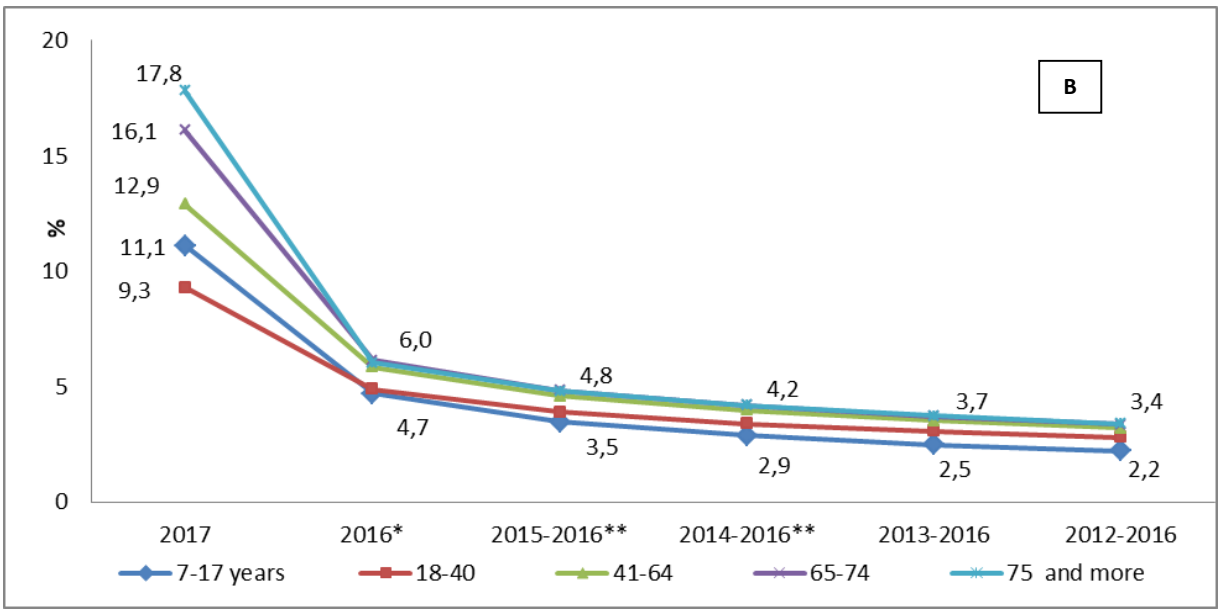


Fig. 2. Percentages of people according to their annual number of deliveries of ATC group R03 drugs in 2017, by age-group (A). Percentages of people with at least one dispensing in 2017 according to the duration of the previous period with no delivery, by age-group (B)





2017: people with a et least one delivery in 2017, 2016*:people with a et least one dispensing in 2017 but not in 2016, 2015-2016*** people with at least one dispensing in 2017 but not In 2016 and 2015…
Note: For the 18-40 year age-group, 11,1% had at least one dispensing in 2017, 4.9% had at least one dispensing in 2017 but not in 2016, 3.9% had at least one dispensing in 2017 but not in 2016-2015; 2.2% had at least one dispensing in 2017, but not in 2016-2012.
Children under the age of 7 years were not studied

Fig. 3. Among people with at least one dispensing of an ATC group R03 drug in 2012, evolution from 2012 to 2017 of the proportion of people according to the number of dispensing (A) and the drug classes dispensed (B)