Off-label drug use in neonates and infants in Spain: A five-year observational study

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Abstract

Objectives: To provide information about the off-label rate of all drug prescriptions in neonates and infants up to 1 year in Spain. Also, to analyse the off-label prescription of medicines under current practice in this age group according to different evidence sources.

Study design: A five-year (2015–2019) exploratory observational study about off-label prescription in neonates and infants (0 to 1 year) at primary health care in Spain. All drug prescriptions in this age group were analysed and classified according to their labelling in off-label or on-label. The drugs prescribed off-label were subsequently reviewed in national formularies and other databases to assess its evidence of use beyond what is recommended in the Summary of Product Characteristics (SmPC).

Results: On average 34.50% of total prescriptions were prescribed off-label according to the SmPC. 17.93% of total prescriptions in neonates and infants up to 1 year old were not based on clinical evidence from SmPC, Pediamécum, BNF or DailyMed. In more than 88% of cases, off-label use was related to the posology section of the SmPC, followed by the therapeutic indications and contraindications sections, in 35.20% and 24.10% of cases, respectively. Almost 13% of off-label drugs were over-the-counter. Salbutamol followed by topical tobramycin and colecalciferol were the drugs most prescribed off-label.

Conclusions: Off-label use of drugs remains as an important public health concern, especially for neonates and infants up to 1 year, who receive the greatest proportion of off-label prescriptions. The evidence-based off-label prescription is a widespread practice that has shown a stable trend during the 5-year study period providing also a certain extent of flexibility to paediatricians in some therapeutic decisions.

Keywords

drug prescription, infants, neonates, off-label use, outpatient, primary health care, Spain
Key Points

- Off-label use of medicines in Spain is an important public health concern, especially, for neonates and infants up to 1 year. Initiatives from Spain, position of the Spanish Paediatrics Association and initiatives from other EU member states aim to reduce paediatric off-label prescribing through availability of knowledge and enlarging clinical evidence.
- Off-label prescribing according to the SmPC remained high in the population under 1 year in primary care. Salbutamol, colecalciferol and tobramycin were most often prescribed off-label. Substantial part of the off-label prescriptions can be justified by clinical evidence beyond the SmPC. This situation raises a warning flag, but on the other hand it could provide flexibility to paediatricians in some therapeutic decisions.
- This novel study adds a 5-year overview about off-label prescriptions in neonates and infants up to 1 year and analyses the time trends in off-label prescribing, which has been missing in scientific literature from 2014 until now.
- Several reliable data sources were screened such as the British National Formulary, DailyMed and Pediamécum, to further classify off-label use depending on the clinical evidence/clinical justification available beyond of what is recommended in the SmPC.
- This is the first extensive study of an exploratory nature that has been carried out in Spain and Europe in primary health care.

1 | INTRODUCTION

There are several reasons why paediatric medicine development has been largely neglected for a long time (e.g., protection from clinical research for ethical reasons, economic considerations related to investigation, and complexity of age subgroups). Currently, there is a broad consensus that childhood deserve access to medicines that have been specially researched and developed for them.\textsuperscript{1–3}

Despite this, the development and testing of paediatric medicines has been far from satisfactory and the need for clinical trials has frequently been underscored,\textsuperscript{2,3} especially for neonates and infants, which are the most vulnerable age groups.\textsuperscript{1} Consequently, paediatricians must rely on their own experience and extrapolation to prescribe rather than on the results of robust clinical research.\textsuperscript{2} Moreover, medicines are often not available in a suitable pharmaceutical form and paediatricians must turn to medicines authorised for adults or children with different age ranges and adapt dosing and pharmaceutical form.\textsuperscript{4} This off-label use of medicines comes with the risk of ineffectiveness and adverse drug reactions (ADRs) in children.\textsuperscript{1,2,5}

Despite the attempt of international harmonisation in paediatric drug development and authorization, each regulatory body in the world has its own complex pathway, which is also subject to local regulation and subsequent barriers. This fact has often been controversial in many countries like the United States (US) or the European Union (EU), due to the increasing need of moving forward faster in paediatric drug regulation from the perspective of clinical practice and real-world evidence.\textsuperscript{6}

Very few studies, such as Suarez-Castañón et al.,\textsuperscript{7} have analysed the evidence of use for off-label medicines in primary health care setting. According to studies conducted in the EU member states, there is a large variation in off-label prevalence and no clear patterns were identified.\textsuperscript{1} A recent systematic literature review addressed unlicensed and off-label prescription of drugs to children in primary health care,\textsuperscript{8} which included six studies conducted between 2000 and 2016, indicated that the incidence of off-label use varied from 29.5% to 51.7% of total drugs prescribed (prospective analysis). The prevalence of off-label drugs ranged from 31.7% to 93.5% in relation to the total number of drugs prescribed (retrospective analysis). The studies included patients from Brazil, France, Malta, Scotland and The Netherlands.

A novel joint policy statement, recently published in Europe, aimed to fill the gap between medicines licensed for paediatric use (regulatory authorisation) and real-world evidence in neonates, infants, children, and adolescents. Its purpose is to offer guidance for health care professionals on when and how to prescribe off-label medicines to children and to provide recommendations for future European policy.\textsuperscript{9} Thus, the main objectives of this study were first to provide information about the off-label rate of all drug prescriptions in neonates and infants up to 1 year in Spain, and secondly to analyse the time trends in off-label medicines prescription under current practice in this age group according to different clinical evidence sources (national, UK, non-EU).

2 | METHODS

2.1 | Study design and setting

A 5-year (from 2015 to 2019) exploratory observational study about off-label prescription in neonates and infants (0–1 year) at primary health care in Spain.
The average births per year in Spain during the study period was close to 400,000. Neonates and infants up to 1 year accounted for 2% of the total population in the country.10

The primary health care workforce in Spain is organised around a multidisciplinary team, with a gatekeeping function which provides free access to prevention and promotion of health, acute and chronic care, home care and community care activities. The core of the team is made up of general practitioners (GPs), who are family and community medicine specialists, paediatricians, nurses, auxiliary nurses, social workers, dentists and administrative staff.

Paediatricians are responsible for the health of children below 15 years old, while patients over the age of 15 are seen by GPs.11

The latest available data (year 2018) indicate that 13,129 primary care centres were registered in Spain to serve 46.7 million people. 65,148 health care professionals were allocated (of which 6,506 were paediatricians). Data collection showed an annual average of 4.89 consultations to paediatricians per patient.12 The health care system in Spain follows a Beveridge model (National Health System), which is characterised by providing universal access to population. Other countries that share the same model are Denmark, Finland, Ireland, Italy, Latvia, Portugal, Sweden and United Kingdom (UK). In the EU countries, the predominant mode of provision in primary health care is private except in Greece, Finland, Latvia, Lithuania, Slovenia and Spain. The organisation in primary health care in Spain is based on groups of GPs and other health professionals, as in Finland, Greece, Ireland, Latvia, Lithuania, Poland, Portugal, Slovenia, Sweden, The Netherlands and UK.12

2.2 | Inclusion criteria

All prescriptions issued by paediatricians in neonates and infants (0–1 year) in primary health care (outpatients). Due to the high number of prescriptions (per year >5,000,000) expected for this age group according to preliminary results, it was decided not to broaden the paediatric population under study,13 such as infants and young children (1–4 years), children (5–11 years) and adolescents (12–15 years).14

2.3 | Exclusion criteria

All prescriptions issued for neonates and infants up to 1 year at hospitals (inpatients). Prescriptions from GPs, nurses and other professionals different from paediatricians in primary health care. Repeated prescriptions from specialists were excluded too.

2.4 | Data sources

Study data collection included the prescription records from a private database (complete national scope) sorted by months of age and drug (branded name, active substance, strength, package and dosage form). The database did not provide information about the type of prescription (paper format or electronic) and the number of patients (neither aggregated nor by age group). Since it was not linked to medical records, both first and repeated prescriptions were considered but undifferentiated.15

The Summary of Product Characteristics (SmPC), the legal document approved as part of the marketing authorisation of each medicine, was the primary source to determine off-label prescriptions.16 Additional data sources were used for further analysis: Pediámicum (a Spanish documentary database of active substances used in Paediatrics),17 British National Formulary (BNF),18 DailyMed19 and the Food and Drug Administration (FDA).20 These sources were visited at different points in time, accordingly to each year of study.

2.5 | Variables

Variables collected were quantitative: demographic (months of age; gender could not be derived from the dataset) and resource use (number of total prescriptions; number and percentage of off-label prescriptions and evidence-based; number and percentage of off-label over-the-counter (OTC) drugs prescribed), as well as qualitative: active substances and therapeutic groups (name and Anatomical Therapeutic Chemical Classification System (ATC) code21), dosage forms and sections of the SmPC where information about authorised age of use was identified (pharmacokinetic properties, special warnings, therapeutic indications, posology and method of administration, pharmaceutical form and/or contraindications).

A prescription is the form used to prescribe a medicine. According to the Spanish regulation, one single prescription could be used to prescribe several packages of the same medicine in specific situations (i.e., insulins and some systemic antibiotics).

The age grouping of study was neonates and infants up to 1 year.14 In addition, four subgroups of age were established (0–2 months, 3–5 months, 6–8 months and 9–11 months) to carry out a sub-analysis about general results on prescription rate according to months of age.

In the present study, off-label drugs were defined as those that were not authorised for this age group according to the information on the SmPC.16 Otherwise, they were on-label.

Off-label prescriptions were subsequently classified as evidence-based and clinically unjustified (not evidence-based), according to the additional data sources listed for data analysis. Sources like Pediámicum,17 BNF18 and DailyMed19 include updated evidence of real clinical practice and the FDA labelling20 may provide different information than the European or Spanish SmPC.16 In summary, these additional sources may include variations from the SmPC information depending on age. In case any of them pointed out information for use in less than one-year old children, the drug was therefore considered off-label on a regulatory basis but evidence-based according to current clinical practice.

The inclusion of the American source, DailyMed, was relevant since sometimes the same medicines have different indications depending on the geographical location and the medicines agency involved, thereby leaving the door open for off-label use in case of discrepancies between territories.
OTC drugs are usually aimed for mild symptoms and self-care. Although they are medicines dispensed directly to a consumer without the need of a prescription from a GP in Spain, they may appear in prescriptions as a reminder to the patient.

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### TABLE 1  Number of prescriptions issued, percentage of total by age group, average percentage per age year in each age group and breakdown by year

| Age groups and year | Number of prescriptions\(^a\) (% of total\(^b\)) | Average prescription rate per age year in each age group\(^c\) |
|---------------------|---------------------------------------------|---------------------------------------------------------------|
|                     | Year 2015       | Year 2016       | Year 2017       | Year 2018       | Year 2019       |
| 0-1 year old        | 5 577 211 (14.61%) | 5 792 875 (14.59%) | 5 270 709 (14.16%) | 5 151 094 (13.49%) | 5 147 123 (14.08%) |
| 1-4 years old       | 14 998 000 (39.28%) | 14 968 103 (37.68%) | 13 594 276 (36.53%) | 13 692 362 (35.85%) | 12 994 784 (35.54%) |
| 5-11 years old      | 13 867 090 (36.32%) | 14 721 271 (37.07%) | 13 875 323 (37.28%) | 14 435 131 (37.80%) | 13 756 368 (37.62%) |
| 12-15 years old     | 3 735 368 (9.79%) | 4 232 233 (10.66%) | 4 476 749 (12.03%) | 4 909 701 (12.86%) | 4 664 659 (12.76%) |
| Total               | 38 177 669       | 39 714 482       | 37 217 057       | 38 188 288       | 36 562 934       |

*Note:* The age groups were neonates and infants up to 1 year (0-1 year old), infants and young children (1-4 years), children (5-11 years) and adolescents (12-15 years). % of prescriptions per age year in each age group and year of study = [Number of prescriptions per age year and year of study/Number of total prescriptions in all paediatric population (0-15 years) by year of study] \(\times 100\). In case of the age group 0-1 year old, the % of prescriptions by age group and year of study and the average prescription rate per age year in each age group and year of study are the same.

\(^a\)Total number of prescriptions = Sum of prescriptions by age group and year of study.

\(^b\)% of prescriptions by age group and year of study = [Number of prescriptions by age group and year of study/Number of total prescriptions in all paediatric population (0-15 years) by year of study] \(\times 100\).

\(^c\)Average prescription rate per age year in each age group and year of study = Mean of % of prescriptions by age year and year of study.

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#### FIGURE 1  Average number of prescriptions issued for patients from 0 to 12 months of age in the 5-year study period.

Legend: The figure represents the average number of prescriptions in the 5-year study period by two-month age periods. The average rate of prescriptions over total are also disclosed. Average number of prescriptions by age group in the 5-year study period = Mean number of prescriptions by age group in the 5-year study period. % of prescriptions by age group in the 5-year study period = [Number of prescriptions by age group/ Number of total prescriptions in the 5-year study period in neonates and infants up to 1 year] \(\times 100\)

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### 2.6  Data analysis

Total number of prescriptions were studied according to labelling, evidence of use in real clinical practice and drug characterisation. A
A descriptive statistical analysis of the data was carried out. Quantitative variables were published as means and percentages. Percentages were also calculated for characterisation of drugs mostly prescribed off-label. Supplementary Table SS1 includes a structured definition of each outcome measure and the corresponding calculation methodology.

The assessment of off-label prescription justified by clinical practice or evidence-based off-label prescription was carried out by two researchers independently; conflicts were resolved through discussion and consensus or consultation with a third reviewer. The screening in the databases or formularies followed this funnel: SmPC (national source; Spain) > Pediamécum (national source; Spain) > BNF (European source; UK) > DailyMed (international, non-European source; USA). So that, if clinical justification for a certain off-label use was identified in Pediamécum or BNF, DailyMed was no longer consulted. BNF was revised to double-check the information obtained from Pediamécum or in case the information at Pediamécum was absent or incomplete. In case neither Pediamécum nor BNF incorporated clinical justification for a certain off-label use, DailyMed was then consulted. If none of the three sources contained results, off-label prescribing was assessed as clinically unjustified.

A statistical analysis comparing the number of prescriptions across neonates and infants was carried out by groups and subgroups of age. First, it was assessed whether each group and subgroup followed a normal distribution (Shapiro-Wilk test). If so, ANOVA and Tukey tests were performed to confirm statistical differences between subgroups ($p < 0.05$).

![Figure 2](image_url) Off-label and evidence-based off-label rate per year. Legend: The figure represents total off-label rate by year, which were further classified depending on whether off-label use was evidence-based or could be clinically justified any way. In this regard, evidence-based off-label prescriptions were divided depending on the source of evidence: Pediamécum and/or British National Formulary (European) and DailyMed (American). % of off-label prescriptions per year = [Number of off-label prescriptions by year of study/Number of total prescriptions by year of study] × 100. % of evidence-based-off-label prescriptions per year = [Sum of evidence-based-off-label prescriptions by year of study/Sum of off-label prescriptions by year of study] × 100. % of evidence-based-off-label (Pediamécum) prescriptions per year = [Sum of evidence-based-off-label (Pediamécum) prescriptions by year of study/Sum of off-label prescriptions by year of study] × 100. % of evidence-based-off-label (BNF) prescriptions per year = [Sum of evidence-based-off-label (BNF) prescriptions per year by study / Sum of off-label prescriptions by year of study] × 100. % of evidence-based-off-label (DailyMed) prescriptions per year = [Sum of evidence-based-off-label (DailyMed) prescriptions by year of study/Sum of off-label prescriptions by year of study] × 100. % of clinically unjustified off-label prescriptions per year = [Sum of clinically unjustified off-label prescriptions per year – [Sum of evidence-based-off-label prescriptions by year of study / Sum of off-label prescriptions by year of study] × 100. Average rate of evidence-based-off-label (Pediamécum) prescriptions in the 5-year study period = Mean of % of evidence-based-off-label prescriptions (Pediamécum) in the 5-year study period. Average rate of evidence-based-off-label (BNF) prescriptions in the 5-year study period = Mean of % of evidence-based-off-label prescriptions (BNF) in the 5-year study period. Average rate of evidence-based-off-label (DailyMed) prescriptions in the 5-year study period = Mean of % of evidence-based-off-label prescriptions (DailyMed) in the 5-year study period.
According to the preliminary analysis conducted by months of age during the first 2 years of the study (2015 and 2016), a single drug could be on-label for a specific month of age, but off-label for another; and in the same way, it could be an off-label prescription justified by clinical practice for a specific month of age, but not evidence-based for another.13

3 | RESULTS

3.1 | General results about total prescriptions

3.1.1 | Prescription rate according to age group

During the 5 years of study, the total number of prescriptions for neonates and infants up to 1 year were quantified and compared to total paediatric prescriptions in Spain (0–15 years) (Table 1). The proportion of prescriptions issued for neonates and infants up to 1 year was relatively high with a maximum rate in 2015, of 14.61% of total prescriptions in the whole study population (0–15 years). This percentage remained stable over the years.

If results were analysed per age year in each age group, the highest prescription rate would be observed among the 0-1 year old population, with 14.19% of the total number of prescriptions for this single year of age (as averaged over the 5 study years). In this regard, the average prescription rate per age year steadily declined in older age groups.

3.1.2 | Prescription rate according to months of age

The number of prescriptions issued in neonates and infants (0–1 year) split by months of age is shown in Figure 1. Note that neonates and infants up to 2 months accounted for an average of 34.15% of total prescriptions in the age group up to 1 year. The highest prescription rate was in the first months of age and progressively dropped as age increased, as shown in Figure 1.

The statistical analysis showed that subgroups followed normal distribution for the number of yearly prescriptions and that subsequent decreases in this number along the age subgroups were all statistically significant (p < 0.05) in the 5-year study period.
| ATC Code | Active substance | Number of off-label prescriptions$^a$ (% of total$^b$) | Year 2015 | Year 2016 | Year 2017 | Year 2018 | Year 2019 |
|----------|------------------|--------------------------------------------------|-----------|-----------|-----------|-----------|-----------|
| R03AC02R03CC02 | Salbutamol | 344 196 (6.17%) | 383 083 (6.61%) | 396 418 (7.52%) | 316 658 (6.15%) | 325 662 (6.33%) |
| S01AA12 | Tobramycin | 146 296 (2.62%) | 150 822 (2.60%) | 159 424 (3.02%) | 172 710 (3.35%) | 143 584 (2.79%) |
| J07CA09 | Diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B | 125 309 (2.25%) | 125 190 (2.16%) | 136 510 (2.59%) | 112 104 (2.18%) | – |
| C05AA01D07AA02D07AB02D07AC16S01BA02 | Hydrocortisone | 92 684 (1.66%) | 98 470 (1.70%) | 90 015 (1.71%) | 83 552 (1.62%) | 66 679 (1.30%) |
| R01BA53 | Phenylephrine, combinations | 88 561 (1.59%) | 126 061 (2.18%) | 67 425 (1.28%) | 94 931 (1.84%) | 55 004 (1.07%) |
| S01AA30 | Combinations of different antibiotics | 66 477 (1.19%) | 78 472 (1.35%) | 70 357 (1.33%) | 76 686 (1.49%) | 90 013 (1.75%) |
| A07CA91 | Oral rehydration salt formulations | 62 339 (1.12%) | 68 773 (1.19%) | 80 142 (1.52%) | 50 398 (0.98%) | 28 708 (0.56%) |
| R05DA09 | Dextromethorphan | 48 456 (0.87%) | – | – | – | – |
| R05CB03 | Carboxistine | 47 520 (0.85%) | – | – | – | – |
| D01AC52 | Miconazole, combinations | 42 637 (0.76%) | – | – | – | – |
| R01AD05R03BA02 | Budesonide | – | 67 267 (1.16%) | 60 489 (1.15%) | 52 266 (1.01%) | 66 217 (1.29%) |
| A01AB09D01AC02G01AF04 | Miconazole | – | 65 365 (1.13%) | – | – | 32 188 (0.63%) |
| D01AC01G01AF02 | Clotrimazole | – | 37 019 (0.64%) | 44 153 (0.84%) | – | – |
| A11CC05 | Colecalciferol | – | – | 242 386 (4.60%) | 209 445 (4.07%) | 156 353 (3.04%) |
| J07BC | Hepatitis vaccines | – | – | – | 52 369 (1.02%) | – |
| A02BC01 | Omeprazole | – | – | – | – | 34 499 (0.67%) |

Note: Active substances could be included under different ATC codes. For instance, hydrocortisone was classified with the following ATC codes: C05AA01, D07AA02, D07AB02, D07AC16 and S01BA02. Codes starting by C05A refer to haemorrhoids and anal fissures treatment (cardiovascular disorder), D07 are corticosteroids used in dermatological preparations and S01 are ophthalmological preparations. The complete ATC code refers to the specific hydrocortisone salt in the formulations (i.e., C05AA01, D07AA02 and S01BA02 – Hydrocortisone plain; D07AB02 – Hydrocortisone butyrate; D07AC16 – Hydrocortisone acetonate). Examples of combinations were the following: Phenylephrine, combinations (i.e., phenylephrine, chlorphenamine and diphenhydramine); combinations of different antibiotics (i.e., gramicidin, neomycin and polymyxin; trimethoprim and polymyxin b); miconazole, combinations (i.e., miconazole and hydrocortisone; miconazole, inosine and guanosine). Number of off-label prescriptions and % of total are only reported for the top 10 active substances.

$^a$Total number of off-label prescriptions by active substance in the 5-year study period = Sum of off-label prescriptions by active substance in the 5-year study period.

$^b$% of off-label prescriptions by active substance in the 5-year study period = [Sum of off-label prescriptions by active substance and year of study/Sum of off-label prescriptions per year of study] × 100.
3.2 Specific results about off-label prescriptions

3.2.1 Off-label prescriptions characterisation

During the 5 years of study, a total of 9,271,296 prescriptions were prescribed off-label according to the SmPC information for neonates and infants up to 1 year. The highest number of off-label prescriptions was recorded in 2017 (\(n = 2,117,090\)), whereas the lowest was in 2015 (\(n = 1,657,200\)).

On average, almost 13% of total off-label prescriptions per year were issued for OTC drugs. The total number of all off-label prescriptions for OTC drugs for neonates and infants up to 1 year in the 5-year study period was 1,188,444. The lowest rate of OTC off-label prescriptions was achieved in 2019 (11.40%; \(n = 196,392\)) and the highest in 2015 (14.63%; \(n = 242,402\)).

3.2.2 Off-label prescriptions and justification by clinical practice

The average off-label prescription rate over the 5-year period was 34.50% (Figure 2). The lowest rate was achieved in 2015 (29.71%) and the highest in 2017 (40.17%). There was at least clinical evidence from a national and/or European source for about half of the total off-label prescriptions.

The evidence-based off-label prescriptions according to the sources Pediamécum, BNF or DailyMed, must be added to the initial on-label ones, which were based on SmPC information (65.50%) and would account for 82.07% of total prescriptions in the 5-year follow-up. Thus, 17.93% of total prescriptions in neonates and children up to 1 year old were not based on clinical evidence from SmPC, Pediamécum, BNF or DailyMed and consequently their use appeared to be clinically unjustified.

Figure 2 shows the split of off-label and evidence-based off-label prescriptions for each year of study. Most evidence-based use was found in Pediamécum and/or BNF.

On the other hand, off-label drugs were also studied in detail according to the different months of age up to 1 year during 2015 and 2016 (Figure 3). The off-label prescription rate by months of age was higher than the average (31.43%) in the first 6 months of age (range: 33.80%–38.55%). In the same way, the evidence of use showed an opposite result. Again, focusing on the average trendline, it showed how evidence-based off-label rate was lower in the first 6 months of age than the average in the first year of life and increased in time (average: 51.57%; range: 40.60%–47.91%).

3.2.3 Sections of the SmPC related to off-label use

According to the SmPC, the section that mostly shown the off-label use of medicines in neonates and infants up to 1 year was the posology section, in more than 88% of off-label prescriptions. The two other sections were the therapeutic indications and the...
contraindications sections, with 35.20% and 24.10% of off-label prescriptions, respectively. Note that total sum may exceed 100% since off-label use could be defined in more than one SmPC section.

3.2.4 | Drugs and therapeutic groups most prescribed off-label

The top 10 drugs and therapeutic groups that were most prescribed off-label between 2015 and 2019 are included in Table 2 and Supplementary Table SS2. The leading group of medicines prescribed off-label was selective beta-2-adrenoreceptor agonists, being salbutamol the most prescribed active substance (>6% of annual off-label prescriptions), followed by topical tobramycin in years 2015–2016 (>2.50% of annual off-label prescriptions) and colecalciferol in years 2017–2019 (>3% of annual off-label prescriptions), respectively (Table 2).

A deeper analysis into all salbutamol prescriptions that were off-label according to the SmPC, showed that almost 100% of off-label prescriptions were evidence-based (Pediamécum and/or BNF) during the years 2015, 2016 and 2019 (98.7%, 99.2% and 100%, respectively). Evidence-based prescriptions were aerosols and suspensions/solutions for inhalation. Conversely, not evidence-based prescriptions were oral dosage forms like syrups.

In relation to tobramycin, the pattern was completely different. All off-label prescriptions, which were ophthalmological (e.g., drops, ointment), were off-label according to the SmPC and not evidence-based according to current clinical practice (Pediamécum, BNF and DailyMed).

For hydrocortisone, phenylephrine combinations and oral rehydration salt formulations an overall decline in the number of off-label prescriptions was observed between 2015 and 2019, while for combinations of different antibiotics an overall incline was observed (not statistically tested).

The therapeutic groups that were mostly prescribed off-label accounted for more than 23% of total off-label prescriptions per study year (Supplementary Table SS2). Dermatological corticosteroids and antifungals, ophthalmological anti-infectives and dosage forms for respiratory diseases all showed a high rate of off-label prescriptions.

In addition, the annual average number of prescriptions according to administration route are shown in Figure 4. Almost 85% of clinically unjustified off-label prescriptions were liquid dosage forms (i.e., solutions, suspensions and syrups). Semisolids such as ointments and several solid forms (i.e., capsules and tablets) accounted for less than 5% each.

4 | DISCUSSION

4.1 | General results about total prescriptions

4.1.1 | Prescription rate according to age group

According to the results obtained in this study, the age group with highest prescription rate was neonates and infants (0–1 year old).

Likewise, Tomlin et al.22 explored the prescription trends in outpatients under 18 years of age in New Zealand. They conducted a 6-year retrospective study (2010–2015) and analysed all subsidised medicines dispensed in community pharmacies. They concluded that the highest prevalence of drug use was in children aged <2 years (i.e., the proportion of children aged <2 years using any medicine in 2015 was 90%). Hales et al.23 also evaluated trends in use of prescription medications among US children and adolescents between 1999 and 2014 by means of a national survey. They concluded that 17.4% of children under 2 years of age had taken any prescription medicine within the last 30 days.

4.1.2 | Prescription rate according to months of age

Prescription rate was higher in the first 6 months of life than in the following, and specifically in the subgroup up to 2 months (on average 34.15% of all prescriptions in the first year of life). This may be due to maturational changes in neonates, which are normally observed throughout childhood but are even more prominent during the first year of life and especially in the first month. In addition to pharmacokinetics and pharmacodynamics of drugs, there may also be neonate-specific diseases which require pharmacological treatment and specific investment in research, as the EU Paediatric Regulation encourages.24 By contrast, in case of common conditions, safety and dosing studies should be promoted for those drugs that despite being addressed to adults, they are already being frequently used off-label in paediatric patients (i.e., salbutamol, colecalciferol and tobramycin). In this regard, sub-analysis by age groups would be also a must.

4.2 | Specific results about off-label prescriptions

4.2.1 | Off-label prescriptions characterisation

Different studies conducted have shown that neonates and infants receive the greatest proportion of off-label drugs, meaning that they have the highest exposure to drugs that are insufficiently documented with regards to efficacy, safety and dosage, even at hospital setting.25 Therefore, this group of age seems to be particularly vulnerable.

Many off-label drug studies concluded their results by determining the prevalence of off-label use and drug characterisation in childhood.26,27 However, studies in neonates and infants were mostly developed at hospital setting (e.g., intensive care units), so comparisons with our novel study become complex since the most relevant medicines described differ from those mostly used in community practice.25

The recent systematic literature review from Almeida Andrade et al.8 pointed out that the highest proportion of unlicensed prescription was related to children under 2 years of age. Another systematic literature review (2018) on off-label medication use in children28 identified 31 studies, with off-label prescription rates from 3.2% to 95%. Only 7 studies were specifically in the neonate population, with off-
label drug use ranging from 26% to 95%. In the US, Yackey et al.27 carried out a retrospective cohort study using a paediatric database that included data for inpatient, ambulatory surgery, emergency department, and observation unit. The authors pointed out that prescriptions to neonates <28 days of age were off-label 51% of the time (95% CI: 50.6%–51.3%). In case of infants 29 days to 1 year old received off-label prescriptions at a rate of 44.8% (95% CI: 44.7%–44.9%).

The present study showed that 34.50% of all prescriptions issued to patients under 1 year old were off-label according to the SmPC. Results found from Spanish hospital studies were higher. Regrettfully, the figures could not be compared to the present study, as disaggregated results for each age group were not disclosed and the setting was different from primary health care. The study conducted by Morales Carpi et al.29 in 2010 described a rate of 51% of off-label prescriptions at emergency room. Other Spanish hospitals, San Cecilio Hospital30 and Gregorio Marañón Hospital31 published 52% and 53.9% rates of off-label prescriptions in 2016, respectively. In these two studies, however, age was not the unique reason for considering off-label use, as it was rather the combination of different items (e.g., therapeutic indication, strength, route of administration and contraindications). In contrast, in the current study the off-label use concerns were most often related to the posology section.

As far as the authors know, the current study is the only one that has evaluated use of OTC drugs in very young children in primary care. The authors found that on average, almost 13% of total off-label prescriptions were issued for OTC drugs. However, the % of off-label OTC use could be even higher, as these drugs do not require prescription to be dispensed and the risk of self-medication should not be neglected. Few studies reported that children in general receive substantial amounts of OTC drugs including natural remedies, which are often regarded as harmless agents. A Swedish review25 estimated that children were likely to receive at least one OTC drug during any given 3-month period and that the evidence related to paediatric use was non-existent. However, those results are only indicative and could not be compared to the present study, as it did not include population under 11 years of age.

According to the results of the 2012–2013 paediatric national survey on off-label drug use in children in Spain (OL-PED), which was endorsed by the Spanish Paediatric Association (AEP) in 2014,32 a significant percentage of paediatricians prescribed medications in their daily clinical practice without knowing whether the drug was indicated in children or at certain age groups. Six hundred and seventy three responses were received, most of them (75%) knew the meaning of off-label use, 61% of them prescribed off-label medicines and just a small percentage of them (22%) wrote it down in the patient medical record as recommended by the Spanish legislation. Although this survey was carried out after the latest paediatric regulation came into force in the EU (2007), authors indicated the need to adopt measures that raised awareness about the use of off-label prescription (e.g., by spontaneous notifications). To our knowledge, no further follow-up has been published on this survey. A second national survey on off-label drug use in children in Spain may be suggested to find out why off-label use remains high despite national and EU initiatives to reduce it through availability of knowledge and enlarging clinical evidence. It may also be relevant to evaluate in a future study whether and which measures to reduce off-label use in children have actually been implemented in Spain in the last years.

4.2.2 | Off-label prescriptions and justification by clinical practice

In this study, the prescriptions that were off-label in the SmPC were analysed twice in order to assess the evidence of use in daily practice according to several international databases.

By contrast, hospital resources usually allow more specific research because electronic health records are available, not being so in Spanish community pharmacies. Besides, electronic health records provide extra information about if off-label use is justified by clinical practice or not.25

Almost 18% of all prescriptions (as determined on SmPC, Pediamécum, BNF or DailyMed) seemed to have the potential to reduce efficacy and put at risk the very young patients included in the study, as they were not clinically justified. Additional data analysis may provide more insight on which medicines were involved in clinically unjustified prescribing. Although harmonisation is a global goal among regulatory agencies, there seemed to be quite differences between the drug information sources consulted.2,3,6 High-level evidence in paediatrics is therefore difficult to reach, even for those treatments that might be effective. As the information found in other sources were different from the SmPC, and considering that, they complemented each other, therefore, it would be strongly recommended that all databases are modified or updated periodically according to the most recent scientific evidence available. This would help to cover the therapeutic needs in vulnerable age groups as neonates and infants, that is still inferior to the adult population.1,33

4.2.3 | Sections of the SmPC related to off-label use

Most off-label prescriptions were found in the posology section. This may be since this section includes many different statements such as ‘the safety and efficacy in paediatric patients have not been established’ and ‘not appropriate or not recommended in patients aged…’.

The low result seen of off-label information in the contraindications section (24.10%) would demonstrate that there has been substantial under-reporting of ADRs in general, when ADR reporting in paediatric population should be a priority. Few studies, though, have analysed the potential association between the off-label use of drugs and the risk of ADRs.32,34,35

4.2.4 | Drugs and therapeutic groups most prescribed off-label

The off-label use of medicines remains an important concern in primary health care for the paediatric population, especially for neonates
and infants up to 1 year who receive the greatest proportion of off-label drugs.

Drugs of most interest in this study (e.g., salbutamol, colcalciferol or tobramycin) have been in the market for decades, which excludes them from being in the primary scope of the latest Paediatric Regulation (1901/2006/EC)\(^3\) in Europe, which is more focused on new product development and authorization.

In recent years, different positions have emerged within the paediatric community on the need for vitamin D supplementation. In 2017, a statement from the European Academy of Paediatrics (EAP)\(^3\) was published in relation to vitamin D supplementation. This document pointed out that all infants up to 1 year of age should receive an oral supplementation of 400 IU/day. It is very likely that this publication triggered the increase of calciferol use, although the data sources consulted did not include it as evidence-based when consulted.

With regards to the decline in the off-label prescription of hydrocortisone, the withdrawal from the market of some products during the last years of study (e.g., some rectal and topical hydrocortisone presentations), could have shifted the use to other corticosteroids, causing a decrease in off-label prescriptions that regretfully is not based on a clinical but commercial justification. In case of phenylephrine combinations, the justification of the off-label prescription decrease could also be explained by the local scenario. This active substance is represented by a unique presentation (a syrup) in the Spanish market, which needs prescription but is not reimbursed and has been gradually increasing its price in the last years.\(^3\) This situation, added to several supply failures that have been identified during the 5-year study period, could have led to a shift in the prescription pattern.

Typical therapeutic areas of off-label use in neonates, derived from the EU study in 2017, included infectious diseases, cardiology, dermatology, pain treatment, alimentary tract and metabolism, respiratory system and central nervous system. Most studies described were carried out at hospital setting (inpatients).\(^1\) Paediatric investigation is currently expanding through therapeutic areas and mostly at specialty health care, with infectious diseases (12%), oncology (10%) and endocrinology/metabolic diseases (9%) at the forefront.\(^3\) However, the diseases with highest number of completed paediatric investigation plans could not be correlated to the real burden of disease in this population group and on the contrary be subrogated to the developing clinical trials in adults.\(^3\)

In case of infants, evidence in primary health care (outpatients) was wider, although disaggregated results by year of age were scarce.\(^1\) For instance, the review carried out by Kimland et al.\(^3\) pointed out that the highest proportion of off-label drug use in children was among topically administered drugs and eye drops, although no further details about younger age groups were disclosed.

A recent publication from our investigation group\(^4\) did not find a decrease of the annual off-label prescription rate in the primary health care setting of the Spanish paediatric population, even though the latest Paediatric Regulation (1901/2006/EC)\(^3\) publication, and more than 10 years after its adoption. In general, prescription of innovations for outpatients in primary health care setting in Spain is scarce, which is usually due to highest prices than the standard of care and uncertainty about effectiveness in the short term. This scenario leads to using medicines with broad experience in the market despite not being authorised for paediatric population in the SmPC, which may pose a safety risk for the most vulnerable paediatric population groups, like neonates and infants (<1 year old).

In addition to the specific regulation that encourages paediatric drug development, big data (i.e., patient registries, real-world data and digital health) will bring an expanded knowledge about paediatric medication use, which will definitely help improving the safety of this population group.\(^4\)

### 5 | LIMITATIONS OF THE STUDY

This study has some limitations that could lead to underestimation of off-label use. In addition, there is an imbalance in the evidence available of off-label use between hospital and primary health care setting in Spain. Thus, the results of most studies found in the literature could not be compared to those presented in this study.

First, this study was focused on the off-label use of authorised medicines and did not include medical devices, compounded formulas, cosmetics, food supplements and medicinal plants. Second, only prescriptions issued by paediatricians at primary health care were considered. This situation could be underestimating the potential total number of off-label prescriptions in the study population, as repeated prescriptions from other medical specialties (i.e., hospital) were not accounted. Third, non-prescription medicines were not accounted (i.e., self-medication and many OTC drugs), although 13% of drugs prescribed off-label were identified as OTC. Fourth, as the data analysed was not linked to medical records, it was not possible to assess if the off-label use was justified by evidence-based information provided by the GPs. Finally, results show potential off-label use from prescriptions, as dispensation data was not provided by the database used.

### 6 | CONCLUSION

The off-label use of drugs remains an important public health concern for the paediatric population, especially for neonates and infants up to 1 year, who receive the greatest proportion of off-label drugs as demonstrated in this study. Therefore, to achieve the ideal therapeutic practice, more new labelling information must be added, as practitioners still rely on the evidence-in-use when off-label drugs are required for their patients. Nonetheless, substantial part of all off-label prescriptions is clinically justified by clinical evidence sources beyond the SmPC.

To sum up, even though expectations for the future are focused in adding more and more clinical trials for new medicines on the market, there is also a need to add more research and more safety information on some older drugs, which are commonly used in paediatric...
patients. As disclosed in this study, these activities would be needed primarily for dermatological corticosteroids and antifungals, ophthalmological anti-infectives and dosage forms for respiratory diseases, which show a high rate of off-label prescriptions.

CONFLICT OF INTEREST
The authors have no conflicts of interest relevant to this article to disclose.

ETHICS STATEMENT
According to Spanish legislation the study is exempt from human research review boards as it is related to prescriptions records from a private database and not linked to medical records.

FINANCIAL DISCLOSURE
The authors have no financial relationships relevant to this article to disclose.

AUTHOR’S CONTRIBUTION
Dr Lizano-Díez designed the study and data collection instruments, carried out the initial analyses and drafted the initial manuscript. Mr Kargodorian designed the data collection instruments, collected data, carried out the initial analyses and drafted the initial manuscript. Dr Piñero-López and Dr Lastra collected data, carried out the initial analyses and reviewed and revised the manuscript. Dr Mariño coordinated and supervised methodology and investigation and critically reviewed the manuscript for important intellectual content. Dr Modamio conceptualised and designed the study, supervised methodology and investigation, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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