





# Off-label use of drugs by age in Brazilian children: a population study

## *Uso off-label de medicamentos segundo a idade em crianças brasileiras: um estudo populacional*

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**ABSTRACT:** *Objective:* To estimate the prevalence of off-label drug use by age in children 12 years old and younger in Brazil. *Method:* Population-based cross-sectional study (National Survey on Access, Use and Promotion of Rational Use of Medicines - PNAUM), including 7,528 children aged 12 years or younger. Face-to-face interviews were used to collect the data in the domiciles. The age-related off-label classification was carried out using the electronic medication compendium of National Agency of Sanitary Surveillance (ANVISA). Sociodemographic characteristics, presence of chronic disease, use of health services and characteristics of the informant were collected. Data were expressed by relative frequencies and 95% confidence intervals. Pearson's chi-square test was used to evaluate the statistical significance of the differences between the groups, with a significance level of 5%. Main outcome measure was the prevalence of off-label use. *Results:* The prevalence of off-label use by age was 18.7% (95%CI 16.4 – 21.3). Children younger than 2 years old presented the highest prevalence of off-label use. The most frequently used off-label drugs by age were amoxicillin, nimesulide and the combination of phenylephrine and brompheniramine. *Conclusion:* The off-label use of drugs by age is common in the Brazilian pediatric population, especially among children under two years old.

**Keywords:** Off-label use. Preschool child. Children. Pharmacoepidemiology. Drug utilization. Health surveys.

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**RESUMO:** *Objetivo:* Estimar a prevalência de uso *off-label* de medicamentos segundo a idade em crianças de 0 a 12 anos no Brasil. *Métodos:* Estudo transversal de base populacional (Pesquisa Nacional sobre Acesso, Utilização e Promoção do Uso Racional de Medicamentos — PNAUM), incluindo 7.528 crianças de 0 a 12 anos de idade. Entrevistas individuais face a face foram utilizadas para coletar os dados nos domicílios. A classificação *off-label* segundo a idade foi realizada por meio de consulta ao compêndio eletrônico da Agência Nacional de Vigilância Sanitária (ANVISA). Características sociodemográficas, presença de doença crônica, uso de serviços de saúde e características do informante foram coletadas. Os dados foram expressos por frequências relativas e intervalos de confiança de 95% (IC95%). O teste do  $\chi^2$  de Pearson foi usado para avaliar a significância estatística das diferenças entre os grupos, com um nível de significância de 5%. A principal medida de desfecho foi a prevalência de uso *off-label* segundo a idade. *Resultados:* A prevalência de uso *off-label* por idade foi de 18,7% (IC95% 16,4–21,3). Crianças com menos de 2 anos apresentaram maior prevalência desse uso em relação às mais velhas. Os medicamentos com maior frequência de uso *off-label* segundo a idade foram amoxicilina, nimesulida e a combinação de fenilefrina com bronfeniramina. *Conclusão:* O uso *off-label* de medicamentos segundo a idade é comum na população pediátrica brasileira, especialmente nas crianças menores de 2 anos de idade.

**Palavras-chave:** Uso *off-label*. Pré-escolar. Criança. Farmacoepidemiologia. Uso de medicamentos. Inquéritos epidemiológicos.

## INTRODUCTION

Off-label drug use is characterized by the use of a medication in a way that is different than what is recommended by the country's regulatory agency with respect to age, dose, indication or route of administration<sup>1</sup>. The lack of specific formulations and pharmaceutical instructions, and even the lack of evidence on efficacy and safety in children has motivated this kind of practice in pediatric medicine<sup>2,3</sup>. The use of off-label and unlicensed drugs is a widespread, growing, and international practice<sup>4</sup> that causes concern for health professionals and patients because of its lack of safety<sup>5</sup>, exposing children to risks that are potentially unnecessary<sup>2,6</sup>.

Studies dealing with children's off-label use of medications have been mostly carried out in health services and point to prevalences ranging from 37.6 to 99.5%.<sup>5,7-9</sup>. The lowest prevalence was observed in a study with outpatients in 2011<sup>5</sup>, and the highest, in a neonatal ICU<sup>9</sup>.

According to Chalumeau et al.<sup>10</sup>, the use of off-label drugs also occurs significantly outside the hospital and in outpatient settings, since a large part of pediatric practice occurs in doctors' offices. However, there is little data with population-based samples. In the United States, the prevalence of off-label prescriptions by age and indication was 62% for individuals from 0 to 17 years old, according to a study carried out between 2001 and 2004 with 7,901 children who had been seen in medical offices<sup>11</sup>. In another study, with prescription data recorded in the Dutch pharmacy database during 2000, 22.7% of the drugs prescribed for children aged 0 to 16 years were classified as off-label<sup>12</sup>.

Studies including off-label use of prescription and non-prescription drugs are even rarer<sup>13</sup>. In Germany, from 2003 to 2006, a study with 17,641 children aged 0 to 17 years old, living in 167 municipalities, estimated a prevalence of off-label drug use of 40.2% for children and adolescents. The percentage of off-label, over-the-counter medication usage was around 30%. The most frequent reasons for classifying the use as off-label were underdose, overdose, indication and age<sup>13</sup>.

Considering the scarcity of population-based studies and the fact that medication use in situations where supervision by a health professional does not happen to the same extent that it occurs in the hospital environment, and thus increasing the risks associated with off-label drug use, this study aims to provide an unprecedented contribution by identifying and characterizing this use according to age in Brazilian households. The aim of the present study was to estimate the prevalence of this type medication use according to age in children aged 0 to 12 years old in Brazil.

## METHODS

The National Survey on Access, Use and Promotion of Rational Use of Medicines (*Pesquisa Nacional sobre Acesso, Utilização e Promoção do Uso Racional de Medicamentos - PNAUM*) was a cross-sectional population-based study carried out between September 2013 and February 2014. The study population was composed of individuals living in permanent, private households in urban areas in the five Brazilian regions. Methodological details of the survey, including sample design and questionnaires, can be found in another publication<sup>14</sup>. In summary, it was a survey conducted through face-to-face interviews, with a probabilistic sample that had three stages. The first corresponded to the municipalities, the second, to the census sectors defined by the 2010 Brazilian Census, and the third, to the households. The selection of individuals within the dwellings was based on the expected proportion of each age and sex to compose the final sample.

The data used in the present analysis refer to the population of individuals aged 0 to 12 years old. Information on the drugs used by the children was obtained through their guardian, who was present at the time of the interview. Specific questionnaires were used to investigate the use of medications for acute or chronic health conditions. The interviewer requested the prescription and/or packaging of the medication taken. This strategy allowed for the name to be registered without classification errors. If these sources were missing, the names declared by the respondent were registered.

Questions about chronic drug use included medication used to treat diabetes, chronic lung disease, or other illness that lasted more than six months. Medications used to treat acute conditions were investigated through the following question: "In the past 15 days, has the 'child's name' used any medication for 'infection', 'stomach or bowel disease', 'fever', 'pain', 'flu or cold', 'diarrhea', 'nausea and/or vomiting'?" Whether or not vitamins had been taken was asked with the following question: "In the past 15 days, has the 'child's name'

taken any vitamin, mineral supplement, appetite stimulant or tonic?” Additionally, the interviewee was asked the following question: “In the past 15 days, has the ‘child’s name’ taken any other medication that has not yet been mentioned?”

The drugs reported by the interviewees were identified in drug lists from the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária* - ANVISA) and classified by the drugs present in their composition. Phytotherapies and other products that were used for therapeutic purposes, and were not on the list of medicines registered with ANVISA (plants or teas, homeopathic products, handicraft products, food supplements, cosmetics and vitamin supplements) were excluded from the analyses.

In this study, the use of off-label medication according to age was considered when the instructions on the package insert were incompatible with the age of the child interviewed.

The classification of each medication according to off-label use by age was performed according to the age or age group written on the package insert, by consulting the *Bulário Eletrônico* database<sup>15</sup>, which makes the leaflets approved by ANVISA available for online consultation. When it was not possible to find the package leaflet of the medication in the *Bulário Eletrônico*, the data available on the website of the manufacturer were used.

The main outcome analyzed was the use off-label according to age classified, according to ANVISA, in: “yes”, when the child used at least one medication considered to be off-label according to age; “No”, when the child did not consume any medication qualified as off-label use according to age; and “unclassified”, when there was no data on the medication (such as concentration or form of presentation) and/or on the individual (such as body weight) that could be classified as off-label.

The analyzes for independent variables were: sex (male/female), age (less than 1 year old, 1 to under 2 years old, 2 to under 5 years old and 5 to 12 years old), presence of chronic disease (yes/no), emergency consultations in the last year (none, one, two or more), hospitalizations in the last year (none, one, two or more), degree of kinship of the informant (father/mother, other), education of the informant (0 to 8 years of study, 9 to 11 years of study, 12 or more years of study) and economic classification (A/B, C, D/E). The latter considered the conditions of the home, the number of goods purchased and the education of the person responsible for the home, according to the Brazilian Economic Classification Criterion (*Critério de Classificação Econômica Brasileiro* - CCEB) of the Brazilian Association of Research Companies (*Associação Brasileira de Empresas de Pesquisa* - ABEP) (<http://www.abep.org/>). Classes A1, A2, B1 and B2 represent high income; C1 and C2 represent average income; and D and E represent low income.

Descriptive and bivariate analyzes were performed, and the main variables were expressed by relative frequencies and respective 95% confidence intervals (95%CI). Pearson’s  $\chi^2$  test was used to assess the statistical significance of the differences between the groups, considering a significance level of 5%. All analyzes were performed using the Statistical Package for the Social Sciences (SPSS) 18.0, and utilized the appropriate set of commands for analyzing complex samples and ensuring the necessary weighting, according to the sample design.

The project (PNAUM) was approved by the National Health Council (*Conselho Nacional de Saúde* - CONEP), report 398,131, September 16, 2013. The guardians of the children were interviewed only after giving their permission, by signing an informed consent form.

## RESULTS

Of the total number of PNAUM participants ( $n = 41,433$ ), 7,528 were individuals aged 12 years old or younger. Of these, 28.9% (95%CI 26.7 - 31.2) took at least 1 medication, making a total of 4,633 medications. Table 1 shows the characteristics of the children who participated in the research and the prevalence of those who took at least one medication. The prevalence of medication use was higher for children with a chronic disease, for those under two years old, for those who consulted emergency services two or more times, and for those who were hospitalized two or more times in the previous year.

Table 2 shows the total prevalence of off-label medicine use according to age and according to the characteristics of the children. The predominance of off-label medication use according to age was 18.7% (95%CI 16.4 - 21.3) among children who took medication. The prevalence of off-label medication use according to age was higher in children under 2 years old. No significant differences were identified in the predominance of off-label medication use according to age with regard to the other variables analyzed.

Of the total number of drugs (4,633), 13.4% were used off-label according to age. When evaluated by age group, the percentages found were: 17.8% in children under one year old; 23.1% in 1 to 2 years; 8.8% in 2 to 5 years; and 15.2% in 5 to 12 years.

Of the total number of drugs classified as off-label according to age, 8.6% were amoxicillin, 6.6% were nimesulide, and 3.6% were the combination of bronfeniramina + phenylephrine. Among children under one year old, amoxicillin was the medication with the highest frequency of off-label use according to age (23.6%), followed by the combination of bronpheniramine + phenylephrine (10.3%). In those aged 1 to 2 years old, amoxicillin was also the most frequent medication (32.7%), followed by the combinations of cyproheptadine + ascorbic acid + propylene glycol + thiamine + pyridoxin a + riboflavin nicotinamide (7.9%). In those aged 2 to 5 years old, budesonide and nimesulide were the most frequent (10.4% each). Finally, in children aged 5 to 12 years old, paracetamol was the most frequent (7.0%), followed by ibuprofen (6.9%).

## DISCUSSION

Several studies address the use of off-label medications, mainly in neonates and hospitalized children<sup>16-18</sup>. They represent a relatively small number of the pediatric population when compared to those who access the health system at all different levels of care<sup>19</sup>. A smaller number of studies used prescription data from administrative databases or research

Table 1. Characteristics of children participating in the National Survey on Access, Use and Promotion of Rational Use of Medicines (*Pesquisa Nacional sobre Acesso, Utilização e Promoção do Uso Racional de Medicamentos - PNAUM*) and the prevalence of children using at least one medication (n = 7,528), 2013-2014.

Characteristics		Children participating in PNAUM (%) (95% CI)	Prevalence of children taking 1 medication (%) (95% CI)	p*
TOTAL		100	28.9 (26.7 – 31.2)	
Sex	Male	49.7 (47.4 – 51.9)	30.3 (27.1 – 33.6)	0.201
	Female	50.3 (48.1 – 52.6)	27.6 (24.8 – 30.5)	
Age	< 1 Year	6.7 (6.2 – 7.3)	48.0 (43.7 – 52.4)	0.000
	1 to < 2 years	6.8 (6.2 – 7.5)	42.5 (38.5 – 46.7)	
	2 to < 5 years	26.9 (25.2 – 28.6)	35.1 (32.4 – 37.9)	
	5 to 12 years	59.6 (57.3 – 61.8)	22.4 (19.6 – 25.5)	
Economic classification (ABEP)	AB	16.8 (14.6 – 19.2)	25.5 (21.6 – 29.8)	0.212
	C	56.2 (53.4 – 58.9)	29.8 (27.1 – 32.6)	
	D/E	27.0 (24.2 – 30.0)	29.1 (25.6 – 33.0)	
Chronic disease	Yes	9.9 (8.6 – 11.3)	72.1 (65.1 – 78.1)	0.000
	No	90.1 (88.7 – 91.4)	24.2 (22.1 – 26.5)	
Emergency consultations**	None	84.1 (81.9 – 86.0)	23.3 (21.3 – 25.5)	0.000
	One	9.5 (8.2 – 11.1)	47.1 (40.3 – 54.0)	
	Two or more	6.4 (5.4 – 7.6)	73.9 (68.6 – 78.7)	
Hospitalizations**	None	95.1 (94.1 – 95.9)	27.3 (25.1 – 29.6)	0.000
	One	4.0 (3.3 – 5.0)	57.5 (48.5 – 66.1)	
	Two or more	0.9 (0.6 – 1.2)	84.1 (73.2 – 91.1)	
Child's informant	Mother/Father	84.7 (82.4-86.7)	30.4 (28.1 – 32.9)	0.000
	Other***	15.3 (13.3 – 17.6)	20.7 (16.6 – 25.4)	
Informant's level of education (years)	0 to 8	48.8 (44.7 – 52.9)	25.7 (23.1 – 28.5)	0.006
	9 to 11	41.6 (37.8 – 45.5)	32.0 (28.1 – 36.2)	
	12 or more	9.6 (8.1 – 11.4)	34.2 (27.8 – 41.1)	

95%CI: 95% confidence index; ABEP: Brazilian Association of Research Companies (*Associação Brasileira de Empresas de Pesquisa*); \*Pearson's  $\chi^2$  test; \*\*referring to the 12 months prior to the interview; \*\*\*grandfather/grandmother, uncle/aunt, brother/sister, nephew/niece, another family member.

in medical offices<sup>7,10,19-21</sup>. Less frequent still are studies that have assessed use from population-based samples, including both prescription drugs and self-medication drugs<sup>5,11,13</sup>. After an extensive review of the literature, not a single study was found in which the use of

Table 2. The off-label use of medications according to age in children participating in the National Survey on Access, Use and Promotion of Rational Use of Medicines (PNAUM) who took at least one medication, 2013–2014.

Characteristics		Prevalence of children taking $\geq 1$ off-label medication (%) (95% CI)	p*
TOTAL		18.7 (16.4 - 21.3)	
Sex	Male	19.4 (16.1 - 23.1)	0.586
	Female	18.1 (15.0 - 21.6)	
Age	< 1 Year	29.3 (24.5 - 34.7)	0.000
	1 to < 2 years	31.0 (26.2 - 36.3)	
	2 to < 5 years	13.2 (10.5 - 16.4)	
	5 to 12 years	17.5 (13.4 - 22.5)	
Economic classification (ABEP)	AB	20.4 (14.2 - 28.4)	0.837
	C	18.7 (15.7 - 22.2)	
	D/E	18.1 (14.3 - 22.5)	
Chronic disease	Yes	19.7 (15.1 - 25.2)	0.677
	No	18.4 (15.8 - 21.4)	
Emergency consultations**	None	18.1 (15.3 - 21.2)	0.066
	One	23.9 (17.6 - 31.7)	
	Two or more	14.6 (11.0 - 19.1)	
Hospitalizations**	None	18.4 (15.9 - 21.1)	0.665
	One	20.8 (14.1 - 29.6)	
	Two or more	14.9 (7.5 - 27.4)	
Child's informant	Mother/Father	18.3 (15.9 - 20.9)	0.353
	Other***	22.5 (14.5 - 33.2)	
Informant's level of education (years)	0 to 8	18.9 (14.9 - 23.6)	0.946
	9 to 11	18.2 (14.7 - 22.2)	
	12 or more	19.4 (12.8 - 28.2)	

95%CI: 95% confidence index; ABEP: Brazilian Association of Research Companies (*Associação Brasileira de Empresas de Pesquisa*); \*Pearson's  $\chi^2$  test; \*\*referring to the 12 months prior to the interview; \*\*\*grandfather/grandmother, uncle/aunt, brother/sister, nephew/niece, another family member.

off-label medication in children had been investigated through interviews with the parents or caregivers of children in order to measure the total prevalence of this use, regardless of if the medications were prescribed or not<sup>13</sup>.

The prevalence of off-label drug use according to age (18.7%; 95%CI 16.4 - 21.3), verified in the present study, is higher than that found for the same category in a study carried out in Germany<sup>13</sup>, but less than results found in a North American study.<sup>11</sup> However, the North American study grouped off-label drug use according to age and indication in the same percentage. About one fifth of Brazilian children use off-label drugs, which is high, considering that the sample investigated is characterized by predominantly healthy children (only 9.9% of the total sample referred to chronic disease).

The use of off-label medication by age occurred more frequently in children under two years of age. In the study by Knopf et al.<sup>13</sup>, which included prescribed drugs and self-medicated drugs, the prevalence of this use was 42.4% among children aged 0 to 2 years old; 48.7% among children aged between three and six years old; 41.3% among children aged 7 to 10 years old; and 36.9% among children aged 11 to 13 years old. Other studies carried out in France, the United States, Italy and Estonia, revealed that children under two years of age demonstrated a higher prevalence of off-label drug use<sup>10,11,20,21</sup>. These findings suggest that, in several countries, in addition to Brazil, drugs that are registered and available in formulations suitable for this age group are less available for prescription and use, increasing the likelihood of off-label usage<sup>3</sup>.

Amoxicillin had the highest frequency of off-label use according to age among the analyzed drugs. In the study by Bazzano et al.<sup>11</sup>, amoxicillin also figured in as the most prescribed off-label drug. In this research, the authors found that most of the prescribed antibiotics were indicated to treat colds and non-specific infections of the upper respiratory tract<sup>11</sup>. In the present study, indication was not evaluated. Although amoxicillin has a well-established use in pediatrics<sup>22</sup>, it would be possible to expect a higher percentage of off-label use if this criterion were also observed.

In this research, products from different manufacturers containing amoxicillin registered by ANVISA were different from the regulatory agency itself with regard to age indications for the same presentation and concentration. Disagreements between Brazilian, British and North American package leaflets and reference information sources (such as guidelines and therapeutic forms) were also found in another study, especially regarding the indicated doses and the way they were expressed<sup>23</sup>. These differences are worth noting, as they can lead to prescription errors.

Nimesulide, a non-steroidal anti-inflammatory drug (NSAID) with indication for use starting at 12 years old, stood out as the second most used off-label drug according to the age. It should be noted that, in several countries, this drug has never been approved for pediatric use and its marketing has been suspended because of the risk of liver damage, among other adverse events<sup>24,25</sup>. In Brazil, until 2007, nimesulide was approved for pediatric use and there are still products that are currently active in oral solutions with concentrations of 10 or 50 mg/mL and dosages per kg of body weight<sup>25</sup>.



The combination of bronpheniramine + phenylephrine, a drug used as a decongestant and antiallergic indicated for use in children older than two years of age, also stood out among the most frequent off-label medications. Antihistamines were the most prescribed off-label drug, as identified in a study conducted by Gonçalves and Heineck<sup>2</sup>, suggesting a lack of drugs with proven safety to treat allergies in children. According to a review performed by Silva et al.<sup>26</sup>, drugs that act on the respiratory system and antiallergic agents were among the most widely used in an off-label manner, and the development of research on their safety and effectiveness, especially for those already available on the market, were not shown to be keeping track of this use.

It is understood that there are many reasons for using off-label medications, and it is not possible to assign responsibility to a single individual or organization. The prescription and use of an off-label drug according to age may be due to the lack of knowledge of the potential risks associated with it, but it can also result from the unavailability of a drug registered for use in the age group in question or even problems with the approved standard package inserts.

The development of specific formulations for children requires actions from the public and private sectors. Foreign experiences, like in the United States (US) and the European Union, have been associated with the increase in the number of clinical trials with individuals under 18 years old<sup>27,28</sup>. In the US, hundreds of studies encouraged by the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act were carried out with the pediatric population between 2007 and 2013, allowing adjustments in the labeling of the drug. A similar number of changes to labels have also been made in the European Union since *Paediatric Regulatio*<sup>27</sup>. In Brazil, the government does not provide incentives for patents, although it provides priority in reviewing the application for the registration of orphan drugs. In 2017, the Ministry of Health of Brazil published, through the Working Group on Pharmaceutical Assistance in Pediatrics, a document in which it recommends some strategies for the development and production of medicines in pediatrics through the national pharmaceutical industry<sup>29</sup>.

Among the limitations of this study, it is worth noting that, because it was not possible to verify the indication of use of a significant portion of the drugs used by the children, for off-label drug use, the lowest approved age was considered when the drug had more than one indication and different minimum ages for each indication. Another limitation was the lack of sufficient data to assess the other off-label uses (for indication, dose, pharmaceutical form and route of administration).

This study is the first to address the off-label use of medicines according to age in a representative sample of the Brazilian pediatric population. It estimated a high prevalence of this use in children, especially among children under 2 years of age. Off-label drug use may be present in the pediatric population due to the unavailability of therapeutic options or due to lack of knowledge or empiricism. Public health policies that encourage the development of research on the safety and efficacy of available and used off-label medications are urgent and necessary in this age group, as well as permanent education programs aimed at prescribers and regulatory actions, health surveillance and pharmacovigilance.

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