OFF-LABEL PEDIATRIC DRUG USE IN INDONESIA: A SYSTEMATIC REVIEW

Dewi Latifatul Ilma[1*], Nialiana Endah Endriastuti[1]

1. Department of Pharmacy, Faculty of Health Sciences, Jenderal Soedirman University, Purwokerto, Indonesia, 53122

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* Corresponding author
 Dewi Latifatul Ilma

Email:
dewilatifatulilma@unsoed.ac.id

ABSTRACT

The phenomenon of off-label drug use has been widely observed in the pediatric population, including in Indonesia. The major concern arising from the prevalence of off-label drug use is the increased risk of adverse drug reactions. We performed a systematic review to describe and provide insight into off-label pediatric drug use in Indonesia. The articles published using English and Indonesian language was systematically searched in five electronic databases, including Pubmed, Scopus, Google Scholar, Garuda, and Neliti. Key terms used for the search were as follows: "off-label use", "off-label","child", "pediatrics", "infant","adolescent", "newborn", "Indonesia". A total of one hundred sixteen studies were initially obtained from an electronic database. Further, after the references were reviewed, ten articles met all the eligibility criteria that were finally selected. The percentage of off-label pediatric drug use was 32.6-89.9%. The off-label categories in the selected studies were age, dosage, contraindication, route of administration, and indication. Among these off-label categories, age was the highest off-label with percentages ranged from 19.8 to 92.9%. Pseudoephedrine hydrochloride and triamcinolone acetonide became the most frequently used drug in that category. Thus we conclude that off-label pediatric drug use is common in Indonesia. Future research should consider the safety of off-label drugs in pediatric, primarily in Indonesia. Clinicians should be aware of off-label drugs in pediatrics and consider the risk-benefit of the drugs when prescribing to children. The authorities need to regulate off-label drug prescribing in pediatrics; therefore, it could improve medication safety and quality.

Keywords: Off-Label Drug, Pediatric, Indonesia, Systematic Review

1. INTRODUCTION

For the approval of a new drug, governmental authorities have to assess its safety, efficacy, and quality. If the drug is approved, the Marketing Authorisation (MA) and the Summaries of Product Characteristics (SPC) will be issued (Mason et al., 2012; Silva et al., 2014). The lack of clinical research for pediatric drugs limits the choice of medicine with a good quality of evidence in this population. Therefore, many drugs commonly prescribed for children are not labeled for use in the pediatric population (Corny et al., 2015; Mir & Geer, 2016; Nithya & Rani Mohan, 2016). Pediatric off-label use refers to pediatric prescription or all pediatric uses of marketed drug not detailed in the Summary of Product Characteristics (SPC) including therapeutic indication, use in age-subsets, appropriate strength (dosage), pharmaceutical form and route of administration (Mir & Geer, 2016; Silva et al., 2014). However, another study considered different off-label categories namely dosage, frequency and route of administration, contraindication, or age range (Mason et al., 2012).

The phenomenon of off-label drug use has been widely observed in the pediatric population. Previous research showed that of the 56,820 prescriptions in the pediatrics hospital, 30.7% were off-label (Delmas et al., 2016). Furthermore, it was observed that 607 drugs (75.8%) were off-label from a total of 800 drugs prescribed for pediatric (Tefera et al., 2017). The off-label drug use was also found to be high among community pharmacists (Easwaran et al., 2017). Although governmental policies may not be sufficient to improve drug use in

children, it is still a good start toward continuing the effort to decrease the use of off-label drugs (Balan et al., 2018; Corny et al., 2015). After the implementation of policies regarding pediatric clinical research, the off-label drug use in pediatric decrease marginally from 18%-66% to 33.2%-46.5% for inpatients and from 10.5%-37.5% to 3.3%-13.5% for outpatients (Corny et al., 2015).

The high rate of off-label use poses a substantial additional risk. Despite the fact that off-label drug use in pediatric generally accepted as standard medical practice, some evidence showed the risk of adverse drug reactions (ADRs). Children are more vulnerable to ADR than adults because of continuous physiological changes (Bellis et al., 2013; Wimmer et al., 2015). Spontaneous ADR reports informed that between 17 and 42.4% of ADR were associated with off-label drug use in pediatric (Mason et al., 2012).

To our knowledge, there have been a lot of studies on off-label pediatric drug use in Indonesia, but no study has conducted a systematic review on that topic. Therefore, we performed a systematic review to describe and provide insight into off-label pediatric drug use in Indonesia, thereby become a reliable source of information for making policy about off-label drug use in pediatric and to promote drug assessment for improving rational prescribing.

2. METHODS
Database and Search Methods
A systematic literature review of studies that analyze the trends of off-label pediatric drug use in Indonesia was undertaken based on several related study articles. Initial searches were conducted in August 2019 using five electronic databases (Pubmed, Scopus, Google Scholar, Neliti, and Garuda). Literature search uses articles in English and Indonesian language, the main term is also used to expand the search. Key terms used for the search were as follows: "off- label use", "off-label, "child", "pediatrics", "infant", "adolescent","newborn", "Indonesia". Search terms were mixed with "AND" and "OR" operators. Furthermore, we also excluded the key term "Indonesia" for articles that published using Indonesian language to ensure that all relevant articles were located. No publication date has imposed for the search study.

Data Collection and Analysis
We included all studies performed in the Indonesian population that provided the trends of off-label pediatric drug use. In addition, those studies should meet our inclusion and exclusion criteria as shown in Table 1.

We used the quality assessment tool by Hawker to analyze the quality of all the included studies (Hawker et al, 2015). This tool consists of nine domains: abstract and title; introduction and aims; sampling; data analysis; ethics and bias; result; transferability/generalizability; and implications and usefulness. The answers for each domain are "good","fair" ,"poor", and "very poor". We converted the answer into the numerical by assigning the answers from 1 point (very poor) to 4 points (good) which produced the minimum score of 9 points and a maximum of 36 points. The result was graded with the following definition: high quality (grade A), 30-36 points; medium quality (B), 24-29 points; low quality (C), 9-24 points (Lorenc et al., 2014). For our study, the result for the quality assessment showed that 3 articles were high quality (grade A), 4 articles medium quality (grade B), and 3 articles low quality (grade C).

Table 1. Inclusion and Exclusion Criteria for The Reviewed Articles

Inclusion Criteria	Exclusion Criteria
1. Published in the English language or Bahasa Indonesia 2. Full text available 3. Study about off-label drugs in pediatric	1. Review article, editorial letter, and comment 2. Specific study about a particular category of off-label drugs

Data were independently extracted by two independent researchers and disagreements were resolved through discussions. Information was extracted from each included study on: authors, year published, language, setting, method, source of data, instrument, patient age range, number of patients and prescriptions and drugs, patients received the off-label drug, prescription of the off-label drug, off-label drug, category of off-label drug, most prescribed off-label drugs, name of drugs prescribed in each category of off-label drug.

3. RESULTS AND DISCUSSION
Study Selection

Since the past two decades, off-label drug use already became a global controversy. Many drugs were used outside their licensed prescribing. This resulted in legislative and regulatory initiatives was taken globally to improve drug use in pediatrics. However, the regulations were issued mostly by developed country namely the United States of America, Canada, Australia, Japan, or Korea (Balan et al., 2018; Silva et al., 2014). In a developing country like Indonesia, there is no clear regulation regarding off-label drug use. The implementation of a National Health Insurance in Indonesia provides a detrimental financial impact for the hospital, which used off-label drugs because it can not be financed by insurance (Rahajeng et al., 2018). Nevertheless, off-label pediatric drug use was still widely observed in several studies. Therefore, it is important to summarize the studies in a systematic review study.

The search from Pubmed, Scopus, Google Scholar, Garuda, and Neliti databases provided a total of 116 articles. Of these, 9 duplicate articles were removed and 107 articles were screened of the title and abstracts. Most of these articles did not meet the criteria. Only 19 articles were assessed for eligibility and required full text reviewed. Finally, the systematic review included 10 articles. The PRISMA diagram of retrieved studies are shown in Figure I.
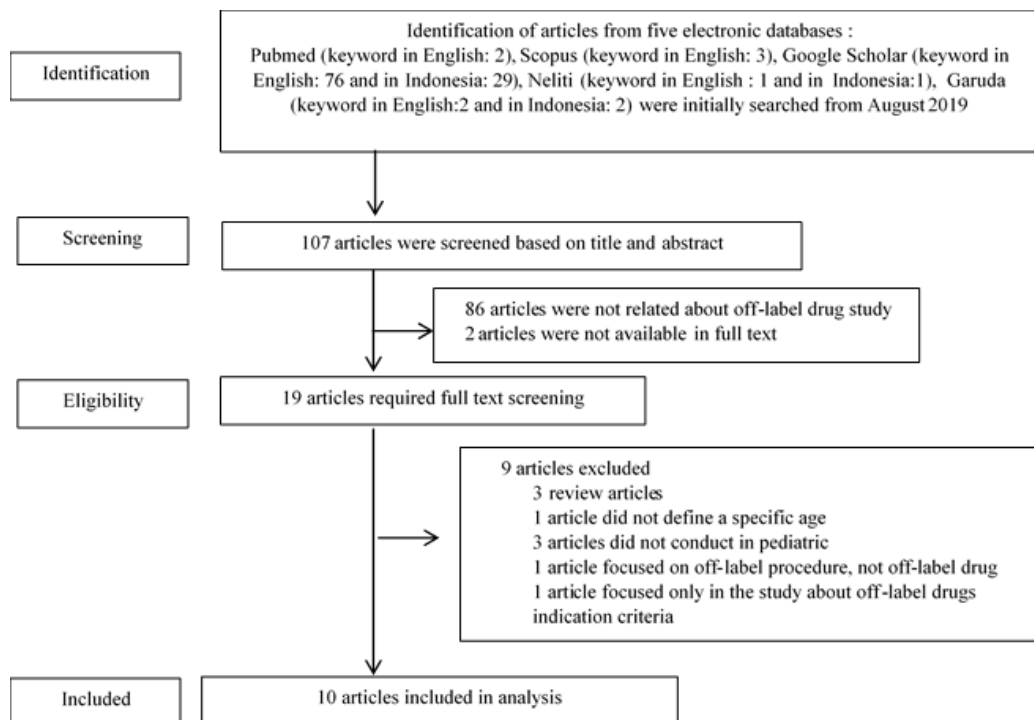

Figure 1. PRISMA diagram of retrieved study

Study Characteristics

Table 2 lists the characteristics of included studies. All ten studies finally selected for the review were conducted between 2013 and 2019. Most of the studies (N=6) were published in Bahasa Indonesia and performed in three different islands in Indonesia, which were Java Island, Borneo Island, and Lombok Island. The selected studies consisted of nine retrospective studies and one prospective study. These studies used between one and five reference sources to analyze the off-label drug use in pediatric, namely Summary of the Product Characteristics, Pediatric Dosage Handbook, British National Formulary, Drug Information Handbook, British National Formulary for Children, Indonesian National Drug Information, Data on Drug in Indonesia, MIMS USA, MIMS Indonesia, Indonesia Drug Speciality Information (ISO Indonesia), and Journals.

The age range of pediatric patients in the studies varied with the largest age range was 18 years, and the smallest age range was two years. Only six studies described the diagnosis of the patients in which respiratory disease became the most common disease in four studies. Two studies were conducted only in patients with nephrotic syndrome or pneumonia (Ramadaniati et al., 2017, 2018). The recruitment sites for the studies were primary healthcare centers, hospitals, private primary healthcare, and community pharmacy. For the study in community pharmacy, the patient's medical data were collected from patient's prescriptions, while the others were collected from the patient's medical records or both the patient's prescription and patient's registration book.

Trends of Off-Label Drug Use in Pediatric

The number of patients ranged from 67-348 in seven studies that provided this data, but only three studies informed the percentage of off-label drug use in pediatric, which ranged from 32.6-89.9% (N=107-209 patients from two available studies data). In the community pharmacies setting, the number of patients "s prescriptions assessed was between 268-4936 prescriptions with 18,6-21% (N=57-107) were off-label. The number of drug use ranged from 297-16516 in nine studies with the percentage of off-label drugs in eight studies ranged from 7- 65.8%, while the other study by Ramadaniati *et al*. (2018) differentiated the percentage of off- label drug use based on the reference sources used to assess the off-label drugs that were Indonesian National Drug Information with the percentage of off-label drug use was 35% (N=405) and British National Formulary for Children was 27.9% (N=319). One study only stated the number of off-label drug use that was 714 drugs (Kartinah et al., 2014). The most frequently used off-label drugs were domperidone (N=5); ondansetron, albuterol, and triamcinolone (N=4); ambroxol, dexamethasone, pseudoephedrine hydrochloride, and ursodeoxycholic acid (N=3).

The result of this review showed that off-label pediatric drug use was also common in Indonesia. The high percentage of off-label drug use was consistent with what has been found in other studies with off-label use in pediatric was 75.8% (N=736), which means more than one-third of drugs prescribed were off-label (Knopf et al., 2013; Palmaro et al., 2015; Tefera et al., 2017). The high rate of off-label use can be explained by many factors. Firstly, the lack of pediatric clinical trials contributed to the limitation of approved drugs in children. Thus, the clinicians considered reliable evidence and their clinical judgment when prescribing off-label drugs (Hada & Ashawat, 2014; Kimland & Odlind, 2012; Ramadaniati et al., 2017). Secondly, the lack of harmonization between pediatric documentation in the existing literature evidence and the authorized drug label affect the physicians" prescribing practice (Tefera et al., 2017). Lastly, pharmacists were initially responsible to optimize patient outcomes by working to

achieve the best possible quality use of medicine and supposed to off‑ label (Easwaran et al., 2017; Khan et al., 2016). Most of them were not aware of the concept of off-label drugs (Mukattash et al., 2018). The needs for expert groups devoted to pediatric treatment, guideline-recommended practice for pediatric, and a regulation to control off-label drug use become unavoidable to guarantee safe and good quality medication for children (Balan et al., 2018; Tefera et al., 2017).

The off-label categories in the selected studies were age, dosage, contraindication, route of administration, and indication (Table 3). All ten studies reported age as the categories of off‑ label drug use, followed by dosage and indication (N=8), and lastly contraindication and route of administration (N=2). When all studies were considered, the off-label rates for each of the categories ranged from 19.8% to 92.9% for age, 9.7% to 79.1% for dosage, 19.7% to 20% for contraindication, 0.9% to 32% for the route of administration, and 0.7% to 30.6% for indication proportionally. However, classified drugs as on-label or off-label based on hierarchical system giving priority as follows age, indication, route of administration, and dosage subsequently (Ramadaniati et al., 2017, 2018). Consequently, these studies assigned only one off-label category per drug, while others assigned more than one off-label category per drug.

Based on this result, the highest percentage of the off-label category was age. The category was also found in all of the studies included in this review. A similar result was reached by Balan *et al*. (2018) whose stated that the most common category of off-label prescribing in children was dosage and age. The drug classified as an off-label category of age when the drug was not recommended or no reference in the SPC below a certain age (Abdulah et al., 2015). The other definition was the administration of drugs outside the age range which the product was licensed (Ramadaniati et al., 2017). The total of off-label drugs identified in the age category were 40 drugs with pseudoephedrine hydrochloride and triamcinolone acetonide (N=4) became the most frequently used. Pseudoephedrine hydrochloride was categorized as off‑ label because the drug use was restricted for children under six years old. Moreover, safety and efficacy were not established in children under 2 years old (Ariati et al., 2015; Setyaningrum et al., 2017, 2019). For triamcinolone acetonide, the use in pediatric was unlicensed for pediatric under six years old (Pratiwi et al., 2013; Setyaningrum et al., 2019).

As for the dosage category, the most commonly used were ambroxol, dexamethasone, and albuterol (N=2) from a total of 18 drugs. Doxycycline and loratadine were the drugs identified in the contradiction category. Meanwhile, albuterol was used two times in the route of administration category. Lastly, for the indication category, the most frequently used off-label drugs were diazepam, domperidone, and ondansetron (N=3) from a total of 13 drugs analyzed.

The major concern arising from the prevalence of off-label pediatric drug use is the increased risk of adverse drug reactions. Pediatrics should be protected from the harm associated with the off-label use of drugs, but at the same time given the best possible treatment from options available (Bellis et al., 2013; Mason et al., 2012; Park, 2014). In this review, contraindication was one of the categories of the off-label drug. Doxycycline and loratadine were the drugs reported in the contradiction category. When a drug is contraindicated, there is the risk for serious adverse drug reaction occurred when the drug is administrated (Park, 2014). Doxycycline is contraindicated in young children under 8 years of age due to the risk of yellow tooth discoloration and dental enamel hypoplasia. However, doxycycline was developed after tetracycline and was labeled with the same side-effects as the earlier tetracyclines.

Furthermore, recent studies report little or no effects of doxycycline on tooth staining or dental enamel hypoplasia in children under 8 years of age (Gaillard, Briolant, Madamet, & Pradines, 2017). As for loratadine, the license is only for pediatric aged two years old or older (Fitzsimons et al., 2015). Although minimum adverse drug reaction was reported from the second generation of antihistamine (Motola et al., 2017), Pratiwi *et al*. (2013) categorized loratadine in a contraindicated category using MIMS USA reference. Off-label uses are generally permitted based on the judgment of the healthcare providers unless there is strong evidence of the association between off-label drug use and a serious adverse drug reaction (Park, 2014). However, the risks and benefits of off-label use have to be assessed, and patients" parents have to be informed accordingly when their children were prescribed off-label drugs (Wimmer et al., 2015). In addition, governmental involvement is necessary to improve the rational use of the drug in pediatric by making a policy to regulate off-label drug use and providing an opportunity to conduct a clinical study in children (Corny et al., 2015; Joseph et al., 2013).

Although our study has provided useful information regarding off-label pediatric drug use in Indonesia, several limitations should be considered. The methods to classify the off-label category were varied between study, which makes the direct comparison difficult. Most of the study classified a drug as off label equivalently in some categories i.e., age, dosage, route of administration, indication, and contraindication, while two studies used the hierarchical system to determine the off-label category. For example, when a drug prescribed for a patient was not recommended based on age and given at higher dose listed on the reference source, it was assigned off-label only for "age" category by the studies using the hierarchical system, while other studies assigned off-label for "age" and "dosage" category for the same drug**.** Furthermore, this review is also suffered from the lack of data provided by the studies, which affected the quality of our findings.

Table 2. Characteristics of the studies reporting off-label pediatric drug use

Author, year	Abdulah et al., 2015	Akbar et al, 2017	Ariati et al, 2015	Hapsari et al, 2018	Kartinah et al., 2014	Pratiwi et al., 2013	Ramadaniati et al., 2017	Ramadaniati et al., 2018	Setyaningrum et al, 2017	Setyaningrum et al, 2019
Language	English	Indonesia	Indonesia	Bahasa Indonesia	English	Indonesia	English	English	Indonesia	Indonesia
Setting	Community Pharmacies	Public Health Center	Hospital (outpatients)	Hospital (outpatients and inpatients)	Hospital (outpatients)	Community Pharmacies	Hospital (inpatients)	Hospital (inpatients)	Community Pharmacies	Private Primary Healthcare
Location (island)	Bandung (Java)	Sleman (Java)	Banjarmasin (Borneo)	Mataram (Lombok)	Banjarmasin (Borneo)	Bandung (Java)	Jakarta (Java)	Jakarta (Java)	Sleman (Java)	Sleman (Java)
Method	Retrospective	Retrospective	Retrospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Source of data	Prescription	Medical record	Prescription, patient registration book	Medical record	Medical record	Prescription	Medical record	Medical record	Prescription	Medical record
Reference	SPC, Pediatric Dosage Handbook, BNF, DIH	DIH, BNF for Children, Pediatric Dosage Handbook, IONI	IONI, SPC, and Journal	DIH, BNF for Children, IONI	BNF for Children, DOI, IONI	DIH, BNF for Children, Pediatric Dosage Handbook, MIMS USA, MIMS Indonesia, ISO	IONI	IONI, BNF for children	DIH, Pediatric Dosage Handbook, BNF Children, IONI	DIH, Pediatric Dosage Handbook, BNF for Children
Patient age range	0-5 years	0-18 years	Pediatric	4-14 years	1 month-18 years	0-2 years	0-18 years	0-18 years	0-11 years	0-11 years
Diagnosis	NA	Most common diagnosis: Respiratory disease (67%)	Most common diagnosis: Respiratory disease	NA	NA	NA	Nephrotic syndrome	Pneumonia	Most common diagnosis: Respiratory disease	Most common diagnosis: Respiratory Disease (54.62%)
Number of patients	NA	100	348	200	264	NA	67	207	NA	119
Number of patients off - label (%)	NA	NA	209 (60.1%)	NA	NA (32.58%)	NA	NA	NA	NA	107 (89.9%)
Number of prescriptions	4936	NA	NA	NA	NA	2741	NA	NA	268	NA
Number of prescriptions	917 (18.6%)	NA	NA	NA	NA	542 (19.77%)	NA	NA	57(21%)	NA

off- label (%)

Number of drugs	16516	297	947	671	NA	8861	1553	1141	816	343
Number of drugs off label (%)	1145 (7%)	25 (8.41%)	564 (59.5%)	61 (9.09%)	714 (NA)	699 (7.89%)	1023 (65.8%),	IONI: 405 (35%), BNF for Children: 319 (27,9%)	98 (11.9%)	107 (31.2%)

NA, not available; SPC, summary of product characteristics; DIH, drug information handbook; BNF, British national formulary; IONI, informasi obat nasional Indonesia/Indonesia national drug information; DOI, data on drug information; MIMS USA, the monthly index of medical specialties United States of America; ISO, informasi specialite obat/drug specialties information

Table 3. Criteria of off-label pediatric drug use

Author, year	Categories of off-label drug (%)	Most prescribed off-label drugs	Off-label drugs in category of age	Off-label drugs in category of dosage	Off-label drugs in category of contraindication	Off-label drugs in category of route of administration	Off-label drugs in category of indication
Abdulah et al., 2015	Age (53%), dosage (27%), contraindication (20%)	Ambroxol hydrochoride, ibuprofen, domperidone, doxycycline, echinaceae purpurea and zinc picolinate, dioctahedral smectite, erdosteine, carbosisteine, triamcinolone, dextromethorphane, vitamin A, bromhexine, diazepam, chlorpheniramine maleat, phenylpropanolamine, nifuroxide, ursoedeoxycholic acid, mometasone furoate, ondansetron, loratadine, alumunium hydrochloride, magnesium hydroxide, dimetyl polysiloxane, cyprohetadine hydrochloride, valproic acid	NA	NA	NA	NA	NA
Akbar et al, 2017	Route of administration (48%), indication (32%), age (20%)	albuterol, glyceryl guaiacolate, domperidone, vitamine B6	Vitamine B6, glyceryl guaiacolate	NA	NA	Albuterol	Domperidone
Ariati et al, 2015	Dosage (79.07%), age (19.85%), indication (1.06%)	Cetirizine, cefixime, cefadroxil, pseudoephedrine, ambroxol, albuterol, ursodeoxycholic acid, lactulose, nystatin, diazepam, domperidone,	Cetirizine, cefixime, cefadroxil, albuterol, pseudoephedrine	Ambroxol, albuterol	NA	NA	Ursodeoxycholic acid, lactulose, nystatin, diazepam, domperidone,
Hapsari et al, 2018	Age (70.5%), indication (14,75%), dosage (14.75%)	Valproic acid, paracetamol, ampicillin, ondansetron	Valproic acid	Paracetamol, ampicillin	NA	NA	Ondansetron

Kartinah et al., 2014	Age (33.06%), dosage (36.29%), indication (30.65%)	Metamizole, prednisone, dexamethasone	Metamizole	Dexamethasone	NA	NA	Prednisone
Pratiwi et al., 2013	Age (70.53%), dosage (9.73%), contraindication (19.74%)	Domperidone, dioctahedral smectite, triamcinolone, erdosteine, doxyxycline, vitamine, carbocisteine, ursodeoxycholic acid, bromhexine, mometasone furoate	Domperidone, triamcinolone, erdosteine, vitamine, carbocisteine, bromhexine, mometasone, ciproheptadine, caolin and pectin, ondansetron, vitamin, chlorpheniramine maleat, metamizole, piracetam, ketotifen	Dioctahedral smectit, ursodeoxycholic acid, dextromethorphane, dimeticon, ibuprofen	Doxyxycline, loratadine	NA	NA
Ramadaniati et al., 2017	Age (75.5%), dosage (23.7%), indication (0.8%)	Prednisolone, lisinopril, valsartan, furosemide, methylprednisolone, amlodipine, carvedilol, losartan, omeprazole, digoxin	NA	NA	NA	NA	NA
Ramadaniati et al., 2018	IONI (dosage 57.04%; age 42.22%; indication 0.74%) BNF for Children (dosage 88%; age 11%, indication 1%)	IONI (ceftriaxone, bactesyn, amikacin, dexamethasone, cefotaxime), BNF for Children (aminophyline, ceftriaxone, dexamethasone, cefotaxime, meropenem)	NA	NA	NA	NA	NA
Setyaningrum et al, 2017	Indication (7.14%), age (92.86%)	Pseudoephedrine, triprolidine, triamcinolone, ciproheptadine, bromfeniramine maleat, dextrometorphan, ondansetrone	Pseudoephedrine, triprolidine, triamcinolone, ciproheptadine, bromfeniramine maleat, dextrometorphan	NA	NA	NA	Ondansetron, ciproheptadine
Setyaningrum et al, 2019	Dosage (49.53%), age (37.38%), indication (12.15%), route of administration (0.94%)	Chlorpheniramine maleat, pseudoephedrine, glyceryl guaiacolate, dextrometorphan, triamcinolon, triprolidine, phenylpropanolamine, cetirizine, dexchlorpheniramine maleat, phenilephrine, ambroxol, albuterol, cetirizine, paracetamol, domperidone, ondansetrone, dexamethasone, nystatin	Chlorpheniramine maleat, pseudoephedrine, glyceryl guaiacolate, dextrometorphan, triamcinolon, triprolidine, phenylpropanolamine, cetirizine, dexchlorpheniramine maleat, phenilephrine	Chlorpheniramine maleat, ambroxol, albuterol, cetirizine, paracetamol, domperidone, ondansetrone, dexamethasone, nystatin	NA	Albuterol	Albuterol, domperidone, ondansetrone

NA, not available; BNF, British national formulary; IONI, informasi obat nasional Indonesia/Indonesia national drug information

4. CONCLUSION

Off-label pediatric drug use is common in Indonesia. Future research should consider the safety of off-label drugs in pediatric, primarily in Indonesia. Clinicians should aware of off- label drugs in pediatric and consider the risk-benefit of the drugs when prescribing to children. The authorities need to regulate the off-label drug prescribing in pediatric, therefore could improve medication safety and quality.

5. ABBREVIATIONS

PRISMA: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis; **MIMS USA**: The monthly index of medical specialities United States of America.

6. ACKNOWLEDGMENT

None.

7. CONFLICT OF INTEREST

The authors declare no conflict of interest.

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