

# Off Label and Unlicensed Drug Prescriptions in Pediatric Medical Units at Tertiary Care Hospitals of Peshawar, Pakistan

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## ABSTRACT

**Background:** Off label and unlicensed prescribing is a global dilemma. The study was designed to investigate the prevalence and predictors of off label and unlicensed prescriptions in pediatric medical wards of Peshawar.

**Materials & Methods:** A prospective, cross-sectional survey was performed over a year in the pediatric medical units of four tertiary care hospitals in Peshawar. Drug profiles of 1375 patients were evaluated by Micromedex.

**Results:** A total of 100 different drugs were prescribed 5708 times to patients admitted in pediatric medical wards, of which 34.34% prescriptions were unlicensed and 52.99% prescriptions were off labelled. Regression analysis revealed that patients prescribed with  $\geq 5$  drugs (OR 0.113; CI 0.041-0.312) had 89% higher odds of receiving unlicensed medications as compared to children receiving  $< 5$  medications, while patients with a hospital stay of duration  $\geq 4$  days (OR 0.423; CI 0.238-0.752) had 58% higher odds of receiving unlicensed drugs.

**Conclusion:** Considerably high prevalence of unlicensed and off label drug prescribing was observed in the medical wards of pediatric department. There is need of improved prescribing strategies to reduce unlicensed and off label prescriptions to ensure better health care of children.

**KEYWORDS:** Off label prescriptions, Unlicensed prescriptions, Pediatrics

## Introduction

Pediatric pharmacotherapy focuses on the safe and effective treatment of neonates, infants, children, and adolescents. In this population, the challenges encountered by healthcare professionals are unique as compared to adults due to varying absorption, distribution, metabolism and elimination, affecting the drug efficacy and safety.<sup>1</sup> There are several reasons affecting the pediatric drug development e.g. lack of controlled clinical trials, low financial assistance by government especially in middle income countries and lacking interest of pharmaceutical industries (due to less profit margin and difficulty in the development of pediatric formulations).<sup>2</sup>

Pediatric drug evaluation studies have been neglected in the past, resulting in inadequate information regarding their safety and efficacy.

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This lack of information about pediatric pharmacotherapy often leads to unlicensed and off label drug use, resulting in increased risk of adverse outcomes.<sup>3</sup> Unlicensed drug use refer to medications which do not have product license or market authorization for use in pediatrics while Off label drug use is the utilization of medications for the purposes other than provided on product license.<sup>4</sup> Drugs are often licensed with little consideration of pediatric population. The product license contains statements such as “no evidence for use in children” or “not recommended for use in children”. This usually reflects the absence of pediatric drug data rather than a specific reason for the drug not to be used. Several studies have been carried out in United States and Europe to assess the prevalence of unlicensed and off label prescriptions.<sup>5, 6</sup> High prevalence of infectious diseases in children have been reported globally including Pakistan.<sup>7, 8, 9</sup> Due to high burden of infectious diseases, there is inappropriate and excessive use of antibiotics among hospitalized children, resulting in the development of resistant pathogens and enormous costs in health care system.<sup>10</sup>

Though pediatric medical wards are the settings with highest number of cases, limited data is available worldwide to evaluate this vulnerable population. In most of the published studies, different settings and methods are used for data collection and analysis, which makes the inter-comparison hard.

So far very few studies have been conducted on this serious issue of pediatric pharmacotherapy. The objective of this study was to determine the prevalence and predictors of off label and unlicensed drug prescriptions in pediatric medical units of tertiary care hospitals of district Peshawar, Pakistan.

## Materials & Methods

A cross-sectional survey was performed from May, 2017 to April, 2018 in pediatric medical wards of four tertiary care hospitals. Of these, three were government hospitals i.e. Hayatabad Medical Complex (HMC), Khyber Teaching Hospital (KTH) and Lady Reading Hospital (LRH) while one was a private hospital i.e. Northwest General Hospital (NWGH). These hospitals served the rural, urban and sub-urban areas of Khyber Pakhtunkhwa, Pakistan. Stratified sampling technique was used to collect data. Sample size was calculated by WHO formula for known populations<sup>11</sup> and found to be 355 for HMC, 370 for KTH, 380 for LRH and 270 for NWGH. Inclusion criteria was set as children admitted to the pediatric medical wards while topical preparations, IV stock solutions and oxygen therapy were excluded during evaluation. The government hospitals were lacking electronic health record (EHR) system so the data was collected manually from patient charts. Data was collected after obtaining consent from all hospitals and ethical principles under the ICH-GCP (Good Clinical Practice) guidelines were followed.<sup>12</sup> Protected Health Information (PHI) of patients were coded and stored. Predesigned proforma was used to record the primary information i.e. patient identification number, name, age, gender, diagnosis, number of prescribed drugs, date of hospital admission and discharge, detailed information regarding drugs administered, their route of administration, dose and frequency. Data was evaluated by Micromedex® (Watson health, IBM Corporation). The license status of the drug and off-label category was evaluated based on the information provided by Micromedex®. Using this information, drugs were classified as licensed or unlicensed; while off label categories included age, dose, indication and administration. Drugs were

classified according to Anatomical Therapeutic Chemical (ATC) classification system.<sup>13</sup>

Statistical analysis was done using SPSS version 20. Variables like gender, age groups, duration of hospital stay, number of prescribed drugs, unlicensed and off-label drugs were expressed in frequencies. Chi square test was applied to assess the association between unlicensed and off label drug use with different hospitals and age groups. Univariate and multivariate logistic regression were used to determine odds ratio with 95% confidence interval for predictors of off-label and unlicensed drug use. Only the significant predictors of univariate model were included for multivariate analysis. Gender, age, duration of hospital stay and number of prescribed drugs were considered as independent variables in the model. Age was stratified using the WHO classification,<sup>14</sup> while medians were used to stratify number of prescribed drugs and hospital stay.

## Results

From the cohort of patients admitted to pediatric medical wards of all the four hospitals, a representative sample of 1375 patients were analyzed, where male population (65.38%) was predominantly higher than female (34.62%). Mean age of the patients was  $37.46 \pm 45.22$  months, and infant was the most prevalent age group. Maximum number of patients received 1 to 3 drugs (48.87%), followed by 4 to 6 drugs (39.64%) and 7 to 9 drugs (11.49%). Mean number of prescribed drugs per patient was  $3.93 \pm 1.85$ . Of the 1375 patients, 1213 (88.22%) had a hospital stay of 1 to 5 days with mean stay  $3.42 \pm 2.18$  days. Demographics of pediatric patients are shown in **Table-1**.

ICD 10 disease classification system was used to categorize diagnosis. The leading causes for hospital admission in medical wards were Acute diarrhea (10.04%), Meningitis (8.58%), Measles (7.64%), Pneumonia (7.20%), Lower respiratory tract infections (6.47%), Acute bronchiolitis (5.45%), Pyrexia of unknown origin (4.07%), Malaria (3.56%), Asthma (3.42%) and Enteric fever (3.20%).

### Therapeutic categories and prescribed drugs

Anti-infective agents for systemic use [2885 times (50.54%)] and respiratory system [783 times (13.72%)] were the most common drug categories. A total of 100 drugs were prescribed 5708 times to pediatric patients. Frequently prescribed off label drugs and categories are shown in **Figure 1**.

**Table 1. General Characteristics of Patients in Pediatric Medical Wards**

Variables	Frequency (%) HMC	Frequency (%) KTH	Frequency (%) LRH	Frequency (%) NWGH	Total
<b>GENDER</b>					
Male	229 (16.65)	248 (18.04)	235 (17.09)	187 (13.6)	899 (65.38)
Female	126 (9.16)	122 (8.87)	145 (10.55)	83 (6.04)	476 (34.62)
<b>AGE GROUPS (MONTHS)</b>					
≤23	203 (14.76)	190 (13.82)	199 (14.47)	150 (10.91)	742 (53.96)
24-143	133 (9.67)	170 (12.36)	151 (10.98)	107 (7.78)	561 (40.8)
≥144	19 (1.38)	10 (0.73)	30 (2.18)	13 (0.95)	72 (5.24)
<b>NO OF PRESCRIBED DRUGS</b>					
1-3	162 (11.78)	193 (14.04)	216 (15.71)	101 (7.35)	672 (48.87)
4-6	143 (10.4)	137 (9.96)	142 (10.33)	123 (8.95)	545 (39.64)
≥7	50 (3.64)	40 (2.91)	22 (1.6)	46 (3.35)	158 (11.49)
<b>HOSPITAL STAY (DAYS)</b>					
1-5	320 (23.27)	323 (23.49)	331 (24.07)	239 (17.38)	1213 (88.22)
6-10	30 (2.18)	45 (3.27)	45 (3.27)	29 (2.11)	149 (10.84)
≥11	5 (0.36)	2 (0.15)	4 (0.29)	2 (0.15)	13 (0.95)
<b>PATIENTS RECEIVED AT LEAST ONE UNLICENSED DRUG</b>					
Y	318 (23.13)	351 (25.53)	362 (26.33)	261 (18.98)	1292 (93.96)
N	37 (2.69)	19 (1.38)	18 (1.31)	9 (0.65)	83 (6.04)
<b>PATIENTS RECEIVED AT LEAST ONE OFF LABEL DRUG</b>					
Y	318 (23.13)	329 (23.93)	354 (25.75)	240 (17.45)	1241 (90.25)
N	37 (2.69)	41 (2.98)	26 (1.89)	30 (2.18)	134 (9.75)

**FDA licensed and off label drugs**

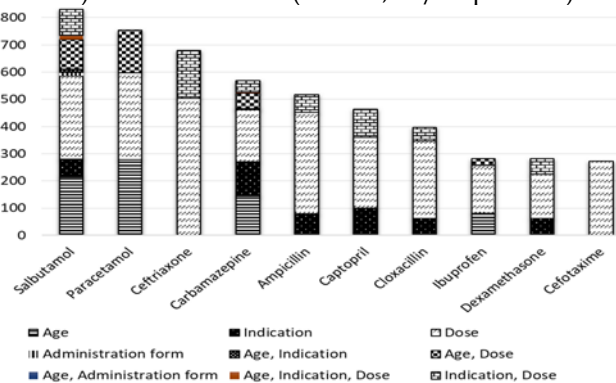
Of the total prescriptions, 34.34% were categorized as unlicensed and 52.99% were off labelled. An overwhelming 93.96% patients (n=1292) received at least one unlicensed drug and 90.25% of the patients (n=1241) received at least one off label drug as shown in **Table-1**. The frequency of patients receiving at least one unlicensed drug was lower in HMC (89.51%) as compared to other three hospitals i.e. 94.86% in KTH, 95.26% in LRH and 96.67% in NWGH. Patients admitted to pediatric ward of LRH (93.15%) were exposed at higher frequency of off label drugs.

Dose was the frequent (35.7%) category for off label prescriptions followed by age (19.4%) and indication (18.28%). Salbutamol, paracetamol and ceftriaxone were the most common drugs prescribed in the wards and contributed the most to off label categories. Dose was also a common reason for off label drug use in all age groups among all hospitals as displayed in **Figures 2 and 3**.

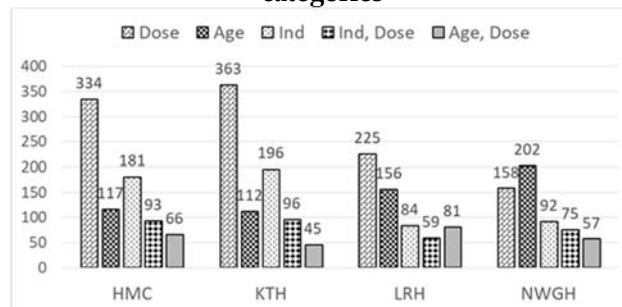
**Association of off label drug use with hospitals and age groups**

No significant difference was observed between off label drug use and type of hospital (p<0.161). However, drugs prescribed as off label were significantly associated with age groups (p<0.0001)

and were frequently found in infants (93.12%, 691/742 patients) and adolescents (91.67%, 66/72 patients).



**Fig 1. Prevalent off label prescribed drugs and their categories**



**Fig 2. Prevalent off label drug categories among hospitals**

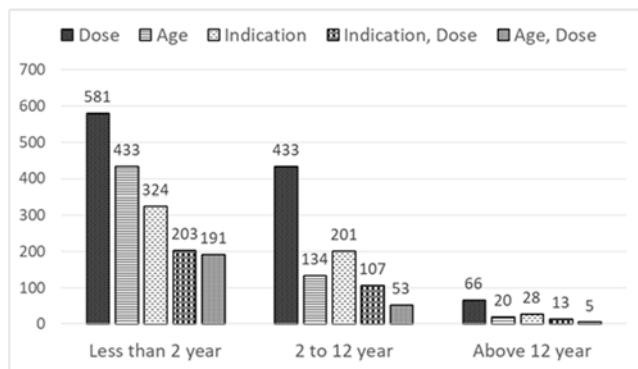


Fig 3. Prevalent off label drug categories among age groups

**Association of unlicensed drug use with hospitals and age groups**

Statistically significant association was observed between unlicensed drug use and type of hospital ( $p < 0.001$ ). Unlicensed drug prescriptions were observed in all hospitals with HMC reported a slightly lower frequency (90%) as compared to KTH (94%), LRH (95%) and NWGH (96%). Also a significant association was observed between unlicensed use of drugs and age groups ( $p < 0.002$ ). Patients of age less than 2 years were highly exposed to unlicensed prescriptions as compared to those with age 2-12 years and >12 years.

Table 2. Predictors of Off Label and Unlicensed Drug Use in Pediatric Medical Wards

OFF LABEL DRUG USE				
Variables	Univariate		Multivariate	
	OR (CI)	P-value	OR (CI)	P-value
<b>GENDER</b>				
Male	1.099 (0.759-1.592)	0.618		
Female	Reference			
<b>AGE GROUPS</b>				
Infants	1.232 (0.509-2.978)	0.644		
Children	0.571 (0.239-1.363)	0.207		
Adolescent	Reference			
<b>NO OF PRESCRIBED DRUGS</b>				
< 5	0.170 (0.091-0.318)	< 0.001***	0.186 (0.099-0.350)	< 0.001***
≥ 5	Reference		Reference	
<b>HOSPITAL STAY (DAYS)</b>				
< 4	0.464 (0.306-0.705)	< 0.001***	0.557 (0.365-0.852)	0.007**
≥ 4	Reference		Reference	
<b>UNLICENSED DRUG USE</b>				
Variables	Univariate		Multivariate	
	OR (CI)	P-value	OR (CI)	P-value
<b>GENDER</b>				
Male	0.905 (0.564-1.453)	0.680		
Female	Reference			
<b>AGE GROUPS</b>				
Infants	1.396 (0.478-4.080)	0.542		
Children	0.615 (0.215-1.757)	0.364		
Adolescent	Reference			
<b>NO OF PRESCRIBED DRUGS</b>				
< 5	0.100 (0.036-0.274)	< 0.001***	0.113 (0.041-0.312)	< 0.001***
≥ 5	Reference		Reference	
<b>HOSPITAL STAY (DAYS)</b>				
< 4	0.345 (0.195-0.610)	< 0.001***	0.423 (0.238-0.752)	0.003**
≥ 4	Reference		Reference	

\*significant at  $p < 0.1$  \*\*significant at  $p < 0.05$  \*\*\*significant at  $p < 0.01$

OR= Odds Ratio, CI= Confidence interval

### **Predictors of off label and unlicensed drug use**

Univariate and multivariate regression analysis showed that patients receiving less than 5 drugs were significantly less likely to receive off label and unlicensed drugs as compared to patients receiving 5 or more drugs. Similarly, patients staying at hospital for less than 4 days were less likely to receive off label and unlicensed drugs as compared to patients staying at hospital for 4 or more days as shown in **Table-2**.

## **Discussion**

Worldwide the prevalence of unlicensed and off label use of drugs is high, describing the fact that pediatric prescribing is based on necessity without ensuring safety, efficacy, and quality. This study was an attempt to show that similar problem exist in pediatric medical wards of Pakistan. The study revealed higher prevalence (34.34%) of unlicensed pediatric drug prescriptions as compared to developed countries e.g 8.3% in Canada.<sup>15,16</sup> In this study, a significant difference was observed in the number of unlicensed prescriptions practiced in different hospitals, possibly due to difference in the prescribing practices in medical wards of these settings. Difference in flow of patients in medical units could be another reason.

The frequency of off label drug use was reported 23-47% in a review published in Canada, closely resembling our findings (52.99%).<sup>16</sup> In contrast, another Canadian study reported the use of off label drugs at the rate of 38.2%, quite lesser than our results.<sup>15</sup> Thus, the prevalence of off label drug prescription varies. Probable reasons include non-availability of effective licensed regimens for a specific disease, treatment failure of standard regimen, lack of alternate therapies or clinical trials in pediatric age groups.<sup>17,18</sup> In this study, infant age group was highly exposed to off label prescriptions contrary to Ethiopian study reporting off-label prescribing more in children age group.<sup>19</sup> Moreover, higher ratio of unlicensed/off label drug prescribing is due to non-availability of data about specific dosing and dosage forms in pediatric age groups in National Essential Drug List (NEDL) of Pakistan.<sup>20</sup> Dosage was the most common (35.7%) off label category followed by age (19.4%) and indication (18.28%) unlike an Indonesian study reporting age (53.2%) as the most common off label category.<sup>21</sup>

In this study, anti-infective agent was frequently (50.3%) observed therapeutic drug category with ceftriaxone (11.83%), cefotaxime (6.08%), ampicillin (4.99%) and metronidazole (2.70%) as highly

prescribed antibiotics. High prevalence of infectious diseases in children could be the reason for this frequent prescription of anti-infective agents. But recently published research on off label drug use in nephrotic syndrome demonstrated cardiovascular drugs as the most common drug category.<sup>21</sup> Inhaled salbutamol was the most common off label prescribed drug followed by paracetamol, resembling the results of study by Schmiel et al.<sup>22</sup> Another study conducted at primary care setup also revealed paracetamol to be frequently prescribed off label drug.<sup>23</sup> Reason for this high prevalence could be the wide use of paracetamol in pediatric wards due to its high efficacy.<sup>24</sup> This study identified the number of medications prescribed as a significant predictor for use of off label and unlicensed prescriptions. Gender and age groups have no significant relationship with off label and unlicensed drug use. Our findings were in accordance with the reports published in Brazil and India.<sup>25,26</sup>

Off label and unlicensed drug use should not be ignored or simply accepted as a part of routine prescribing practice. Lack of clinical drug trials in pediatrics is often used to justify this inappropriate usage of drugs.<sup>5,6</sup> Efforts are required to overcome this dilemma by encouraging pharmaceutical companies and researchers to assess more medicines to get adequate data on their quality, safety and efficacy in children.<sup>27</sup> Like US and Europe, Pakistan should also incorporate pediatric prescribing drug licensing system into health regulatory body. Current study will help the regulators in formulating steps to improve the prescribing pattern in this vulnerable population. Some of the limitations of this study include consideration of only tertiary care and inpatient settings. Therefore, outcomes need to be generalized in population with caution. Moreover, many drugs such as anticancer and immunosuppressive agents are frequently used in pediatrics and need to be included in further studies. Therefore, similar studies are suggested to expand to primary health care and outpatient settings to validate the data.

## **Conclusion**

The study reports high prevalence of unlicensed and off label drug prescribing practices in pediatrics. Clinical drug trials should be performed both in adults and children to maintain the standards of drug safety and efficacy. Drug prescribing policies and revised clinical protocols should be adopted to improve the pediatric pharmacotherapy.

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## References

1. Bellis JR, Kirkham JJ, Thiesen S, Conroy EJ, Bracken LE, Mannix HL, et al. Adverse drug reactions and off-label and unlicensed medicines in children: a nested case? Control study of inpatients in a pediatric hospital. *BMC medicine*. 2013;11(1):238.
2. Ivanovska V, Rademaker CM, van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: a review of challenges and progress. *Pediatrics*. 2014;134(2):361-72.
3. De Las Salas R, Soto CMV. Pharmacovigilance in Pediatric Population. *Pharmacovigilance: IntechOpen*; 2019.
4. Turner S, Nunn A, Choonara I. Unlicensed drug use in children in the UK. *Paediatr Perinat Drug Ther*. 1997;1(52):5.
5. van der Linden P, Bakker E, Van der Lely N, Eland I, Stricker B, van den Anker J. Unlicensed and off-label drug use in a paediatric ward of a general hospital in the Netherlands. *European journal of clinical pharmacology*. 2002;58(4):293-7.
6. Sturkenboom M, Felisi M, Manfredi C, Neubert A, Cantarutti L, Padula R, et al. Paediatric status and off-label use of drugs in children in Italy, United Kingdom and the Netherlands. *Pharmaceuticals Policy and Law*. 2009;11(1, 2):51-9.
7. Cuningham W, McVernon J, Lydeamore MJ, Andrews RM, Carapetis J, Kearns T, et al. High burden of infectious disease and antibiotic use in early life in Australian Aboriginal communities. *Australian and New Zealand journal of public health*. 2019;43(2):149-55.
8. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. *American journal of respiratory and critical care medicine*. 2003;167(5):695-701.
9. Martínón-Torres F, Salas A, Rivero-Calle I, Cebeý-López M, Pardo-Seco J, Herberg JA, et al. Life-threatening infections in children in Europe (the EUCLIDS Project): a prospective cohort study. *The lancet child & adolescent health*. 2018;2(6):404-14.
10. Soltani J, Pouladfar G, Versporten A, Sharland M, Goossens H, Jafarpour Z, et al. Point prevalence survey of antimicrobial prescription and infection in pediatric and neonatal wards of two Iranian teaching hospitals. *Erciyes Medical Journal/Erciyes Tip Dergisi*. 2019;41(1):25-32.
11. Machin D, Campbell MJ, Tan SB, Tan SH. *Sample Sizes for Clinical, Laboratory and Epidemiology Studies*: Wiley Online Library; 2018.
12. Guideline IHT. Guideline for good clinical practice. *J Postgrad Med*. 2001;47(3):199-203.
13. Organization WH. The anatomical therapeutic chemical classification system with defined daily doses (ATC/DDD). Oslo: WHO. 2006.
14. Knoppert D, Reed M, Benavides S, Totton J, Hoff D, Norris K. Position paper: Paediatric age categories to be used in differentiating between listing on a model essential medicines list for children. The World Health Organization Available at <http://archives.who.int/eml/expcom/children/Items/PositionPaperAgeGroups.pdf>. 2007.
15. Corny J, Bailey B, Lebel D, Bussières J-F. Unlicensed and off-label drug use in paediatrics in a mother-child tertiary care hospital. *Paediatrics & child health*. 2016;21(2):83-7.
16. Corny J, Lebel D, Bailey B, Bussières J-F. Unlicensed and off-label drug use in children before and after pediatric governmental initiatives. *The Journal of Pediatric Pharmacology and Therapeutics*. 2015;20(4):316-28.
17. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. *British journal of clinical pharmacology*. 2015;79(3):357-69.
18. Moulis F, Durrieu G, Lapeyre-Mestre M. Off-label and unlicensed drug use in children population. *Therapies*. 2018;73(2):135-49.
19. Tefera YG, Gebresillassie BM, Mekuria AB, Abebe TB, Erku DA, Seid N, et al. Off-label drug use in hospitalized children: a prospective observational study at Gondar University Referral Hospital, Northwestern Ethiopia. *Pharmacology research & perspectives*. 2017;5(2).
20. Aslam M. National essential medicine list. In: Islamabad DRAP, editor. 2016 ed. Pakistan: Ministry of National Health services, Regulations and Coordination 2016.
21. Ramadaniati H, Khairani S, Permatasari D, Tambunan T. DI-003 Off-label and unlicensed drug use in paediatric outpatients with nephrotic syndrome: an Indonesian context. *British Medical Journal Publishing Group*; 2017.
22. Schmiedl S, Fischer R, Ibáñez L, Fortuny J, Klungel OH, Reynolds R, et al. Utilisation and off-label prescriptions of respiratory drugs in children. *PloS one*. 2014;9(9):e105110.
23. Kazouini A, Mohammed BS, Simpson CR, Helms PJ, McLay JS. Paracetamol prescribing in primary care: too little and too much? *British journal of clinical pharmacology*. 2011;72(3):500-4.
24. Narayan K, Cooper S, Morphet J, Innes K. Effectiveness of paracetamol versus ibuprofen administration in febrile children: A systematic literature review. *Journal of Paediatrics and Child Health*. 2017;53(8):800-7.
25. Gomes VP, da Silva KM, Chagas SO, dos Santos Magalhães IR. Off-label and unlicensed utilization of drugs in a Brazilian pediatric hospital. *Farm Hosp*. 2015;39(3):176-80.

26. Bose D, Muraraiah S, Chandrashekar H. Evaluation of patterns and predictors of off-label prescribing of antidepressants in psychiatry at a tertiary care hospital- An analytical cross-sectional study. National Journal of Physiology, Pharmacy and Pharmacology. 2017;7(2):183-8.
27. Nahata M. Licensing of medicines for children in the USA. Paediatr Perinat Drug Ther. 1997;1(50):1.

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- B. Active Participation in Active Methodology
- C. Interpretation/ Analysis and Discussion