

## Brief Original Article

# Off-label antibiotic use in a specialized children care hospital in Punjab, Pakistan: Findings and implications

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### Abstract

**Introduction:** Most of the antibiotics currently used in pediatrics are either unlicensed or being prescribed outside the specifications of product label (off-label prescribing). The aim of this study was to assess the extent of off-label antibiotic use in pediatrics.

**Methodology:** A six month longitudinal off-label antibiotic utilization survey was carried out from January to June, 2018. A structured questionnaire was designed to collect detailed information for each pediatric patient admitted to participating health center. The data included basic demographic and clinical diagnosis with details of prescribed antibiotics (formulation, dose, dosage, route of administration and indication for use). Data were analyzed using Social packages for Statistical Sciences (SPSS) version 21.0.

**Results:** Of 1,810 admissions, 1,795 (99.2%) patients received antibiotics. Out of these, a total of 451 (25.1%) patients (326 patients admitted in the medical ward and 125 patients in ICUs) received at least one unlicensed/off-label antibiotic. Antibiotics were predominantly prescribed for the treatment of infections (n = 311, 69.0%). The majority of the pediatric patients who received off-label antibiotic suffered from respiratory tract infections (n = 223, 49.4%), skin and soft tissue infections (n = 53, 11.8%), gastrointestinal tract infections (n = 56, 12.4%) and other infections (n = 46, 10.2%). Co-amoxiclav (n = 190, 42.1%) was the most frequently off-label prescribed antibiotic to pediatric patients. An inappropriate dose for patients (n = 430, 95.3%) was the most frequent cause of prescribing off-label antibiotics.

**Conclusions:** Further evaluation of health and economic outcomes of off-label prescribing and determinants influencing the drug choice is required.

**Key words:** Off-label drug; antibiotic use; pediatrics; off-label prescribing.

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### Introduction

Rational drug use in the pediatric population is a major concern around the globe for clinicians and regulatory organizations due to the paucity of evidence-based literature on safety and efficacy of antibiotics in pediatrics. Most of the drugs prescribed to pediatrics are utilized outside the specifications of licensed drug which include the indication, dose, route of administration, and age groups of patients [1-4]. Use of off-label/unlicensed drugs in the pediatric population is widespread that mainly occurs in medical and surgical wards as well as in intensive care units (ICUs) [2,5]. Use of off-label drugs gives rise to inconsiderable adverse drug event that requires hospitalization and additional therapies [6-9]. The European community has introduced the guidelines on clinical investigation of drugs in pediatrics that is considered as positive approach related to encouragement of clinical trials for

conditions in pediatrics [10,11]. Despite these guidelines, there are certain barriers where pharmaceutical industries may have been resistant to conduct clinical trials in pediatrics. These barriers include ethical conflicts, issues with blood sampling, and problems in enlisting the adequate number of children [1]. The most commonly prescribed off-label drugs in pediatrics are antibiotics [12].

Infections have always been a prime issue in pediatrics with substantial morbidity and mortality [13]. Most of the medications including essential drugs are not tested and approved for use in children which may lead to medication errors. Several studies documented that medication errors are 3 times more frequent in children than adults [14]. A study reported higher mortality rates in neonates who received a combination of sulphisoxazole and penicillin than those who received oxytetracycline [15]. A higher incidence rate

of kernicterus has been reported in pediatrics receiving sulphonamide (highly protein bound drug that results in the displacement of bilirubin from albumin) and penicillin [16]. Data on adults cannot be supposed to anticipate the adverse events of drugs in pediatrics [17]. Drug metabolism in children may show differences with respect to that in adults. An altered metabolism of chloramphenicol results in grey baby syndrome in the newborn or infant in which cyanosis, vomiting, cardiorespiratory failure and abdominal distention are developed [18]. Reduction of the dose of chloramphenicol may result in the prevention of the development of grey baby syndrome [19]. Tetracycline if given in pregnancy or to pediatrics under age of eight years, it can cause harm to teeth and bones [1]. In order to reduce drug toxicity, it is essential to understand the correlation between drug metabolism and age [1]. Many literatures have been published worldwide regarding off-label/unlicensed drug use in pediatric population.

**Table 1.** Demographic characteristics and common indications of pediatric population.

Variables	Frequency (%) (n = 451)
<b>Gender</b>	
Male	298 (66.1)
Female	153 (33.9)
<b>Wards</b>	
Medical Ward	326 (72.3)
ICU's	125 (27.7)
<b>Age Groups</b>	
Neonates	114 (25.3)
Infants	190 (42.1)
Child	147 (32.6)
<b>Organ system</b>	
Respiratory system	223 (49.4)
GIT	56 (12.4)
Skin	53 (11.8)
General	46 (10.2)
Nervous system	44 (9.7)
Cardiac	8 (1.8)
Urinary tract	8 (1.8)
Kidney disease	6 (1.3)
Endocrinology	3 (0.7)
Electrolyte Imbalance	1 (0.2)
Genetics	2 (0.4)
Joints	1 (0.2)
<b>Infections</b>	<b>311 (69.0)</b>
Community acquired infections	279 (61.8)
Hospital acquired infections	31 (6.8)
Others	1 (1.0)
<b>Prophylaxis</b>	<b>140 (31.0)</b>
Medical prophylaxis	122 (27.0)
Surgical prophylaxis	15 (3.3)
Others	3 (1.6)

ICU: Intensive care unit; GIT: Gastrointestinal tract.

However, in Pakistan, there is scarcity of data on the pattern and magnitude of off-label/unlicensed antibiotic use in pediatrics [20,21]. Therefore, the aim of the present study was to assess the extent of off-label/unlicensed antibiotic use in pediatrics.

## Methodology

### Study design

A six month longitudinal off-label antibiotic utilization survey was carried out from January to June, 2018 in a pediatric hospital in public sector receiving patients from Punjab. The Children's Hospital and Institute of Child Health Lahore is one of the largest public private children hospital in Pakistan that provides both inpatient and outpatient services with all possible diagnostic facilities. The total bed strength has been reached to 1,050. Antibiotic containing prescriptions were assessed for all inpatients admitted in general medical wards, intensive care units, neonatal units and pediatric medical wards of the hospital in Lahore, Pakistan. The study was approved by Human Ethical Committee of University College of Pharmacy, Punjab University, Lahore (HEC/PUCP/1,954) and Ethical Review Board of The Children's Hospital and Institute of Child Health Lahore (8,227). Parents or legal guardians were informed about the aim of the survey and written consent was taken from them.

### Data Collection

A written prescription for all inpatients pediatrics under the age of 12 was collected during the study period. The age-groups of the pediatric were divided into neonates (birth to 1 month), infants (1 month to 2 years) and children (2 to 12 years). We used two types of variables including socio-demographic characteristics and clinical characteristics and current medical history to evaluate the prescribed drug (brand name, generic name, indication, dose, frequency and route of administration). We excluded the prescriptions containing a drug that did not require a license. When required, additional data were extracted from wards nurses and prescribing healthcare practitioners regarding drug information during hospitalization. The data included age, gender, weight, and clinical diagnosis with the details of prescribed antibiotics (formulation, dose, dosage, route of administration and indication for use).

Off-label antibiotic use was evaluated on the basis of data mentioned in British National Formulary and on the leaflet of the product as well as information which could be obtained from pharmaceutical companies [22]. The off-label use was defined as the drug which was

administered for an unapproved indication or in an unapproved age group, dose, frequency and route of administration [23]. Some drugs were considered off-label with more than one reasons.

### Statistical Analysis

Final data were analyzed using Social Packages for Statistical Sciences (SPSS) version 21.0. The frequencies and percentages were used to indicate the demographic characteristics and drug-related variables.

## Results

The number of patients hospitalized during the study period was 1,810. Of 1,810 admissions, 1795 patients received antibiotics. The study involved a total of 451 patients (326 patients admitted in the medical ward and 125 patients in ICUs) who received at least one unlicensed/off-label drug. Majority of the patients were males (n = 298, 66.1%) (Table 1). The extent of off-label prescribing was higher in infants (42.1%) than in neonates and children  $\geq 2$  years. Antibiotics were predominantly prescribed for the treatment of infections (n = 311, 69.0%). A total of 279 patients received antibiotics for community-acquired infection (CAP) and 31 patients for hospital-acquired infections. About 122 patients received antibiotics for medical prophylaxis, followed by surgical prophylaxis (n = 15, 3.3%). Majority of the patients suffered from respiratory tract infections (n = 223, 49.4%), skin and soft tissue infections (n = 53, 11.8%), gastrointestinal tract infections (n = 56, 12.4%) and other infections (n = 46, 10.2%) (Table 1).

Off-label antibiotics prescribed to pediatrics were described in Table 2. Co-amoxiclav (n = 190, 42.1%) was the most frequently off-label prescribed antibiotic

followed by ceftriaxone (n = 162, 35.9%), ciprofloxacin (n = 70, 15.5%), meropenem (n = 30, 6.7%), piperacillin and tazobactam (n = 21, 4.7%), amikacin (n = 13, 2.9%) and vancomycin (n = 4, 0.9%). The distribution of antibiotics by age groups showed that ciprofloxacin (n = 45, 39.5%) were prescribed mainly in neonates, co-amoxiclav (n = 102, 53.7%) in infants and ceftriaxone in children  $\geq 2$  years. The most frequent (95.3%) cause of prescribing off-label antibiotic was due to the administration of an unregistered dose, followed by different age groups (n = 26, 5.8%), indication (n = 22, 4.9%), unlicensed drug (n = 29, 6.4%) and frequency (n = 7, 1.5%).

## Discussion

Over the past few years, multisite studies have been carried out that clearly indicated the frequent use of the off-label antibiotics in pediatrics, particularly among neonates [24,25]. To the best of our knowledge, this is the first study conducted in Pakistan to assess the nature and magnitude of off-label antibiotics use in overall pediatric population. Based on our findings, the overall prevalence of the prescription of off-label drug was 25.1%, which was similar to that in Germany (36%) and Netherlands (44%) [25,26]. The off-label/unlicensed drug was frequently prescribed to males than females. Our findings reported that the higher prevalence rate of the prescribed off-label drug was observed among infants. However, several studies reported that the magnitude of off-label prescribing was accounted to be between 15.0% and 60.0% in infants and 90.0% in neonates [1,27,28].

Co-amoxiclav, ceftriaxone, and ciprofloxacin were frequently used as an off-label/unlicensed drug. This finding was different when compared to the other study

**Table 2.** Antibiotics used for off-label/unlicensed indications.

Variables	Neonates (n = 114)	Infants (n = 190)	Child (n = 147)	Total
<b>Drug prescribed as off label</b>				
Co-amoxiclav	40 (35.0%)	102 (53.7%)	48 (32.6%)	190 (42.1%)
Ceftriaxone	10 (8.7%)	85 (44.7%)	67 (45.5%)	162 (35.9%)
Ciprofloxacin	45 (39.5%)	5 (2.6%)	20 (13.6%)	70 (15.5%)
Meropenam	20 (17.5%)	5 (2.6%)	5 (3.4%)	30 (6.7%)
Piperacillin and Tazobactam	0	6 (3.2%)	15 (10.2%)	21 (4.7%)
Amikacin	10 (8.8%)	1 (0.5%)	2 (1.4%)	13 (2.9%)
Vancomycin	0	2 (1.1%)	2 (1.4%)	4 (0.9%)
<b>Condition of prescribing off label drug</b>				
Dose	96 (84.2%)	189 (99.5%)	145 (98.6%)	430 (95.3%)
Indication	10 (8.8%)	4 (2.10%)	8 (5.4%)	22 (4.9%)
Age	17 (15%)	3 (1.6%)	6 (4.1%)	26 (5.8%)
Unlicensed in children	20 (17.5%)	3 (1.5%)	6 (4.1%)	29 (6.4%)
Frequency	4 (3.5%)	2 (1.1%)	1 (0.7%)	7 (1.5%)

conducted in Ethiopia which reported ceftriaxone, cloxacillin, and gentamicin as the commonly used off-label antibiotic used [29]. Ciprofloxacin was frequently used as the off-label drug among neonates. Quinolones are not recommended for use in pediatrics but several studies on quinolones have clearly revealed that they can be administered to pediatrics with maximum therapeutic effect and minimum or no significant toxicity [30,31]. The most frequent condition of prescribing off-label antibiotic use in our study was inappropriate dosing. Several studies reported similar outputs conducted in different regions of the world [1,12,25,32]. Inappropriate dosing is of major concern for antibiotic use regarding the development of resistance [33,34]. If the drug is under dosed, there may be no therapeutic effect but may cause a risk of adverse drug reactions.

Despite the widespread use of the off-label/unlicensed drug, the significance of drug safety and efficacy in children has been acquiring less attention in the developing countries [27,29,35]. Lack of harmonization between authorized drug label and pediatric documentation in evidence-based literature which affects the prescribing behavior of physicians could be the main reason of the use of off-label/unlicensed drug in the pediatric population [29]. Expert groups fully dedicated to pediatric drug treatment are required within the administration of the drug and therapeutic committees, which could formulate new data and deliver the relevant data to prescribing physicians [29]. World Health Organization (WHO) adopted “Better Medicine For Children” that not only highlights its major concern on off-label/unlicensed drug but also improves drug safety and efficacy in the pediatric population [36]. In order to ensure quality information on safety and efficacy for the various pediatric drugs, the strict drug approval procedure should be followed.

The current study has some limitations because it was carried out only in one hospital and the sample size was relatively small. Therefore, the results evaluated concerning off-label antibiotic use may not be representative of patients outside the hospital. Lack of pharmacist role in Pakistan, may be a reason for the irrational use of antibiotics. Therefore, there is a need to evaluate the situation at general practitioners (GP) level.

## Conclusion

Despite the frequent use of the off-label/unlicensed drug in pediatrics, our findings demonstrate that off-label prescribing accounted for 25.1%. The main

contributor to off-label prescribing is an inappropriate dose which may predispose the children to the occurrence of side effects without a therapeutic effect and promotes the development of antibiotic resistance. Implementation of the evidence-based approach in prescribing antibiotics by formulating more quality literature on the safety and efficacy of off-label drug would improve the appropriate use of antibiotics in the pediatric population. More studies are required to investigate the situation at a national level. Further evaluation of public and economic healthcare outcomes of off-label prescribing and determinants influencing drug choice is required.

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## References

1. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, Knoepfel C, Seyberth H, Pandolfini C, Raffaelli MP (2000) Survey of unlicensed and off label drug use in paediatric wards in European countries. *BMJ* 320: 79-82.
2. Turner S, Longworth A, Nunn AJ, Choonara I (1998) Unlicensed and off label drug use in paediatric wards: prospective study. *BMJ* 316: 343-345.
3. Bücheler R, Schwab M, Mörike K, Kalchthaler B, Mohr H, Schröder H, Schwoerer P, Gleiter CH (2002) Off label prescribing to children in primary care in Germany: retrospective cohort study. *BMJ* 324: 1311-1312.
4. Pandolfini C, Campi R, Clavenna A, Cazzato T, Bonati M (2005) Italian paediatricians and off-label prescriptions: Loyal to regulatory or guideline standards? *Acta Paediatrica* 94: 753-757.
5. Tefera Y G, Gebresillassie BM, Mekuria AB, Abebe TB, Erku DA, Seid N, Beshir HB (2017) Off-label drug use in hospitalized children: a prospective observational study at Gondar University Referral Hospital, Northwestern Ethiopia. *Pharmacol Res Perspect* 5: e00304.
6. Clarkson A, Choonara I (2002) Surveillance for fatal suspected adverse drug reactions in the UK. *Arch Dis Child* 87: 462-466.
7. Choonara I, Conroy S (2002) Unlicensed and Off-Label Drug Use in Children. *Drug Saf* 25: 1-5.
8. Turner S, Nunn A, Fielding K, Choonara I (1999) Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatrica* 88: 965-968.
9. Johann-Liang R, Wyeth J, Chen M, Cope J U (2009) Pediatric drug surveillance and the Food and Drug Administration's adverse event reporting system: an overview of reports, 2003–2007. *Pharmacoepidemiol Drug Saf* 18: 24-27.
10. Choonara I, Dunne J (1998) Licensing of medicines. *Arch Dis Child* 78: 402-403.
11. Riordan F A I (2000) Use of unlabelled and off licence drugs in children: Use of unlicensed drugs may be recommended in guidelines. *BMJ* 320: 1210.

12. Porta A, Esposito S, Menson E, Spyridis N, Tsolia M, Sharland M, Principi N (2010) Off-label antibiotic use in children in three European countries. *Euro J Clin Pharmacol* 66: 919-927.
13. Saleem Z, Hassali MA (2019) Travellers take heed: Outbreak of extensively drug resistant (XDR) typhoid fever in Pakistan and a warning from the US CDC. *Travel Med Infect Dis* 27: 127.
14. Sharif SI, Nassar AH, Al-Hamami FK, Hassanein MM, Elmi AH, Sharif RS (2015) Trends of pediatric outpatients prescribing in Umm Al Quwain, United Arab Emirates. *J Pharm Pharmacol* 6: 9.
15. Silverman WA, Andersen DH, Blanc WA, Crozier DN (1956) A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. *Pediatr* 18: 614-625.
16. Dunn PM (1964) The possible relationship between the maternal administration of sulphamethoxypyridazine and hyperbilirubinaemia in the newborn. *Int J Gynaecol Obstet* 71: 128-131.
17. Choonara I, Gill A, Nunn A (1996) Drug toxicity and surveillance in children. *Br J Clin Pharmacol* 42: 407-410.
18. Sutherland JM (1959) Fatal cardiovascular collapse of infants receiving large amounts of chloramphenicol. *AMA J Dis Child* 97: 761-767.
19. Weiss CF, Glazko AJ, Weston JK (1960) Chloramphenicol in the newborn infant: a physiologic explanation of its toxicity when given in excessive doses. *N Engl J Med* 262: 787-794.
20. Saleem Z, Hassali MA, Hashmi FK (2018) Pakistan's national action plan for antimicrobial resistance: translating ideas into reality. *Lancet Infect Dis* 18: 1066-1067.
21. Saleem Z, Hassali MA, Versporten A, Godman B, Hashmi FK, Goossens H, Saleem F (2019) A multicenter point prevalence survey of antibiotic use in Punjab, Pakistan: findings and implications. *Expert Rev Anti Infect Ther* 17: 285-293.
22. Royal Pharmaceutical Society of Great Britain. (2017). British national formulary for children, London, Pharmaceutical Press 281-402.
23. Santos DB, Clavenna A, Bonati M, Coelho HLL (2008) Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil. *Euro J Clin Pharmacol* 64: 1111.
24. Mukattash T, Trew K, Hawwa AF, McElnay JC (2012) Children's views on unlicensed/off-label paediatric prescribing and paediatric clinical trials. *Euro J Clin Pharmacol* 68: 141-148.
25. Knopf H, Wolf I-K, Sarganas G, Zhuang W, Rascher W, Neubert A (2013) Off-label medicine use in children and adolescents: results of a population-based study in Germany. *BMC public health* 13: 631.
26. Linden VD, Bakker E, Eland I, Sticker B, Anker J (2002) Unlicensed and off-label drug use in a paediatric ward of a general hospital in the Netherlands. *Euro J Clin Pharmacol* 58: 293-297.
27. Bavdekar S, Sadawarte PA, Gogtay NJ, Jain SS, Jadhav S (2009) Off-label drug use in a Pediatric Intensive Care Unit. *Ind J Pediatr* 76: 1113-1118.
28. Cuzzolin L, Atzei A, Fanos V (2006) Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Expert Opin Drug Saf* 5: 703-718.
29. Tefera YG, Gebresillassie BM, Mekuria AB, Abebe TB, Erku DA, Seid N, Beshir HB (2017) Off-label drug use in hospitalized children: a prospective observational study at Gondar University Referral Hospital, Northwestern Ethiopia. *Pharmacol Res Perspect* 5: e00304-e00304.
30. Mandell LA, Low DE, Peterson LR, Hooper D, Klugman KP, Wise R, Schaad UB, Courvalin P (2002) The battle against emerging antibiotic resistance: Should fluoroquinolones be used to treat children? *Clin Infect Dis* 35: 721-727.
31. Schaad UB (2005) Fluoroquinolone antibiotics in infants and children. *Infect Dis Clin North Am* 19: 617-628.
32. Ekins-Daukes S, Helms PJ, Simpson CR, Taylor MW, McLay JS (2004) Off-label prescribing to children in primary care: retrospective observational study. *Euro J Clin Pharmacol* 60: 349-353.
33. McDonnell NG (2008) Antibiotic overuse: the influence of social norms. *J Am Coll Surg* 207: 265.
34. Dryden M, Johnson AP, Ashiru-Oredope D, Sharland M (2011) Using antibiotics responsibly: right drug, right time, right dose, right duration. *J Antimicrob Chemother* 66: 2441-2443.
35. Aamir M, Khan JA, Shakeel F, Shareef R, Shah N (2018) Drug utilization in neonatal setting of Pakistan: focus on unlicensed and off label drug prescribing. *BMC Pediatr* 18: 242-242.
36. Hoppu K, Anabwani G, Garcia-Bournissen F, Gazarian M, Kearns GL, Nakamura H, Peterson RG, Sri Ranganathan S, de Wildt SN (2012) The status of paediatric medicines initiatives around the world—what has happened and what has not? *Euro J Clin Pharmacol* 68: 1-10.

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