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RESEARCH ARTICLE

Off-label antibiotic use among paediatric in-patients: a mixed-method prospective study at a tertiary hospital in southwestern Uganda

Bonniface Obura[1,2] · **Paul E. Alele**[1] · **Celestino Obua**[1]

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Abstract

Background The off-label use of drugs to treat children is a global practice attributed to the traditional exclusion of children from clinical trials mainly due to practical and ethical reasons. Off-label drug use carries both benefits and risks, but data regarding this use pattern are scanty in sub-Saharan Africa. *Objective* To determine the incidence and predictors of off-label antibiotic use in children less than 5 years admitted at Mbarara Regional Referral Hospital (MRRH) in southwestern Uganda. *Setting* A prospective drug utilisation study was conducted among in-patients at the Paediatric Ward of MRRH from May to June 2019. *Methods* Clinical records and treatment notes of all children aged 0 to 59 months with at least one antibiotic prescription during the admission period were reviewed and included for data collection. Key informant interviews were conducted with physicians attending to patients in the Paediatric Ward. *Main outcome measure* Off-label use and potential predictors of off-label antibiotic use. *Results* Of 427 children admitted to the Paediatric Ward, 165 (38.6%) received 366 antibiotic prescriptions. However, 359 prescriptions belonging to 162 patients were analyzed. Off-label prescriptions occurred in 18.9% (95% CI: 14.9–23.0) of antibiotic prescriptions. Two categories of off-label prescriptions were found: off-label frequency of administration (n = 55, 80.9%), and off-label doses (n = 13, 19.1%). Ceftriaxone was the most common antibiotic prescribed at off-label doses, (n = 6, 8.8%) while ampicillin was the most common antibiotic prescribed with an off-label frequency of administration, (n = 39, 57.3%). Infants (1–23 months) received the majority (47.1%) of off-label antibiotic prescriptions; neonates (0–28 days) received 27.9%, and children (24–59 months) received 25% of the prescriptions. Controlling for sex and disease severity, age category remained significantly associated with off-label antibiotic use on multivariate analysis. *Conclusion* Off-label frequency of administration was the major category of off-label drug use, while off-label dose was the minor category. Age was a significant factor for off-label antibiotic prescription, with infants receiving the highest number of off-label prescriptions. Attending physicians identified several justifiable circumstances that warrant off-label antibiotic use and support emerging "well-founded" off-label uses of antibiotics in different paediatric age groups.

Keywords Antibiotics · Evidence-based pharmacotherapy · Infants · Neonates · Prescribing · "Well-founded" off-label use

Impacts on practice

- Paediatric patients between 1 month and 5 years were more likely to receive off-label antibiotic prescriptions than neonates; pharmacists and physicians, therefore, ought to review and monitor these patients routinely to avoid ill-founded off-label prescriptions and the emergence of adverse effects among those patients.
- Well-founded off-label antibiotic use in paediatric practice is common and considered appropriate in low-resource settings where the emergence of evidence from clinical practice supports the safety and effectiveness of the drugs.

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✉ Paul E. Alele
paulalele@must.ac.ug

[1] Department of Pharmacology and Therapeutics, Mbarara University of Science and Technology, Mbarara, Uganda

[2] Department of Pharmacology, Lira University, Lira, Uganda

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- Physicians' decision-making regarding off-label prescribing is influenced by treatment failure with recommended conventional therapies in children diagnosed with severe illness such as pneumonia that does not respond to intravenous treatments with traditional combinations such as ampicillin and gentamicin.
- Prescribers should carefully weigh risks versus benefits of off-label antibiotic use, especially where insufficient data are available regarding the susceptibility of the causative organisms to the drug being used.

Introduction

The off-label use of drugs to treat children is common globally and has largely been attributed to the traditional exclusion of children from clinical trials mainly due to practical and ethical reasons [1–5]. Off-label drug use refers to the use of a marketed drug outside the terms of the market authorization regarding the recommended therapeutic indication, dose, frequency, patient age, and the route of administration [4, 6]. Approval of a new drug for clinical use requires that the manufacturer submit a new drug application to drug regulatory authorities to enable registration (market authorization) of the new product [7]. In Uganda, the National Drug Policy and Authority Act Cap 206 governs how medicinal products and medical devices are licensed and sold. When a manufacturer of a pharmaceutical product seeks a marketing license for a drug, it must demonstrate through appropriate in vitro tests, in vivo tests and clinical trials, that the drug is safe and effective for the intended use [7]. The application dossier for marketing authorization contains information about the drug's safety, effectiveness, quality, details of the manufacturing process, packaging, and labelling.

The regulatory body in Uganda is the National Drug Authority, which reviews the application and scientifically evaluates the drug for purposes of ascertaining its efficacy, safety and quality. Formal approval is granted once the Authority is satisfied that the drug in respect of which the application is made has not been registered before and that the use of the drug is likely to prove beneficial [7, 8]. Henceforth, the manufacturer of a registered drug is allowed to market and sell the drug in the country for its approved use(s). A new drug application dossier also details a summary of product characteristics (SmPC) and product labels that spell out information for healthcare professionals and consumers on how to use the finished pharmaceutical product safely and effectively and specifically spells out the indications for which the manufacturer has applied and received approval. [7].

Off-label drug use does not intrinsically imply improper, illegal, investigational or contraindicated use, but rather implies that no evidence or insufficient evidence has been provided to regulatory authorities to allow inclusion for particular use in the product label [9]. While off-label prescribing allows innovativeness by physicians to exploit a drug's potential effectiveness in circumstances such as treatment failure to approved conventional therapies, and for rare disease conditions for which there exist no approved therapies, potentially undesirable effects of off-label use also exist [10]. These undesirable effects include increased risk of adverse reactions, increased health care costs, and liability for pharmaceutical manufacturers and health care practitioners [9–12]. Moreover, treatment in hospitals in Uganda is not fully covered by public funding and the cost to parents may be a factor in the treatment that children receive. For instance, in some cases, parents may not afford to pay for tests such as culture and sensitivity testing that may be necessary for appropriate prescribing.

Aim of the study

Despite the considerable debate on off-label antibiotic use in children globally, few studies in sub-Saharan Africa have evaluated off-label antibiotic use although antibiotics remain the most commonly prescribed drugs in paediatrics [13–16]. In Uganda and much of sub-Saharan Africa, hardly any data exist on the extent of off-label use of antibiotics in children. The current study, therefore, sought to determine the incidence and predictors of off-label antibiotic use in children less than 5 years hospitalized at a tertiary hospital in Uganda.

Ethics approval

This study was approved by the Research Ethics Committee of Mbarara University of Science and Technology (approval number: 10/03-19). Written informed consent was obtained before conducting the interviews. Permission to access data from the patient files was obtained from the Hospital administration and data from patient medical records were confidentially collected and deidentified.

Methods

Study design, setting and study population

A prospective study on antibiotic utilisation was conducted among hospitalized patients aged 0 to 59 months at the Paediatric Ward of Mbarara Regional Referral Hospital (MRRH), a 600-bed government hospital affiliated to Mbarara University of Science and Technology. The hospital serves as a regional referral centre for southwestern Uganda and paediatric clinical services are centered in the 70-bed general children's ward, as well as in the specialized units for

neonatal care, critical care, and nutritional therapy. The Paediatric Ward admits approximately 5000 patients per year.

Data collection and processing

Patient clinical records and treatment notes of all children aged 0 to 59 months admitted during May and June 2019 in the Paediatric Ward at MRRH were reviewed at study initiation and daily during the study period. Children with at least one antibiotic prescription were included for data collection of baseline data, demographics, clinical conditions, and prescriptions involving antibiotic treatments. Thereafter, daily assessments of the patients' clinical notes and treatment sheets were conducted until discharge, death, or loss to follow-up. Both baseline and daily follow-up patient data were collected on a data collection form and included patient demographics (age, sex, and weight), clinical characteristics (diagnosis and disease severity), and details of the prescribed antibiotic medication. Data collection continued for 6 weeks, between May and June 2019.

The paediatric patients were grouped into 3 categories according to age: neonates (0–28 days old), infants (28 days–23 months old), and children (24–59 months old) using the European Medicines Agency (EMA) criteria for the classification of age. Categorization according to age was done because the paediatric population represents a continuum of growth and development with significant changes in body composition occurring in a particular growth phase. Developmental changes in physiology and, consequently, in pharmacology account for substantial individual variation in drug response and influence the efficacy, toxicity, and dosing regimen of medicines used in children [17].

Off-label antibiotic use was determined by comparing the actual use with the stipulated intended use(s) as stated in the SmPC and the Basic Paediatric Protocol of Uganda, and the condition for which it was prescribed [6, 16]. The Basic Paediatric Protocol for Uganda is a guideline for paediatric clinical practice taught in Ugandan medical schools as the standard of paediatric inpatient care in the country. The Protocol, which was developed after a consensus meeting between the Uganda Ministry of Health, clinical researchers, and Ugandan medical schools, is widely accepted in hospitals and was adapted from a World Health Organization publication for children [18]. To ensure valid determination of on- or off-label status of a prescription, two members of the research team independently categorized each prescription. In the event of any disagreements between the researchers, in determination of on- or off-label status of a prescription, these were discussed with the research supervisor until a consensus was reached on the appropriate category.

Patient age, sex, and disease severity were analyzed as potential predictors of off-label use because these are variables taken into consideration during routine drug prescribing. Neonates and severely ill patients may be less likely to receive off-label prescriptions owing to higher risks of adverse events [17, 19]. The difference in pharmacokinetic and pharmacodynamic parameters between males and females may influence their chances of receiving off-label antibiotic prescriptions [20, 21].

We conducted ten semi-structured key informant (KI) interviews with the physicians attending to patients at the Paediatric Ward who comprised one paediatric specialist, five general practitioners, and four intern doctors (in total 4 women and 6 men) to gain possible explanations for the off-label use of antibiotics. The KI interviews were based on an interview guide with open-ended questions. We used convenience sampling to select physicians for the interview based on their areas of specialization. The physicians were asked for their definitions of off-label prescribing and whether they perceived the practice to be common in paediatrics. This was followed by a discussion of their knowledge and experience with prescribing antibiotics off-label. Interviews were conducted until data saturation occurred, at which point no new themes emerged with subsequent interviews during data collection, and no new participants were interviewed [22, 23]. To minimize bias in the information collected from the physicians during the interview, the physicians were not identified with their prescription records.

Statistical analysis

Descriptive statistics were used to describe patient demographics and clinical characteristics and to report the incidence of off-label antibiotic use. Univariate and multivariate logistic regression analyses were used to determine potential predictors of off-label antibiotic use. Patient age, sex, and disease severity were analyzed as potential predictors of off-label use. Unadjusted odds ratios with their corresponding 95% CI were reported following univariate analysis. All factors with p value < 0.2 at univariate analysis and those with a biological plausibility to influence prescribing were considered in the multivariate analysis. Adjusted odds ratios with their corresponding 95% CI were reported and a variable was considered significant if it had a p-value < 0.05. Data were entered into EpiData (version 4) and analyses performed using STATA (version 12). Qualitative data from interviews were analyzed using thematic content analysis. This involved interpretation of the content of written notes and interview transcripts systematically through the process of coding and identifying emergent themes [24].

Results

Study population, demographic and clinical characteristics

In the 2 months of the study, 427 children were admitted to the Paediatric Ward. Of these, 165 patients (38.6%) received 366 antibiotic prescriptions; however, 7 prescriptions belonging to 3 patients were excluded from analysis due to non-receipt of the prescribed antibiotics, leaving 162 patients and 359 antibiotic prescriptions in the final analysis and an average of 2.2 antibiotics prescribed per patient (Table 1). Of the children whose prescriptions were analyzed the majority were males (n = 87, 53.7%). The majority of patients were neonates (43.8%) followed by infants (32.7%) and then children (23.5%).

The most common patient diagnosis was pneumonia (n = 68, 42%), followed by neonatal sepsis (n = 55, 34%), with few cases of bronchiolitis (n = 6, 3.7%), septicemia (n = 6, 3.7%), cellulitis (n = 5, 3.1%), and meningitis (n = 5, 3.1%). The other diagnoses (n = 17, 10.4%) comprised congenital syphilis, upper respiratory tract infections, gastroenteritis, otitis media, soft tissue injury, and diarrhea.

The most commonly prescribed antibiotics were gentamicin (n = 151, 42.1%) and ampicillin (n = 111, 30.9%) for parenteral administration (Fig. 1).

Off-label antibiotic prescriptions

Off-label prescriptions occurred in 18.9% (95% CI 14.9–23.0) of antibiotic prescriptions. Two categories of off-label prescriptions were found; the majority was the off-label frequency of administration (n = 55, 80.9%), and the other was off-label doses (n = 13, 19.1%). Ceftriaxone was the most common antibiotic prescribed at off-label doses, (n = 6, 8.8%) while ampicillin was the most common antibiotic prescribed with the off-label frequency of administration, (n = 39, 57.3%), (Table 2). The reasons for off-label classification were lower or higher doses or frequency of administration than recommended.

Off-label prescribing in age categories

Infants (1–23 months) received the majority (47.1%) of off-label antibiotic prescriptions; neonates (0–28 days) received 27.9%, and children (24–59 months) received 25% of the prescriptions. Controlling for sex and disease severity, the age category remained significantly associated with off-label antibiotic use on multivariate regression analysis. Infants (AOR = 3.11, 95% CI 1.39–6.99) and children (AOR = 2.5, 95% CI 1.10–6.11) were significantly more likely to receive off-label antibiotics than neonates (Table 3).

Table 1 Distribution of patients and prescriptions in the different age categories

Age category	Age	Males	Females	Total N (%)	Prescriptions N (%)
Neonates	0–28 days	41	30	71 (43.8)	155 (43.2)
Infants	1–23 months	26	27	53 (32.7)	130 (36.2)
Children	24–59 months	20	18	38 (23.5)	74 (20.6)
Total	0–59 months	87	75	162 (100)	359[a] (100)

Male neonates received the majority of prescriptions, while female children received the least

[a]An average of 2.2 antibiotics per patient

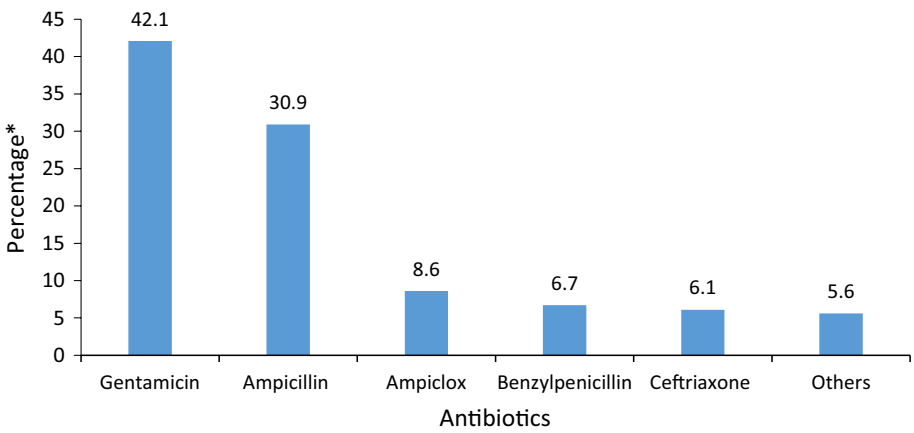

Fig. 1 Commonly prescribed antibiotics. *Percentage of antibiotics prescribed. The other prescribed antibiotics included: metronidazole, amoxicillin, cloxacillin, and erythromycin

Table 2 Categories of off-label antibiotic prescriptions

Off-label category	Prescribed antibiotic[a]	Number of prescriptions, n (%) 68 (18.9)
Off-label dose	Ceftriaxone	6 (8.8)
	Ampicillin-cloxacillin	4 (5.9)
	Gentamicin	1 (1.5)
	Benzylpenicillin	1 (1.5)
	Metronidazole	1 (1.5)
Off-label frequency of administration	Ampicillin	39 (57.3)
	Ampicillin-cloxacillin	9 (13.2)
	Metronidazole	5 (7.4)
	Cloxacillin	2 (2.9)

[a]Antibiotics prescribed at off-label dose or frequency of administration

Table 3 Bivariate and multivariate logistic regressions with off-label as a dependent variable

Explanatory variable	COR (95% CI)	AOR (95% CI)	*p*-value*
Age category			
0–28 days	Ref.	Ref.	
1–23 months	3.57 (1.67–7.75)	3.11 (1.39–6.98)	0.006
24–59 months	2.78 (1.19–6.49)	2.59 (1.09–6.10)	0.03
Sex			
Male	Ref.	Ref.	0.966
Female	1.14 (0.60–2.16)	1.01 (0.52–1.98)	
Disease severity			
No	Ref.	Ref.	0.256
Yes	2.00 (1.04–3.88)	1.50 (0.74–3.04)	

COR crude odds ratio, *AOR* adjusted odds ratio, *CI* confidence interval, *ref* referent group

*Reported *p*-values correspond to the AOR

**Significant *p*-values; $p < 0.05$

Key informant interviews

Three main themes emerged from the interviews: knowledge of off-label use, justification of off-label use, and risks of off-label antibiotic use.

Knowledge of off-label use

Physicians were generally knowledgeable about the term "off-label" antibiotic use. Most of the respondents had heard the term "off-label" use and attempted to define the term:

> "Off-label use is when a drug is licensed to treat a particular disease but then it is being used to treat other diseases…." (Interviewee # 07)

> "Antibiotics are abused… they are prescribed in conditions where they are not meant to be used… in viral upper respiratory infections…" (Interviewee # 06)

However, some respondents considered the term "off-label" antibiotic use as being synonymous with "irrational" antibiotic use.

Justification of off-label use

The majority of respondents acknowledged that under certain circumstances, off-label use of a drug (antibiotic) may be used as a treatment option for a patient. Three such circumstances appeared prominently: in the event of treatment failure with recommended conventional therapies, in treatment of patients with rare disease conditions for which no formal approved therapy is available, and in the event of emerging evidence to support the off-label use of a particular antibiotic. Treatment failure seems to present a real nightmare for the attending physician:

> "In desperate times people do things, when you have used all what is supposed to be used but the patient isn't improving" (Interviewee # 07)

Some physicians also considered the severity of the patient's condition as reason enough to prescribe an antibiotic off-label.

> "You have a kid who is severely ill, you want something that is going to clear the micro-organism fast…. instead of starting with ampicillin…for example, azithromycin lacks sufficient information for use in children less than 6 months but we use it (in that group) … with good results" (Interviewee # 04)

Physicians' clinical experience with the use of particular antibiotics and the opinions of senior colleagues also played a vital role in the off-label use of antibiotics. The junior practitioners relied heavily on the opinions and expertise of their senior colleagues in decision making regarding off-label use of drugs. If a senior consultant successfully used a drug off-label, the junior practitioners were more likely to adopt that particular off-label use during routine clinical practice. Expert opinion constituted a major source of information for general practitioners on potential off-label uses of antibiotics.

> "You can prescribe a drug (off-label) based on how you have used it sometimes in another patient." (Interviewee # 01)

Risks of off-label antibiotic use

All respondents agreed that off-label use of antibiotics poses significant risks and challenges in clinical practice. Participants expressed worries about the potential toxicity that could arise from the use of antibiotics in age groups where there is a lack of documentation about the safety profile of the drug.

> "It (off-label use) strictly has adverse effects…" (Interviewee # 03)

Off-label antibiotic use was also viewed as a potential promoter of antibiotic resistance especially antibiotic use for indications where no sufficient data is available about the susceptibility of the causative organisms to the antibiotic being used.

Discussion

The off-label use of antibiotics in children has been an area of significant clinical interest given the emergent antimicrobial resistance patterns and lack of sufficient data from clinical trials to guide rational antibiotic use in children. Despite considerable research on off-label antibiotic use in children in well-resourced countries globally, data on off-label prescribing are scant in developing countries like Uganda. The current study aimed at providing data to support rational antibiotic use in children by determining the incidence and predictors of off-label antibiotic use in children less than 5 years at a tertiary hospital in southwestern Uganda.

The incidence of off-label antibiotic use (18.9%) among in-patient children reported in our study lies within the range reported by previous studies. A systematic literature review on the frequency of off-label antibiotic use in clinical practice reported the percentages of off-label prescriptions of antibiotics to vary from 1 to 94% among children [25]. This wide variation in percentages was attributed to the inclusion of studies from different countries and continents where differences in licensing of the drugs prevail, and to the differences in age groups of the paediatric populations of each of the included studies.

Gentamicin and ampicillin were the most frequently prescribed antibiotics in the current study, presumably because the majority of the patients had a diagnosis of either pneumonia or neonatal sepsis. Current Uganda Clinical Guidelines for Paediatrics (Basic Paediatric Protocol) recommend a combination of intravenous ampicillin plus gentamicin as first-line treatment for severe pneumonia. Ampicillin and metronidazole were commonly prescribed at an off-label frequency while ceftriaxone was the most commonly prescribed antibiotic at off-label doses, a finding consistent with previous studies [6, 16, 26]. A recent study reported ceftriaxone as the most commonly prescribed off-label antibiotic at a frequency of 20.7%, followed by cloxacillin (10.6%) [16]. Similar results were reported by another study that also found ceftriaxone to be the most frequently used antibiotic at an off-label dose with a frequency of 27% [6]. Ampicillin/cloxacillin combination was prescribed at both off-label dosage and frequency in the current study. The possible explanations for the observed pattern of off-label use of penicillins and cephalosporins lie in the extensive clinical experience with these classes of antibiotics coupled with their broad-spectrum, few adverse effects, and relatively low price [25].

The categories of off-label antibiotic use were due to lower or higher doses (19.1%) and frequency of administration (80.9%). In the current study, higher than recommended doses ($\geq$ 100 mg/kg/day vs. 80 mg/kg/day) of ceftriaxone were administered in children with severe pneumonia not responding to treatment with the combination of ampicillin and gentamicin. Similar results were reported in follow-up studies of drug utilisation in Brazil and the Netherlands [27, 28].

We found the age category to be significantly associated with off-label antibiotic use, a finding consistent with previous studies, which showed a relationship between off-label drug prescription and age [6, 16]. Infants and children aged 24–59 months were at significantly increased risk of receiving an off-label antibiotic prescription compared to neonates. The increased risk of infants receiving off-label antibiotic prescriptions could have resulted from the fact that the majority of infants in the current study presented with severe cases of infectious diseases.

This study also highlighted circumstances under which physicians considered an off-label use of antibiotics as an appropriate treatment option for a patient. The emergence of evidence from clinical practice that supports the safety, efficacy, and effectiveness of off-label use of antibiotics played a critical role in physicians' decision-making regarding off-label prescribing. Treatment failure with recommended conventional therapies inspired physicians to seek for alternative options to treat patients even if it meant prescribing an off-label medication. Children diagnosed with severe pneumonia and did not respond to intravenous treatment with a combination of ampicillin and gentamicin had a switch in treatment to high dose, $\geq$ 100 mg/kg/day ceftriaxone.

Notably also, off-label prescribing by the physicians interviewed was guided by their clinical experience in using the drugs recommended in the paediatric clinical practice guideline. Because of the severity of illness in some children, physicians prescribed drugs based on prior success with those drugs, and did not perform culture and sensitivity testing in the children that we enrolled in this study. In addition, the Paediatric Ward of MRRH, like other wards in this tertiary hospital, is a publicly funded health facility and

many parents of severely ill children are unable to afford costly, but necessary tests, forcing clinicians to often prescribing treatment empirically.

However, even in such justifiable situations, attempts should be made to distinguish between "well-founded" and "ill-founded" off-label use. In contrast to "ill-founded", "well-founded" off-label prescriptions are recommended in clinical practice guidelines or pharmacotherapeutic handbooks based on a systematic examination of the published literature [17, 29]. The efficacy of "ill-founded" off-label prescription is often questionable and adverse drug reactions and unjustified healthcare costs may result [29].

Our study had some limitations. First, we conducted this study at only one tertiary hospital in southwestern Uganda. Nevertheless, the hospital is a major referral and training institution that receives patients from a wide and diverse geographical area. A nationwide multicentre study, possibly involving both smaller and larger health facilities is warranted to obtain more generalizable results that can inform current practice and promote evidence-based and rational antibiotic use. Second, we did not examine institutional factors, such as the availability of first-line drugs in the hospital pharmacy that may have contributed to off-label prescribing. As recommended by the Uganda Current Clinical Guidelines for Paediatrics, however, the first-line antibiotics for treating conditions such as severe pneumonia in children were available to the prescribing doctors at the time of the study.

Conclusion

Age was a significant factor for off-label antibiotic prescribing, a practice that was common among the paediatric inpatients studied. Sufficient data from clinical trials should be made accessible to support emerging "well-founded" off-label uses of antibiotics in different paediatric age groups.

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Conflicts of interest The authors declare no competing interests.

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