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RESEARCH ARTICLE

High prevalence of off-label and unlicensed paediatric prescribing in a hospital in Indonesia during the period Aug.—Oct. 2014

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Abstract

Background

Data on off-label and unlicensed prescribing in children in Indonesia is limited. The aims of this study were to determine the prevalence of off-label and unlicensed prescribing for paediatric patients in a public hospital, Indonesia.

Method

A retrospective cross-sectional study of 200 randomly selected paediatric patients admitted to hospital between August and October 2014, collected patient details and all drugs prescribed. Licensed drugs were classified as off-label if there was a non-compliance with the Product Information for age, weight, indication, dose, frequency and route of administration, if there was a contraindication, special precautions or not recommended for children. Unlicensed drugs were those not approved for use in Indonesia. The main outcome was the prevalence of off-label or unlicensed prescribing to infants, children and adolescents and the impact of age group on off-label prescribing.

Results

A total of 200 patients received 1961 medicines of which 1807/1961 (92.1%) were licensed and 154/1961 (7.9%) were unlicensed. There were 1403/1961 (71.5%) drugs prescribed off-label. More than half of the total drugs (n = 1066; 54.4%) were administered parenterally. Every patient was prescribed at least one off-label drug. Indication (n = 810; 34.6%) was the most common reason for off-label prescribing. Ranitidine was the most frequent drug prescribed off label. Darplex® (dihydroartemisinin and piperaquine), although manufactured in Indonesia, was unlicensed. There was a significant difference between age group and off-label prescribing in that children were prescribed significantly less off-label drugs (p<0.0003).

Conclusion

This study revealed a high prevalence of off-label and unlicensed drug use in paediatric patients in this hospital, exposing them to drug treatments or regimens that had not been approved by regulatory authorities. The high incidence of invasive parenteral prescribing is of concern for paediatric patients. Incentives are needed to encourage specific drug evaluation in paediatric populations.

Introduction

Many drugs prescribed for paediatric patients have undergone limited scientific evaluation with only an estimated one-third of them having been evaluated in clinical trials in this population.[1] Clinical trials that evaluate drug efficacy, safety and quality are required for registration.[2, 3] However, until recently clinical trials were limited in paediatric populations due to perceived ethical concerns regarding patient risk from research.[1, 4] Consequently, many drugs prescribed for children have been assumed to be safe and effective based on studies performed in adult populations.[5]

Children should not be perceived to be 'small adults' since their pharmacokinetics and pharmacodynamics vary throughout childhood, leaving large uncertainty about the relative efficacy of drugs with respect to adult populations.[6–8] Despite this, many drugs are used 'off-label' or outside their licensed recommendations. The use of off-label medicines refers to the use of a licensed drug at a different dose, indication, age or route of administration from that stated in the approved Product Information (PI).[2, 9] Unlicensed medicines include the reformulation of a licensed drug to provide a modified dosage form considered more suitable for administration but not licensed for paediatric administration, or the specific administration of drugs not licensed in Indonesia.[5]

Despite the introduction of several initiatives to stimulate more research into investigating drug use in children, including the Food and Drug Administration's (FDA's) 'Pharmaceuticals for Children Act' which was last amended in 2007, and the European Medicines Agency's (EMA's) 'European's Union's Paediatric Regulation' in 2007, it has been reported that children are still under-represented with respect to participating in clinical trials and more work is required to ensure safe use of medicines in children.[10] It is estimated that for the last decade, in hospital settings, the use of off-label drugs ranged from 12.2% to 70.6%.[3] Developing countries are most acutely affected[1] since persons aged between zero to 18 years make up a large proportion of the population[11] and are most vulnerable to diseases.[2]

The prescribing of off-label and unlicensed medicines may be unavoidable in situations where there is no alternative and the benefits potentially outweigh the risks.[1, 2] However, there is a potential public health risk for patients as there is uncertainty about efficacy and toxicity, that may result from off-label or unlicensed medicine use.[12] There may also be a risk associated with compounding drugs to produce a new formulation as there is often no safety information on drug interactions, stability or efficacy due to the potential changes in bioavailability.[2]

Indonesia, a developing country, requires drugs to be licensed by the National Agency of Drug and Food Control before they are marketed. In order to be granted a licensing number, a drug has to be evaluated to ensure it meets the requirements of safety, efficacy and quality. Drug licensing has two stages—pre-licensing and licensing.[13] Drugs prescribed or dispensed

off-label are not associated with a statutory responsibility of the prescribing physician or dispensing pharmacist.

The primary aims of this study were to determine the prevalence of off-label and unlicensed prescribing in paediatric patients in a medical ward of a public general hospital in Indonesia and to identify drugs most commonly prescribed off-label and unlicensed.

Materials and methods

Ethical approval

This study was approved by the human research ethics committee at Curtin University (approval number: RHDS-08-15) and by the Director of Abepura's Hospital, Papua, Indonesia (445/82.7/RSUD-Abe/ll/2015). Individual patient consent was not required as de-identified data were collected retrospectively.

Data collection

This cross-sectional study collected medical record data retrospectively from a three-month period 1st August to 31st October 2014 in a paediatric medical ward in Abepura Hospital, Papua, Indonesia, which is a general tertiary hospital. No surgery patients were admitted to the medical ward and all patients were aged from 1 month to 14 years of age.

Of the total 307 patients admitted to the ward over this period, 200 were randomly selected using an on-line randomiser. This number was considered to give a reasonably accurate (±7%) estimate of the prevalence of off-label and unlicensed medicines in this ward. A data collection form was developed and used to collect data from patient medical records. Collected data were transferred to an Excel spread sheet which included information about patient demographics (age, date of birth, weight, gender, length of stay), reasons for admission, past medical history and prescribed drugs (name, indication, strength, dose, frequency, dosage form, route of administration and date of prescription). The following prescribing data were excluded from this study: traditional herbal medicines, standard intravenous replacement solutions, oxygen, total parenteral nutrition and blood products.

Classification

Patients were classified according to the European Medicines Agency (EMA) age classification [14] as newborn infants (0 to 27 days), infants (28 day to 23 months), children (2 to 11 years) and adolescents (12 to 18 years). All drugs were coded using the World Health Organization (WHO) anatomical therapeutic chemical (ATC) classification.[15]

The licensing status of all medicines was determined using the database from the Indonesian National Agency of Drug and Food Control.[16] Drugs with no information on the database were classified unlicensed. Each licensed drug was checked against the Product Information (PI) of the Indonesian MIMS[17, 18] to determine whether or not it was off-label. If there was no information on MIMS, the Indonesian National Medicine Information[19] was consulted. Drugs were classified off-label for the following reasons:

1. Age/ Weight: Drugs prescribed outside the age or weight range from that in the PI. When there was no information for paediatric use, the drug was also considered off-label for age

2. Indication: The use of the drug was not for the indication(s) listed in the PI

3. Dose/ Frequency: Drugs prescribed at a lower or higher dose/ frequency from that listed in the PI. An allowance of ± 10% was permitted for rounding.

4. Route of administration: Drugs administered via a different route from that stated in the PI

5. Contraindication/not recommended/special precaution: Drugs where the PI stated they were contraindicated, drugs with unmet special precautions of specific age groups or those not recommended in the PI.

It was possible for a drug to be classified as off-label for more than one reason. If a drug was licensed but prescribed in a formulation that was unlicensed, then it was classified as unlicensed.

Statistical analysis

Descriptive statistics were used for demographic data and to determine the extent of the frequency of off-label and unlicensed prescribing with respect to patients and with respect to the number of medicines prescribed. A Generalized Estimating Equation (GEE) was used to explore factors associated with a drug being given 'off-label' as opposed to 'on-label' (excluding the relatively small proportion of unlicensed drugs). This model was used because it took into account any correlations between the drugs being prescribed to the same patient. The following independent variables were included in the model: gender, age group, body weight, length of hospital stay, ATC drug category and diagnoses. Initially, all independent variables were included in the model, then the least significant was dropped, one at a time, until all variables remaining in the model were significantly associated with the outcome (a 'backwards elimination' strategy). Finally, pairwise interactions between independent variables remaining in the model were tested for statistical significance. All data were analysed using the SAS version 9.2 software, and a p-value <0.05 was taken to indicate a statistically significant association in all tests.

A Pearson's chi-square test was performed to compare the difference in off-label and unlicensed prescribing between the age groups. Where the numbers were too small for Chi-square to be considered accurate (expected frequency in at least one cell of the table less than 5), Fisher's Exact test was used instead.

Results

Patient demographics

Of 200 randomly selected medical records, 124 (62.0%) were males and 76 (38.0%) were females. The median age of patients was 1.7 years (range: one month– 13.2 years). The median weight of patients was 9.5 kg (range: 3.8–44.0 kg). The median length of hospital stay was 9 days (range: 2 to 33 days).

With respect to the age of paediatric patients, there were no newborns, 114 (57.0%) infants 80 (40.0%) children and 6 (3.0%) adolescents.

The 200 patients were diagnosed with 430 different indications. Acute gastroenteritis and/or diarrhoea was a common reason for patient admission and was listed as a diagnosis for 106/200 (53.0%) of admissions. Other reasons included dehydration (n = 93/200; 46.5%) and malaria (either *Plasmodium falciparum* or *Plasmodium vivax*) (n = 45/200; 22.5%).

Drugs classified as off-label and unlicensed

A total of 1961 drugs were prescribed to 200 patients, of which 1807 (92.1%) were licensed. There were 154 (7.8%) unlicensed drugs and 1403 (71.5%) were prescribed off-label. More than half of the total drugs prescribed (n = 1066; 54.4%) were administered parenterally.

Table 1. The 10 most commonly prescribed drugs with their off-label and unlicensed status. The numbers in the columns are the number of prescriptions of the drug and the percentage of these which are on/off-label or unlicensed.

Ten most common medications of 1961 prescribed drugs	Prescribed On-label		Prescribed Off-label		Unlicensed medicines	
	N	(%)	n	(%)	n	(%)
Paracetamol (n = 246; 12.5%)	59	24.0	187	76.0	0	0.0
Ranitidine (n = 230; 11.7%)	1	0.4	229	99.6	0	0.0
Cefotaxime (n = 187; 9.5%)	26	13.9	161	86.1	0	0.0
Ondansetron (n = 174; 8.9%)	0	0.0	174	100.0	0	0.0
Zinc sulfate (n = 134; 6.8%)	97	72.4	37	27.6	0	0.0
Liprolac®* (n = 119; 6.1%)	88	74.0	31	26.1	0	0.0
Cefixime (n = 115; 5.9%)	12	10.4	88	76.5	15	13.0
Gentamicin (n = 104; 5.3%)	9	8.7	95	91.4	0	0.0
Ceftriaxone (n = 69; 3.5%)	16	23.2	53	76.8	0	0.0
Artesunate (n = 57; 2.9%)	0	0.0	57	100.0	0	0.0

*Liprolac® (2.5g powder) sachets consist of viable cells 1,25 x 109 CFU (*Streptococcus thermophilus* 10 mg, *Lactobacillus rhamnosus* 3 mg, *Lactobacillus acidophilus* 3 mg, *Bifidobacterium longum* 1.25 mg, *Bifidobacterium bifidum* 1.25 mg), polydextrose 869.63 mg, fructooligosaccharide 375 mg, lactulose mixed powder 125 mg, vitamin C 35 mg, vitamin E 8.125 mg, vitamin A 3.60 mg, pyridoxine HCl 1.13 mg, vitamin B2 0.75 mg, thiamine HCl 0.70 mg).

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The ten most commonly prescribed drugs overall, including those that were prescribed off-label or unlicensed are shown in Table 1 (the complete list of all drugs is available as S1 Table). Of the 1403 off-label medicines, ranitidine, ondansetron, gentamicin and artesunate showed high levels of this prescribing. Table 2 shows the main reasons, and particular combinations of reasons, for off-label use of the medicines listed in Table 1 (an alphabetical list of all drugs prescribed off-label is included as a table in S2 Table). Several drugs including ranitidine and ondansetron were off-label for several reasons. Both age/weight and indication were high contributors to off-label prescribing. Cefotaxime and ceftriaxone were frequently prescribed in the absence of any indication for their need. This often related to them being prescribed for gastroenteritis. No microbiology data were collected to ascertain any bacterial involvement.

Based on the total number of 154 unlicensed medicines, the ten drugs most frequently prescribed were Darplex® (dihydroartemisinin and piperaquine) (n = 30; 19.5%), cough powder '14' (a combination of ambroxol, guaifenesin, chlorpheniramine maleate and vitamin C) (n = 28; 18.2%), primaquine (n = 18; 11.7%), cefixime (n = 15; 9.7%), elemental iron (n = 6; 3.9%), phenobarbitone (n = 6; 3.9%), cough powder '3' (a combination of ambroxol, dexamethasone, salbutamol and tremenza) (n = 5; 3.2%), sucralfate (n = 5; 3.2%), colistin sulphate (n = 4; 2.6%) and fluconazole (n = 4; 2.6%). Among unlicensed medicines, Darplex® although manufactured in Indonesia was not a registered product in Indonesia. Both sucralfate and elemental iron were imported. All other drugs were compounded preparations.

Drug use based on the anatomical therapeutic chemical (ATC) classification

The most commonly prescribed ATC category was the alimentary tract and metabolism (Class A) (n = 776/1961; 39.6% of all drugs), with ranitidine (n = 230; 29.6% of the 776 drugs within this class) and ondansetron (n = 174/776; 22.4%) most frequently prescribed. Ondansetron was always prescribed off-label and ranitidine 99.6% of the time. The second most frequently prescribed ATC category was anti-infectives (Class J) (n = 533/1961; 27.2%) with cefotaxime, cefixime and gentamicin most commonly prescribed. Usually gentamicin was off-label 95/104

Table 2. The reasons, or particular combination of reasons, for off-label use of the ten most common medicines shown in Table 1. Under each drug name are the number of prescriptions (n), and the number of patients (N).

Drug	Frequency (n)	Age/ weight	Indication	Dose/ frequency	Contra-indication	Special Precautions
				Reason for off-label classification		
Ranitidine (n = 229 N = 196)	219	■	■			■
	6	■				■
	1	■				
	1	■	■			
	1	■		■		
	1	■			■	
Paracetamol (n = 187, N = 138)	148	■				
	39			■		
Ondansetron (n = 174, N = 135)	127	■		■		
	45		■	■		
	1	■				■
	1			■		■
Cefotaxime (n = 161, N = 132)	156		■			
	4		■		■	
	1		■			
Gentamicin (n = 95, N = 85)	56		■	■		
	23		■			
	16			■		
Cefixime (n = 88, N = 88)	41		■			
	27		■	■		
	9			■		
	6		■		■	
	5				■	
Artesunate (n = 57, N = 46)	38	■				
	17	■		■		
	1			■		
	1	■	■			
Ceftriaxone (n = 53, N = 48)	51		■			
	3		■	■		
Zinc sulfate (n = 37, N = 36)	35			■		
	2	■				
Liprolac (n = 31, N = 30)	31			■		

The interpretation of results in Table 2 is as follows—for 23 prescriptions, gentamicin was off-label due to indication. However, for 56 (separate) prescriptions, gentamicin was off-label due to indication as well as dose/ frequency. In total there were 95 off-label prescriptions for gentamicin, for a total of 85 patients.

(91.3%). The third most commonly prescribed ATC category was the nervous system (Class N) (n = 274/1961; 14.0%).

Amongst the unlicensed drugs, the most common ATC category was antiparasitic products, insecticides and repellents (Class P) (n = 49, 31.8% of 154 unlicensed drugs) which included Darplex® (n = 29; 59.2% of the 49 drugs in the class) and primaquine (n = 18/49; 36.7%).

Patient prescribing

The median number of drugs prescribed per person was 9 drugs (range: 4–20). All 200 patients (100%) were given at least one off-label drug and 108 (54%) of them received at least one

Table 3. Level of off-label and unlicensed prescribing to patients according to age classification.

Age groups	Patients with at least one prescribed drug that was:			
	Off-label		Unlicensed	
	n = 200	(%)	n = 108	(%)
Infants (n = 114; 57.0%)	114	100	60	52.6
Children (n = 80; 40.0%)	80	100	43	53.8
Adolescents (n = 6; 3.0%)	6	100	5	83.3

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unlicensed medicine (Table 3). There appeared to be no difference between age groups in the proportion of patients who received at least one unlicensed drug (Fisher's Exact test; p = 0.38). The distribution of off-label and unlicensed prescribing of the 1961 drugs in infants, children and adolescents is summarized in Table 4. While it appeared that the use of off-label drugs was more common for adolescents than infants, no significant association was evident between age-group and the use of off-label drugs (GEE model, univariate p = 0.090).

Reasons for off-label and unlicensed prescribing

Of the 1403 drugs which were prescribed 'off-label', the most common reason given was indication (diagnosis) (n = 810; 57.7%), followed by age/weight (n = 655; 46.7%), dose/frequency (n = 579; 41.3%) and the use of contraindicated drugs or those with special precautions or not recommended to be used in the patient age prescribed (n = 294; 21.0%). No drug was off-label for route of administration. Neither length of stay (2–3 days vs 4–6 days, p = 0.063; 7+ days vs 4–6 days, p = 0.11) nor gender (p = 0.92) were associated with the rate of off-label prescribing.

The GEE model shows several factors that were independently associated with off-label prescribing (Table 5). While age group appeared to be significantly associated with off-label prescribing based on univariate analysis (Infants: 77.7%; Children: 76.4%; Adolescents: 91.2%; with the p-value for Adolescents vs others p = 0.01), this difference did not persist after adjustment for the other independent variables in the model. As there were no neonates admitted to this ward, it was not possible to determine if off-label prescribing would have been more or less frequent in this age group.

Other independent variables in the GEE model were dropped as they appeared to be not significantly associated with the outcome (including gender, body weight, length of hospital stay, ATC drug category and diagnoses). The p-values for the variables which were dropped were: gender (p = 0.92), weight (0.20). We divided LOS into short (2–3 days), medium (4–6 days), and long (7+ days). With medium stay as the reference, the p-value for short was p = 0.063, and for long stay it was p = 0.11, and therefore it was also dropped from the final model. ATC categories and diagnoses which were not included in the final model were dropped because they showed no significant association. It is notable that an indication of tuberculosis was associated with lower off-label prescribing (p = 0.0037), and malaria was associated with a higher rate (p = 0.0004). The specific ATC codes also influenced off-label

Table 4. Frequency of off-label and unlicensed prescribing based on total drugs prescribed.

Age groups	Medicines not off-label or unlicensed		Off-label medicines		Unlicensed medicines	
	n = 404	(%)	n = 1403	(%)	n = 154	(%)
Infants (n = 1144)	236	20.6	824	72.0	84	7.3
Children (n = 755)	163	21.6	527	69.8	65	8.6
Adolescents (n = 62)	5	8.1	52	83.9	5	8.1

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Table 5. Analysis of association with a drug being defined as off-label using a Generalized Estimating Equation (GEE). (n = 1807 licensed drugs prescribed on or off-label). The "n" in the first column shows the total number of drugs prescribed, while the "n" in the second column shows the number which were off-label.

Variable	Number of off-label drugs n (%)	Odds Ratio	95% Confidence Interval	p-value
Tuberculosis				
No (n = 1677)	1316 (78.5)	1 (reference)		
Yes (n = 130)	87 (66.9)	0.53	0.35–0.82	0.0037
Malaria				
No (n = 1435)	1087 (75.8)	1 (reference)		
Yes (n = 372)	316 (85.0)	1.73	1.28–2.34	0.0004
ATC Class				
N* class (n = 266)	200 (75.2)	1 (reference)		
A# class (n = 764)	529 (69.2)	0.68	0.49–0.94	0.0205
Other classes (n = 237)	208 (87.8)	1.92	1.16–3.20	0.0116
ATC Class J : Bronchitis**				
No: No (n = 1178)	868 (73.7)	1 (reference)		
No: Yes (n = 123)	102 (82.9)	1.81	1.08–3.02	0.0231
Yes: No (n = 447)	412 (92.2)	3.87	2.18–6.89	<0.0001
Yes: Yes (n = 59)	21 (35.6)	0.20	0.11–0.35	<0.0001

* = drugs affecting the nervous system;

= alimentary and metabolism drugs;

** = anti-infectives.

prescribing, with Class A (alimentary tract drugs) having a lower rate of off-label use than Class N (nervous system drugs), and other classes having a higher rate of off-label use. ATC Class J (anti-infective agents) showed an interaction with bronchitis so that in the absence of bronchitis, Class J drugs were more likely to be used off-label, but when bronchitis was present, Class J drugs were less likely to be used off-label. The number of cases where both bronchitis was present and a Class J drug was used, was small (n = 59), but the difference in use in an off-label fashion was quite clear, and therefore statistically significant.

Discussion

To the best of our knowledge this is the first study to report the prevalence of off-label and unlicensed prescribing in a paediatric medical ward in a public general tertiary hospital setting in Indonesia. Previous studies in Indonesia have reported on the prevalence of off-label and unlicensed prescribing in 67 paediatric inpatients with nephrotic syndrome (aged less than 18 years)[20] and off-label use of anticonvulsants at a private hospital (age not specified).[21] It is not possible to make a direct comparison between the results of these studies with the current findings due to the differences in setting and age of the paediatric patients.

The current study found that off-label and unlicensed prescribing was a common practice in this Indonesian hospital setting. Similar findings have been reported in other studies.[11, 22–28] The median number of drugs prescribed was relatively high at nine per patient (range: 4–20 drugs). In a hospital study in Malaysia (also a Southeast Asian country) in which the median age of the study population was two years, researchers reported that the median number of drugs prescribed per child was four (range 1–52).[28] In our study population, the median age was similar (1.7 years) but the median number of drugs prescribed was much higher. Similar findings were also reported in a study in Finland, in which the median number

of drugs in preterm infants and children aged 2–11 years, was 15 (range 2–29) and 9 (range 0–36) respectively.[25] In the current study, there was also a high rate of injection prescribing. Injection rates are often high in developing countries because of a perception that this route of administration is more effective.[29] The high rate of injection prescribing is also of concern to the World Health Organization.[30] These findings raise potential public health issues.

The extent of off-label medicines

A high prevalence of off-label prescribing was found (71.6%) compared to other studies in similar settings in Palestine (31.3%),[11] Germany (31%),[24] Australia (31.8%),[22] Slovak Republic (22%),[31] and Finland (42%).[25] Although these differences may be partly due to the different patient populations with different indications compared to other countries, they may also be due to the use of different definitions of off-label.[12] Unlike some previous studies, this study included as off-label drugs, those which were contraindicated, those with special precautions, and those drugs not recommended for use in children. Moreover, there may be differences in the contents of the Product Information (PI) for the same active ingredient between countries due to differences in registration data submitted.[12, 32]

Off-label drugs

Ranitidine, which was the second most frequently prescribed drug overall, was the most commonly prescribed off-label drug. It was off-label for age and indication because there was no specific age in children at which ranitidine was licensed for parenteral use and it was also prescribed without a clear diagnosis (indication). Several other studies have reported the use of ranitidine among the ten most commonly prescribed off-label drugs. However, these studies were conducted in a surgical ward, PICU, neonate intensive care unit, and paediatric emergency unit.[26, 33] All drugs in the 'cardiovascular system' classifications were prescribed off-label due to dose/ frequency and indication.

Reasons for a drug to be off-label

In a recent review, researchers reported that the hospital setting influenced the reason for off-label prescribing, with age and dose most commonly reported reasons for off-label prescribing in neonatal intensive care units; dose, age and indication in paediatric intensive care units; dose ad age in general paediatric wards and dose in the emergency department.[12] In the current study, the most common reason for off-label prescribing was for indication. For example, a parenteral formulation of ondansetron was only indicated for nausea in children with chemotherapy but none of the children on this ward was undergoing chemotherapy hence ondansetron was off-label for all the prescriptions. Other studies have also reported that ondansetron was prescribed off-label due to indication.[34, 35] In addition, the prescribing pattern of antibiotics in this hospital may have contributed significantly to the off-label category based on the indication. For example, cefotaxime was prescribed for many acute gastrointestinal cases although there was no registered indication in the PI for acute gastroenteritis. Age category was associated with a small but statistically significant lower level of off-label prescribing for children (aged 2–11 years) compared to infants or adolescents. The rate of off-label prescribing was however high for all age groups. This is concerning as several studies have reported that off-label prescribing is a risk factor for developing adverse reactions.[36, 37] As highlighted by Bonati et al.,[38] when drugs are prescribed off-label for specific diseases for which indications are not included in the manufacturer's PI, evidence for their use should be established.[38] Additionally, such prescribing may raise medico-legal issues.[39]

It is notable that the prescribing of antibiotics (often as injections) in the management of gastroenteritis was high. No microbiology testing was performed on any potential pathogens, however antibiotics were not registered for this diagnosis. Where antibiotics were an appropriate selection, a lower level of off-label prescribing occurred. Inappropriate antibiotic prescribing has the potential to lead to resistance.[40]

Unlicensed prescribing

The percentage of unlicensed medicines prescribed in this study (7.9%) conformed within the range of 5.5%–28% reported by other studies in similar settings.[11, 25] A number of studies in developing transitional countries such as Palestine[11] and Malaysia[28] also reported that most unlicensed drugs were extemporaneous preparations produced from capsules or tablets in order to obtain a lower dosage which was not available in the registered products. For instance, the preparation of 3 mg primaquine was made from a 15 mg tablet crushed to aliquot the desired dosage. Such formulations introduce uncertainty of the stability and bioavailability of the mixtures.[2]

The use of extemporaneous preparations was also aimed to reduce the number of oral drug administrations. Darplex® was the most frequent unlicensed drug because it was unregistered in Indonesia. It is a combination of dihydroartemisinin and piperaquine phosphate, which is one of the WHO recommended combination drugs to treat malaria. The reason why Darplex® was unregistered in Indonesia is unknown.

Informed consent

There was no informed consent documented for the administration of off-label or unlicensed medicines in this hospital. Informed consent may be appropriate when drugs without the support of clinical data or high quality evidence are prescribed of use in children.[22]

Limitations

Despite the high prevalence of off-label use in paediatric patients reported in this study, there were some limitations. As this was a retrospective study, some data may have been missing. Further, the data were collected in 2015, so it is possible some prescribing has changed since that date. Although the data were collected over a three month period from August to October, as the hospital was located at sea level near the equator, it has a tropical climate and little seasonal variation. Hence potential biased analysis toward seasonal effects is unlikely. As the study did not include neonates and adolescents older than 14 years of age, it may not be an accurate representation of the complete paediatric population. Also, this study may not be comparable to other parts of Indonesia as they may have different patterns of diseases. An evaluation of the safety and efficacy of the drugs prescribed off-label in this study was outside the scope of this research however, there is a need for these evaluations in future studies.

Conclusion

This study reports a high prevalence of both off-label and unlicensed prescribing in paediatric patients in a general medical ward in a hospital setting in Indonesia. Antibiotic prescribing for unlicensed indications was a major contributor and potential public health issue related to these findings. Specific disease states such as tuberculosis resulted in significantly lower off-label prescribing. Prescribers in Indonesia should be made aware of the findings of this study.

Supporting information

S1 Table. All drugs with off-label and unlicensed status.
(DOCX)

S2 Table. Reasons, or combination of reasons, for off-label prescribing.
(DOCX)

Acknowledgments

Author Contributions

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References

1. Ivanovska V, Rademaker CM, van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: a review of challenges and progress. Pediatrics. 2014; 134(2):361–372. https://doi.org/10.1542/peds.2013-3225 PMID: 25022739

2. Yamashiro Y, Martin J, Gazarian M, Kling S, Nakamura H, Matsui A, et al. Drug development: the use of unlicensed/off-label medicines in pediatrics. Journal of pediatric gastroenterology and nutrition. 2012; 55(5):506–510. https://doi.org/10.1097/MPG.0b013e318272af1f PMID: 22983373

3. Magalhães J, Rodrigues AT, Roque F, Figueiras A, Falcão A, Herdeiro MT. Use of off-label and unlicenced drugs in hospitalised paediatric patients: a systematic review. European journal of clinical pharmacology. 2015; 71(1):1–13. https://doi.org/10.1007/s00228-014-1768-9 PMID: 25318905

4. State of paediatric medicines in the EU– 10 years of the EU paediatric regulation Eurpean Union. 2017. https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/2017_childrensmedicines_report_en.pdf

5. Knellwolf A-L, Bauzon S, Alberighi ODC, Lutsar I, Bácsy E, Alfarez D, et al. Framework conditions facilitating paediatric clinical research. Italian journal of pediatrics. 2011; 37(1):12.

6. Contopoulos-Ioannidis DG, Baltogianni MS, Ioannidis JP. Comparative effectiveness of medical interventions in adults versus children. The Journal of pediatrics. 2010; 157(2):322–330. e17. https://doi.org/10.1016/j.jpeds.2010.02.011 PMID: 20434730

7. Lathyris D, Panagiotou OA, Baltogianni M, Ioannidis JP, Contopoulos-Ioannidis DG. Safety of medical interventions in children versus adults. Pediatrics. 2014; 133(3):e666–e673. https://doi.org/10.1542/peds.2013-3128 PMID: 24567023

8. Allegaert K, Van De Velde M, van den Anker J. Neonatal clinical pharmacology. Pediatric Anesthesia. 2014; 24(1):30–38. https://doi.org/10.1111/pan.12176 PMID: 23617305

9. Review of laws, regulations, and uses of off-label drugs in Indonesia—Final report. 2017. http://adphealth.org/upload/resource/Review_of_Laws_Regulations_and_Uses_of_Off-label_Drugs_in_Indonesia_2018_ADP.pdf

10. 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):316–328. PMID: 26380572

11. Khdour MR, Hallak HO, Alayasa KS, AlShahed QN, Hawwa AF, McElnay JC. Extent and nature of unlicensed and off-label medicine use in hospitalised children in Palestine. International journal of clinical pharmacy. 2011; 33(4):650–655. https://doi.org/10.1007/s11096-011-9520-3 PMID: 21567279

12. Balan S, Hassali MAA, Mak VS. Two decades of off-label prescribing in children: a literature review. World Journal of Pediatrics. 2018; 14(6):528–540. https://doi.org/10.1007/s12519-018-0186-y PMID: 30218415

13. The Head of Drug and Food Controller Agency. Regulation of the head of drug and food controller agency (number HK.03.1.23.10.11.08481 of 2011) concerning criteria and procedure of drug registration 2011. http://www.flevin.com/id/lgso/translations/JICAMirror/english/4886_HK.03.1.23.10.11.08481_e.html

14. Clinical Investigation of Medicinal Products in the Pediatric Population (E11). EU: Adopted by CPMP, July 2000, issued as CPMP/ICH/2711/99. Published in the Federal Register: FDA; 2001. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf

15. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2015 2015. http://www.whocc.no/atc_ddd_index/

16. The National Agency of Drug and Food Control. Registration database. Indonesia. 2015. https://www.pom.go.id/new/

17. MIMS Indonesia 2015. Monthly Index of Medical Specialities (eMIMS). 2015 [cited In: Indonesia: MIMS. http://www.mimsonline.com/Indonesia/home/Index#

18. MIMS Indonesia: Petunjuk Konsultasi 14 2014/2015 ed. Jakarta (Indonesia): BIP (Buana Ilmu Populer). 2015. https://www.mims.com/indonesia

19. Indonesian National Medicine Information 2013. http://pionas.pom.go.id/book/ioni

20. Ramadaniati HU, Tambunan T, Khairani S, Adisty HS. Off-label and unlicensed prescribing in paediatric inpatients with nephrotic syndrome in a major teaching hospital: An Indonesian context. Asian J Pharm Clin Res. 2017; 10(1):355–359.

21. Rahajeng B, Ikawati Z, Andayani TM, Dwiprahasto I. A retrospective study—the off-label use of anticonvulsants at a private hospital in Indonesia. 2018. IJPPS. 10(5): 119–122

22. Czarniak P, Bint L, Favié L, Parsons R, Hughes J, Sunderland B. Clinical setting influences off-label and unlicensed prescribing in a paediatric teaching hospital. PloS one. 2015; 10(3):e0120630. https://doi.org/10.1371/journal.pone.0120630 PMID: 25756896

23. Delmas S, Bourdon O, Brion F, Prot-Labarthe S. Unlicensed and off-label medicines and prescriptions: A descriptive analysis of the medicines formulary and of the 56,800 prescriptions in a paediatric hospital.

24. Hsien L, Breddemann A, Frobel A-K, Heusch A, Schmidt KG, Läer S. Off-label drug use among hospitalised children: identifying areas with the highest need for research. Pharmacy world & science. 2008; 30(5):497–502.

25. Lindell-Osuagwu L, Hakkarainen M, Sepponen K, Vainio K, Naaranlahti T, Kokki H. Prescribing for off-label use and unauthorized medicines in three paediatric wards in Finland, the status before and after the E uropean U nion P aediatric R egulation. Journal of clinical pharmacy and therapeutics. 2014; 39 (2):144–153. https://doi.org/10.1111/jcpt.12119 PMID: 24329556

26. Bavdekar S, Sadawarte PA, Gogtay NJ, Jain SS, Jadhav S. Off-label drug use in a Pediatric Intensive Care Unit. The Indian Journal of Pediatrics. 2009; 76(11):1113–1118. https://doi.org/10.1007/s12098-009-0238-3 PMID: 20092023

27. Ferreira Ld A, Ibiapina Cd C, Machado MGP, Fagundes EDT. High prevalence of off-label and unlicensed drug prescribing in a Brazilian intensive care unit. Revista da Associação Médica Brasileira. 2012; 58(1):82–87. PMID: 22392321

28. Lee JL, Redzuan AM, Shah NM. Unlicensed and off-label use of medicines in children admitted to the intensive care units of a hospital in Malaysia. International journal of clinical pharmacy. 2013; 35 (6):1025–1029. https://doi.org/10.1007/s11096-013-9846-0 PMID: 24022725

29. Li Y, Xu J, Wang F, Wang B, Liu L, Hou W, et al. Overprescribing in China, driven by financial incentives, results in very high use of antibiotics, injections, and corticosteroids. Health affairs. 2012; 31(5):1075–1082. https://doi.org/10.1377/hlthaff.2010.0965 PMID: 22566449

30. World Health Organisation. Towards the safe and appropriate use of injections worldwide: progress report 2000–2001 [Internet]. 2002 https://apps.who.int/iris/handle/10665/67810

31. Slažneva J, Kovács L, Kuželová M. Off-label drug use among hospitalized children: identifying extent and nature. Acta Facultatis Pharmaceuticae Universitatis Comenianae. 2012; 59(1):48–54.

32. Carnovale C, Conti V, Perrone V, Antoniazzi S, Pozzi M, Merlino L, et al. Paediatric drug use with focus on off-label prescriptions in Lombardy and implications for therapeutic approaches. European journal of pediatrics. 2013; 172(12):1679–1685. https://doi.org/10.1007/s00431-013-2111-7 PMID: 23913312

33. Laforgia N, Nuccio MM, Schettini F, Dell'Aera M, Gasbarro AR, Dell'Erba A, et al. Off-label and unlicensed drug use among neonatal intensive care units in Southern Italy. Pediatrics International. 2014; 56(1):57–59. https://doi.org/10.1111/ped.12190 PMID: 23937449

34. Ballard CD, Peterson GM, Thompson AJ, Beggs SA. Off-label use of medicines in paediatric inpatients at an A ustralian teaching hospital. Journal of paediatrics and child health. 2013; 49(1):38–42. https://doi.org/10.1111/jpc.12065 PMID: 23279160

35. Landwehr C, Richardson J, Bint L, Parsons R, Sunderland B, Czarniak P. Cross-sectional survey of off-label and unlicensed prescribing for inpatients at a paediatric teaching hospital in Western Australia. PloS one. 2019; 14(1):e0210237. https://doi.org/10.1371/journal.pone.0210237 PMID: 30620749

36. Jonville-Bera A, Bera F, Autret-Leca E. Are incorrectly used drugs more frequently involved in adverse drug reactions? A prospective study. European journal of clinical pharmacology. 2005; 61(3):231–236. https://doi.org/10.1007/s00228-004-0881-6 PMID: 15824914

37. Wallerstedt SM, Brunlöf G, Sundström A. Rates of spontaneous reports of adverse drug reactions for drugs reported in children. Drug safety. 2011; 34(8):669–682. https://doi.org/10.2165/11591730-000000000-00000 PMID: 21751827

38. Bonati M, Jacqz-Aigrain E, Choonara I. Licensed medicines, off-label use or evidence-based. Which is most important? Archives of diseases in childhood. 2017; 102(1):53–54.

39. Hill P. Off licence and off label prescribing in children: litigation fears for physicians. Archives of disease in childhood. 2005; 90(suppl 1):i17–i18.

40. Sabtu N, Enoch D, Brown N. Antibiotic resistance: what, why, where, when and how? British medical bulletin. 2015; 116(1)