DIA

Therapeutic Innovation
& Regulatory Science
2020, Vol. 54(3) 492-506

https://doi.org/10.1007/s43441-019-00081-7

Pediatric Antibiotic Pack Size Compliance With the Dosage Regimen: A Descriptive Study

Iram Malik, MPhil[1], Muhammad Atif, PhD[1], Fatima Riaz, MPhil[1], Saima Asghar, MPhil[1], and Nafees Ahmad, PhD[2]

Abstract

Background: The unavailability of appropriate pediatric drug pack size is a global issue. Antibiotics are the lifesaving and most frequently prescribed therapeutic agents given to pediatrics. The objective of this study was to assess the compliance of pediatric antibiotic pack size with the standard dosage regimen. *Methods:* A descriptive study design was employed. Data were collected from a community pharmacy in Bahawalpur, Pakistan, between August 1, 2017, and September 30, 2017. Five most commonly prescribed antibiotics were selected and calculations were made to check the appropriateness of packaging size by comparing the quantity of product in the available pack with the dosage regimen recommended by the British National Formulary for Children (BNFC). *Results:* Only 16 clarithromycin, 9 amoxicillin, 1 cefotaxime, and 1 metronidazole packaging sizes were sufficient to meet the dosage regimen for treatment. None of the available pack sizes for gentamicin matched the recommended duration of treatment. The study findings revealed that the available pack sizes either had leftover or a shortfall of antibiotic formulation. Highly inappropriate dosage forms (containing either excess and less quantity) of antibiotics were intravenous infusions and oral suspensions. *Conclusion:* The study concluded that the packaging sizes of antibiotics failed to supply the recommended dosage regimen to pediatrics for common indications. This may contribute to development of antibiotic resistance among pediatric patients. Health policy makers should devise strict rules and regulations to ensure the availability of child-specific antibiotic pack sizes.

Keywords

antibiotic pack sizes, pediatric formulations, compliance, pediatric dosage regimen, leftover medicine, irrational antibiotic use, antibiotic resistance, British National Formulary for Children

Background

The pediatric population embodies a spectrum of diverse physiologies extending from preterm newborn infant to the adolescent.[1] Child's ability to tolerate different dosage forms varies widely, and there may be 50-fold alteration in the quantity of dose required during childhood as compared with adult.[2] Pediatrics should not be considered as "miniature men and women."[1] Pediatrics need a variety of dosage forms in different strengths and concentrations allowing adequate treatment and administration of accurate age-appropriate dose.[2,3] The European Medicines Agency (EMA) defines an age-appropriate pediatric dosage form as one that is suitable for use in the target age group(s) and has suitable composition, packaging, dosing frequency, dosage form, and dosing device.[4] While an "age-appropriate" dosage form is stated as "a dosage form for which a child of a specific age would have the natural ability to use without the product having to be altered from its original 'intended' presentation, prior to administration."[5] But the access to the age-appropriate pediatric formulations and packaging sizes is challenging in both developing and developed countries.[6-8] According to a report, approximately 8 million children (age <5 years) die each year because of priority health issues, and many of these fatalities could be avoided by ensuring the access to appropriate child-specific essential medicines.[9]

Antibiotics are the lifesaving and the most frequently prescribed therapeutic agents given to pediatrics.[10] However, the appropriateness of the available antibiotic pack sizes for their

[1] Department of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Pakistan
[2] Faculty of Pharmacy and Health Sciences, University of Balochistan, Quetta, Pakistan

Submitted 27-Feb-2019; accepted 7-May-2019; published online 6-Jan-2020

Corresponding Author:
Muhammad Atif, PhD, Department of Pharmacy, The Islamia University of Bahawalpur, Railway Road Campus, Bahawalpur 63100, Pakistan.
Email: pharmacist_atif@yahoo.com

use in pediatrics is questionable.[11,12] Use of inappropriate antibiotic pack sizes in pediatrics may result in toxicity, medication errors (MEs), administration errors (ie, dosage calculation errors, dilution errors), development of antimicrobial resistance, increased mortality and morbidity risk, wastage of resources, and higher treatment costs.[8,13-16] Moreover, lack of suitable packaging sizes is also associated with augmented use of unlicensed and extemporaneously prepared products on a regular basis.[17] There could be many reasons for unavailability of age-appropriate antibiotic pack sizes. For example, most of the drugs are primarily developed for adults, and therefore the formulations and packaging sizes are only available for them.[11] Beside this, numerous drugs remain unlicensed or unlabeled to be used in pediatric populations, and because of these reasons companies do not generally market appropriate dosage forms for pediatric patients.[18] Moreover, pediatric formulations have low profit and demand,[19] and in general pharmaceutical industries manufacture a particular dosage form only if it is marketable and yields good profit.[19]

Pediatrics represents a major part of the population in the lower and middle income countries (LIMCs).[20] The recurrent and early use of antibiotics is increasing strikingly in LMICs, where infectious diseases are the primary reason of child death.[10,21] Pakistan, an LMIC, is a young nation of more than 52% residents under 19 years of age.[22] The neonatal and infant mortality rate (48 neonatal and 56 infant deaths per 1000 live births) is highest in the country.[23] One of the contributing factors associated with a high mortality rate among pediatrics is infectious diseases and subsequent irrational use of antibiotics.[22,24,25] Several parent- or caregiver-related attributes, for example, lack of health literacy, unsupervised self-medication,[26] unnecessary and suboptimal consumption of antibiotics, and over-the-counter (OTC) purchase of antibiotics[27-30] might be responsible for the irrational use of antibiotics. Similarly, unavailability of age-appropriate packaging sizes of antibiotics could be another factor that leads to inappropriate use of antibiotics among pediatrics. In most of the drug stores in Pakistan, pharmacists are not available and, therefore, patients and caregivers are dealt with by the pharmacy workers having inadequate education and insufficient medicines-related knowledge.[31-33] This may further expose the pediatrics to adverse outcomes associated with the use of inappropriate antibiotic pack sizes. In this context, it is important to know whether the available packaging sizes of antibiotics match the recommended dosage regimen in pediatrics for common indications. Despite the seriousness of the issue, there is a dearth of literature on this worldwide and Pakistan specifically. Therefore, this study was aimed to assess pediatrics antibiotic pack sizes' compliance with the standard dosage regimen for various indications in Pakistan.

Methodology

Study Setting

The study was conducted at a community pharmacy (Pharmacy X) located in Bahawalpur. Bahawalpur is located in the Punjab province and is the 12th largest city of Pakistan with an approximate population of 3,668,106 people.[34] There are more than 500 drug stores in Bahawalpur, and most of them operate without the supervision of a pharmacist.[33] The selected community pharmacy is one of the few community pharmacies in Bahawalpur that run under the supervision of a community pharmacist.

Study Design

A descriptive study design was employed to achieve the study objectives. We selected most frequently prescribed antibiotics (all packaging sizes and dosage forms) in Pakistan for pediatric indications. The standard pediatric dosage regimen for various indications was obtained from the British National Formulary for Children (BNFC)[35] and these were compared with the available packaging sizes of selected antibiotics. According to BNFC, the terms used to categorize different pediatric stages of development include preterm neonate (born at <37 weeks gestation), term neonate (born at 37-42 weeks gestation), post-term neonate (born at >42 weeks gestation), neonate (0-28 days of age), infant (28 days to 24 months), child (2-12 years) and adolescent (12-18 years).[35] In this study, later four categories were considered for accessing the appropriateness of available pack size with the dosage regimen requirement.

Selection of Antibiotic and Data Collection

In this study, 5 antibiotics, that is, clarithromycin, metronidazole, cefotaxime, amoxicillin, and gentamycin, were selected that are most commonly prescribed antibiotics for different pediatrics indications in Pakistan.[24,25,36] Data were collected between August 1, 2017, and September 30, 2017. Information about packaging size and dosage forms of antibiotics intended to be used solely in pediatric patients, irrespective of available brand, was obtained from Pharmacy X. Most recent version (24th edition, 2016) of Pharma Guide was also referred to ensure that no pediatric packaging size and dosage form were missed.[37] A data collection tool was designed to achieve the study objectives. It included information about the type of infection, age of child, type of dosage form, dose, strength, frequency, and duration of antibiotic therapy and final calculations.

Data Analysis

- In the first step, dose range (lower and upper range) was calculated on the basis of weight of a child of a particular age group.
- In the second step, dose per day was calculated by multiplying the dose (lower and upper range) with the dosage frequency.
- In the third step, the total amount of drug used for the whole treatment duration was calculated by multiplying the dose per day (upper and lower range) with the total number of days of treatment.

- In the fourth step, the quantity of dosage form (in milliliters) to be used for the whole treatment duration was calculated by using the calculated dose range (lower and upper) for the whole treatment duration and available strength.
- In the last step, a calculation was made by subtracting the volume of dosage form required for the whole treatment duration (lower and upper range) from the available volume of the dosage form (an example provided in the Supplemental Material 1).

For intravenous injection and infusions, analysis was made according to the dose in milligrams because they were available in powder form and administered after reconstitution. Consequently, the fixed volume of injection or infusion could not be determined after reconstitution. Furthermore, in case of injection or infusion, volume of the dosage form to be used was calculated on the basis of dosing frequency and duration of therapy because one vial or ampoule cannot be used after reconstitution for next dose because of stability and sterility issues.

- In the first step, the number of vials or quantity required to be used was calculated by multiplying the duration of therapy with frequency.
- In the second step, the quantity of drug in milligrams (extra or less per vial or ampoule) was calculated by subtracting the required dose from available strength.
- In the third step, the extra amount of drug (in milligrams) per day was calculated by multiplying the extra amount of drug per dose (lower and upper range) with the dosing frequency.
- In the fourth step, we calculated the extra amount of drug (in milligrams) for the whole duration of therapy by multiplying the extra amount of drug per day (lower and upper range) with the recommended duration of therapy (an example provided in the Supplemental Material 1).

Ethical Approval

This article does not contain any studies with human or animal subjects performed by any of the authors.

Note

Pack size

For purpose of this study, pack size was defined as "units per pack," that is, the number of tablets or capsules in one blister, or the number of suppositories in one pack, or the number of milliliters in one bottle of syrup, or the suspensions and amount of drug in one ampoule or vial.

Appropriate pack size

In this study, the term "appropriate pack size" refers to "pack size having quantity and/or volume of formulation sufficient to meet the standard dosage regimen requirement."[8,38] The pack size unable to comply with the foregoing requirements was considered as inappropriate.

Results

Available strengths and quantity of different dosage forms of clarithromycin, cefotaxime, metronidazole, amoxicillin, and gentamicin are given in Supplemental Material 2.

Clarithromycin

Overall, 71 calculations were made for clarithromycin (Supplemental Material 3). In only 16 cases, the quantity of dosage form was sufficient to meet the dosage regimen required for treatment. But the remaining 55 findings demonstrated that the available packaging sizes either had leftover (excess quantity) or shortfall (less quantity) of the formulation based on the upper and lower dosage regimen of clarithromycin. A highly inappropriate dosage form containing an excess amount of clarithromycin formulation was IV infusion, that is, 473.75 to 467.75 mg extra per dose, 947.5 to 935.5 mg extra per day, and 1871 to 4737.5 mg extra for the whole duration of treatment, indicated to be used in neonates of 0-1 month suffering from pneumonia, sinusitis, or mild to moderate skin and soft tissue infection. In addition, a highly inappropriate dosage form depicting shortfall of clarithromycin was suspension, that is, 80 mL less in maximum available pack size indicated in children of 4-8 years suffering from a throat infection (Table 1).

Cefotaxime

Overall, 23 calculations were made for cefotaxime (Supplemental Material 4). Only in 1 case, the quantity was sufficient to meet the dosage regimen required for treatment. But the rest of the findings demonstrated that the available packaging sizes either had leftover or a shortfall of cefotaxime formulation. A highly inappropriate dosage form containing an excess quantity of cefotaxime was IV infusion, that is, 157.5 to 147.5 mg extra per dose, 472.5 to 442.5 mg extra per day, and 3307.5 to 3097.5 mg extra for the whole treatment duration, indicated to be used in neonates of 7-21 days suffering from haemophilus epiglottis and septicemia. In addition, a highly inappropriate dosage form depicting shortfall of cefotaxime formulation was also IV infusion or injection, that is, 11,250-mg less (based on the upper dose range) for the whole duration of treatment indicated in children of 12-18 years suffering from haemophilus epiglottis and septicemia (Table 2).

Metronidazole

Overall, 39 calculations were made for metronidazole (Supplemental Material 5). In only 1 case, the quantity was sufficient to meet the dosage regimen for treatment. But the rest of the findings demonstrated that the available packaging sizes either had leftover or a shortfall of metronidazole formulation. A highly inappropriate dosage form containing excess amount of metronidazole was IV infusion, that is, 467.75 to 459.5

Table 1. Clarithromycin Calculations.

Age (Weight)	Dosage Form	Dose	Strength	Dosing Frequency	Duration of Therapy	Dose/Day and Dose/Day × No. of Days	Quantity of Dosage Form to Be Used	Calculation	Result
Indication: Pneumonia, sinusitis, mild to moderate skin and soft tissue infection, prevention of pertussis									
0-1 mo (3.5 to 4.3kg)	IV Infusion	26.25-32.5 mg	500 mg	2 times a day	2-5 d	52.5-64.50 mg 52.5-64.50 mg × (2-5) = 105-322.5 mg	4-10 vials	• 473.75-467.75 mg extra per dose. • 947.5-935.5 mg extra per day. • 1871-4737.5 mg extra for whole duration.	Inappropriate
1-6 mo (4.3-7.7 kg)	IV infusion	7.5 mg/kg (32.25-57.75 mg)	500 mg	2 times a day	2-5 d	64.50-115.5 mg 64.50-115.5 mg × (2-5) = 129-577.5 mg	4-10 vials	• 467.75-442.25 mg extra per dose. • 935.5-884.5 mg extra per day. • 1769-4677.5 mg extra for whole duration.	Inappropriate
1-2 y (8-11 kg)	IV Infusion	7.5 mg/kg (60-82.5 mg)	500 mg	2 times a day	2-5 d	120-165 mg 120-165 mg × (2-5) = 240-825 mg	4-10 vials	• 440-417.5 mg extra per dose. • 880-835 mg extra per day. • 1670-4400 mg extra for whole duration.	Inappropriate
2-4 y (12-19 kg)	Suspension	125 mg /5 mL	125 mg /5 mL	2 times a day	7 d	250 mg 250 mg × 7 = 1750 mg	70 mL	• Quantity is exactly equal to available pack size, ie, 70 mL	Appropriate
8-12 y (30-40 kg)	Suspension	250 mg	125 mg /5 mL	2 times a day	7 d	500 mg 500 mg × 7 = 3500 mg	140 mL	• Quantity is exactly equivalent to available pack size, ie, 2 × 70 mL	Appropriate
8-12 y (30-40 kg)	Suspension	250 mg	250 mg /5 mL	2 times a day	7 d	500 mg 500 mg × 7 = 3500 mg	70 mL	• Quantity is exactly equivalent to available pack size, ie, 70 mL	Appropriate
12-18 y	Suspension	250 mg	125 mg /5 mL	2 times a day	7 d	500 mg 500 × 7 = 3500 mg	140 mL	• Quantity is exactly equivalent to available pack size, ie, 2 × 70 mL	Appropriate
12-18 y	Suspension	250 mg	250 mg /5 mL	2 times a day	7 d	500 mg 500 × 7 = 3500 mg	70 mL	• Quantity is exactly equivalent to available pack size, ie, 70 mL	Appropriate
Indication: Throat infections									
6-12 mo (7.7-10 kg)	Suspension	62.5 mg	125 mg /5 mL	2 times a day	10 d	125 mg 125 mg × 10 = 1250 mg	50 mL	• Quantity is exactly equivalent to pack size, ie, 50 mL	Appropriate
1-2 y (8-11 kg)	Suspension	62.5 mg	125 mg /5 mL	2 times a day	10 d	125 mg 125 mg × 10 = 1250 mg	50 mL	• Quantity is exactly equivalent to pack size, ie, 50 mL	Appropriate

(continued)

Table 1. (continued)

Age (Weight)	Dosage Form	Dose	Strength	Dosing Frequency	Duration of Therapy	Dose/Day and Dose/Day × No. of Days	Quantity of Dosage Form to Be Used	Calculation	Result
2-4 y (12-19 kg)	Suspension	125 mg	125 mg /5 mL	2 times a day	10 d	250 mg 250 mg × 10 = 2500 mg	100 mL	• Quantity is exactly equal to available pack size, ie, 2 × 50 mL	Appropriate
								• 30 mL less in maximum available pack size of suspension, ie, 70 mL	Inappropriate
4-8 y (20-29 kg)	Suspension	187.5 mg	125 mg /5 mL	2 times a day	10 d	375 mg 375 mg × 10 = 3750 mg	150 mL	• 80 mL less in maximum available pack size of suspension, ie, 70 mL	Inappropriate
								• Quantity is exactly equal to required quantity (ie, 150 mL) after combining 1 × 70 mL, 1 × 50 mL and 1 × 30 pack sizes.	Appropriate
8-12 y (30-40 kg)	Suspension	250 mg	125 mg /5 mL	2 times a day	10 d	500 mg 500 mg × 5 = 5000 mg	200 mL	• Quantity is exactly available as 2 × 70 mL and 1 × 60 mL	Appropriate
								• 10 mL extra for pack size of 3 × 70 mL	Inappropriate
8-12 y (30-40 kg)	Suspension	250 mg	250 mg /5 mL	2 times a day	10 d	500 mg 500 mg × 5 = 5000 mg	100 mL	• 30 mL less in available pack size of suspension, ie, 70 mL	Inappropriate
12-18 y	Suspension	250 mg	250 mg /5 mL	2 times a day	10 d	500 mg 500 mg × 5 = 5000 mg	100 mL	• Quantity is exactly equivalent in pack sizes of 1 × 30 mL and 1 × 70 mL	Appropriate
12-18 y	Tablet	250 mg	250 mg per tab	2 times a day	10 d	500 mg 500 mg × 5 = 5000 mg	20 tablets	• Quantity equal to 2 available pack size of tablets (1 pack size = 10 tablets)	Appropriate
Indication: Otitis media									
2-4 y (12-19 kg)	Suspension	125 mg	125 mg /5 mL	2 times a day	5 d	250 mg 250 mg × 5 = 1250 mg	50 mL	• Quantity is exactly equal to available pack size, ie, 50 mL	Appropriate
8-12 y (30-40 kg)	Suspension	250 mg	125 mg /5 mL	2 times a day	5 d	500 mg 500 mg × 5 = 2500 mg	100 mL	• Quantity is exactly available as 1 × 30 mL and 1 × 70 mL	Appropriate
12-18 y	Suspension	250 mg	125 mg /5 mL	2 times a day	5 d	500 mg 500 mg × 5 = 2500 mg	100 mL	• Quantity is exactly equivalent in pack sizes of 1 × 70 mL and 1 × 30 mL	Appropriate
12-18 y	Tablet	250 mg	250 mg per tab	2 times a day	5 d	500 mg 500 mg × 5 = 2500 mg	10 tablets	• Quantity equal to available pack size of tablets (1 pack = 10 tablets)	Appropriate

Abbreviation: IV, intravenous;

Table 2. Cefotaxime Calculations.

Age (Weight)	Dosage Form	Dose	Strength	Dosing Frequency	Duration of Therapy	Dose/Day and Dose/Day × No. of Days	Quantity of Dosage Form to Be Used	Calculation	Result
Indication: Congenital gonococcal conjunctivitis									
Neonate (3.5 kg)	IM injection	100 mg/kg (350 mg)	0.25 g	Single bolus	1 d	350 mg	1 vial	• 100 mg less per dose	Inappropriate
Indication: Uncomplicated gonorrhea									
12-18 y (39-55 y)	IM injection	500 mg as a single dose	0.5 g/2 mL	1 time a day	1 d	500 mg	1 vial.	• Quantity is exactly equivalent to available pack size, ie, 500 mg.	Appropriate
Indication: Haemophilus epiglottis and septicemia									
7-21 d (3.7-4.1 kg)	IM/IV injection or IV infusion	25 mg/kg (92.5-102.5 mg)	0.25 g	3 times a day	7 d	277.5-307.5 mg 277.5-307.5 mg × 7 = 1942.5-2152.5 mg	21 vials	• 157.5-147.5 mg extra per dose. • 472.5-442.5 mg extra per day. • 3307.5-3097.5 mg extra for whole duration.	Inappropriate
21-28 d (4.1-4.3 kg)	IM/IV injection or IV infusion	25 mg/kg (102.5-107.5 mg)	0.25 g	3 times a day	7 d	307.5-322.5 mg 307.5-322.5 mg× 7 = 2152.5-2257.5 mg	21 vials	• 147.5-142.5 mg extra per dose. • 442.5-427.5 mg extra per day. • 3097.5-2992.5 mg extra for whole duration.	Inappropriate
12-18 y (39-55 y)	IM/IV injection or IV infusion	50 mg/kg (1950-2750 mg)	2 g	3 times a day	5 d	5850-8250 mg 5850-8250 mg× 5 = 29,250-41,250 mg	15 vials	• 50 mg extra for lower dose range. • 750 mg less for upper dose range and 1250 mg extra for 2 × dose. • 150 mg extra for lower dose range per day. • 2250 mg less for upper dose range and 3750 mg extra for 2 × dose per day. • 750 mg extra for lower dose range for whole duration. • 11,250 mg less for upper dose range and 18,750 mg extra for 2 × dose for whole duration	Inappropriate
Indication: Meningitis									
1-5 y (9-18 kg)	IV injection or IV infusion	50 mg/kg (450-900 mg)	1.0 g	4 times a day	10 d	1800-3600 mg 1800-3600 mg × 10 = 18,000-36,000 mg	40 vials	• 100 mg extra per dose. • 400 mg extra per day. • 4000 mg extra for whole duration.	Inappropriate
5-12 y (18-39 y)	IM/IV injection or IV infusion	50 mg/kg (900- 1950 mg)	1 g	4 times a day	10 d	3600-7800 mg 3600-7800 mg × 10 = 36,000-78,000 mg	40 vials	• 100 mg extra per dose. • 400 mg extra per day. • 4000 mg extra for whole duration.	Inappropriate
12-18 y (39-55 y)	IM/IV injection or IV infusion	50 mg/kg (1950- 2750 mg)	2 g	4 times a day	10 d	5850-8250 mg 5850-8250 mg × 1 = 58,500-82,500 mg	40 vials	• 50 mg extra for lower dose range. • 750 mg less for upper dose range and 1250 mg extra for 2 × dose. • 200 mg extra for lower dose range per day. • 3000 mg less for upper dose range and 5000 mg extra for 2 × dose per day. • 2000 mg extra for lower dose range for whole duration. • 7500 mg less for upper dose range and 50,000 mg extra for 2 × dose for whole duration	Inappropriate

Abbreviations: IM, intramuscular; IV, intravenous.

mg extra per dose, 1403.25 to 1378.5 mg extra per day and 9822.75 to 9649.5 mg for the whole treatment duration, indicated to be used in child of 1 to 2 months suffering from anaerobic infections. In addition, a highly inappropriate dosage form depicting shortfall of metronidazole formulation was suspension, that is, 10 mL less (for lower dose range) or 45 mL less (for upper dose range) in a pack of 60 mL, indicated in children of 1 to 6 years suffering from *Helicobacter pylori* infection (Table 3).

Amoxicillin

Overall, 59 calculations were made for amoxicillin (Supplemental Material 6). In only 9 cases, the quantity of formulations was sufficient to meet the dosage regimen for treatment. But the rest of the findings demonstrated that the available packaging sizes either had leftover or a shortfall of amoxicillin formulation. A highly inappropriate dosage form containing excess amount of amoxicillin was IV infusion, that is, 4200 mg extra for lower dose range (if 4 packs of 1-g strength were dispensed for whole duration) and 25,200 mg extra for the higher dose range (if 6 packs of 1-g strength were dispensed for whole duration), indicated in children of 12-18 years suffering from meningitis. Whereas, highly inappropriate dosage form depicting shortfall of amoxicillin formulation was suspension, that is, 15 mL less in minimum available strength indicated in children of 1 month to 1 year age suffering from acute otitis media (Table 4).

Gentamicin

Overall, 23 calculations were made for gentamicin (Supplemental Material 7). No gentamicin formulation was sufficient to meet the dosage regimen for treatment. All the findings demonstrated that the available packaging sizes contained leftover antibiotic formulation. A highly inappropriate dosage form containing excess amount of gentamicin was IV infusion, that is, 187.5 mg extra per day and 2625 mg extra for the whole treatment duration indicated in 5-12-year-old children suffering from septicemia, meningitis, biliary tract infections, acute pyelonephritis, endocarditis, pneumonia, and Listeria meningitis (Table 5).

Among the selected antibiotics, none of the gentamicin pack size and only 1 cefotaxime and metronidazole pack size was found appropriate in terms of the quantity required to complete the dosage regimen, while the antibiotic having most appropriate available packaging sizes was clarithromycin (Figure 1).

Discussion

The unavailability of age-appropriate medicine formulations and their packaging sizes is a global issue. Use of age-inappropriate formulations and packaging sizes may lead to irrational antibiotic use in pediatrics.[8,9,14] In 2007, the WHO campaign "make medicines child size" first highlighted this issue and stressed further research regarding the availability of appropriate child-specific medicinal formulations.[39] To our knowledge, this is the first study to determine the pediatric antibiotic pack size compliance with the dosage regimen in Pakistan. The findings of this study depicted a prominent discrepancy between the dosage regimen recommended by BNFC for pediatric patients and the quantity of product in antibiotic packs.

In this study, only 16 clarithromycin, 9 amoxicillin, 1 cefotaxime, and 1 metronidazole preparations were sufficient to meet the dosage regimen requirement for treatment, and none of the packaging sizes matched the dosage recommendations for gentamicin. These findings are comparable to the findings of a previous study which showed that only 4 of 32 antibiotic pack sizes were sufficient to meet the regimen, while the remaining packs either contained less quantity of antibiotic or had leftover doses.[8] The reasons behind the unavailability of appropriate antibiotic pack sizes could be lack of registered pediatric formulations and/or manufacturers' reluctance and lack of motivation to manufacture child-specific formulations because of the low profit margin or demand.[6,40,41] A UK study revealed that merely 30% of the formulations in the essential medicine list were considered as age-appropriate for neonates, infants, and young children.[42,43] Additionally, poor understanding of the differences between the pediatric and adult drug formulations among the health policy makers and pediatric healthcare team, and a lack of antibiotic packaging in accordance with recommended guidelines could be the other reasons of inappropriate packaging sizes.[8,44] Unavailability of age-appropriate packaging sizes leads to the manipulation of dose by pediatricians. Such manipulations may result in safety and efficacy issues, administration errors, or other unforeseen effects.[1,45]

In this study, excess quantities of antibiotics were observed in most of the available packaging sizes. Comparable findings were reported by an Australian study which showed that overall 31.3% of the prescribed formulations contained an excess quantity or had leftover doses of antibiotics.[8] This could be due to the fact that these formulations and packaging sizes were designed for adults or older children.[46] The leftover or excess quantity of an antibiotic formulation may lead to irrational drug use practices, for example, reuse or sharing of unprescribed antibiotics, which further increases the risk of drug interactions, difficulty in identifying the underlying disease, and development of antibiotic resistance.[42,47] Many studies reported that it was a very common practice among people to use leftover antibiotics for self-diagnosed or emergency conditions and sharing them with other family members or friends without even checking the expiry dates.[48-50] On the other hand, the extra amount of product, if not used, leads to wastage of medicine and may pose a financial burden on patients and the healthcare system.[46] An Iranian study found that the wastage and the cost associated with inappropriate formulation was higher in pediatrics as compared to adults, and antibiotics were the most wasted class of medicines.[46]

Table 3. Metronidazole Calculations.

Age (Weight)	Dosage Form	Dose	Strength	Dosing Frequency	Duration of Therapy	Dose/Day and Dose/Day × No. of Days	Quantity of Dosage Form to Be Used	Calculation	Result
Indication: Anaerobic infections									
1 mo to 2 mo (4.3-5.4 kg)	IV infusion	Day 1 15 mg/kg LD (64.5-81 mg)+ 7.5 mg /kg (32.25-40.5 mg) × 2	500 mg	1st dose + 2 times a day	7 d	(64.5-81 mg)+ (32.25- 40.5 mg) × 2 = 139.0-162 mg	21 vials	• 435.5-419 mg extra per loading dose. • 467.75-459.5 mg extra per dose. • 1403.25-1378.5 mg extra per day.	Inappropriate
		Day 2-6 7.5 mg/kg (32.25-40.5 mg)	500 mg	3 times a day		(96.75-121.5 mg) × 6 = 580.5-729 mg		• 9822.75-9649.5 mg extra for whole duration.	Inappropriate
2 mo to 1 y (5.4-9 kg)	IV infusion	7.5 mg/kg (40.5-67.5 mg)	500 mg	3 times a day	7 d	121.5-202.5 mg 121.5-202.5 mg × 7 = 850.5-1417.5 mg	21 vials	• 459.5-432.5 mg extra per dose. • 1378.5-1297.5 mg extra per day. • 9649.5-9082.5 mg for whole duration.	Inappropriate
1-5 y (9-18 kg)	IV infusion	7.5 mg/kg (67.5-135 mg)	500 mg	3 times a day	7 d	202.5-405 mg 202.5-405 mg × 7 = 1417.5-2835 mg	21 vials	• 432.5-365 mg extra per dose. • 1297.5-1095 mg extra per day. • 9082.5-7665 mg extra for whole duration.	Inappropriate
10-12 y	Suppositories	Day 1-3 1 g Day 4-7 1 g	1 g 1 g	3 times a day 2 times a day	7 d	3 g × 3 = 9 g 2 g × 4 = 8 g	17 suppositories	• 7 less in 1 pack and 3 extra in 2 packs.	Inappropriate
Indication: *Helicobacter pylori* infection									
1-5 y	Suspension	100 mg	200 mg /5 mL	2 times a day or 3 times a day	14 d	200 or 300 mg 200 or 300 mg × 14 = 2800 or 4200 mg	70 mL or 105 mL	• 10 mL or 45 mL less in 1 pack of 60 mL and 50 or 15 mL extra in 2 packs.	Inappropriate
5-6 y	Suspension	100 mg	200 mg /5 mL	2 times a day or 3 times a day	14 d	200 or 300 mg × 14 = 2800 or 4200 mg	70 mL or 105 mL	• 10 mL or 45 mL less in 1 pack of 60 mL and 50 or 15 mL extra in 2 packs.	Inappropriate
Indication: Surgical prophylaxis									
5-12 y (18-39 kg)	IV infusion	30 mg/kg (540-1170 mg)	500 mg	Before procedure	1 d	540-1170 mg	2-3 vials	• For lower dose range, 40 mg less per vial and 460 mg extra per 2 vials. • For higher dose range, 170 mL less per 2 vials and 330 mg extra per 3 vials.	Inappropriate
12-18 y (39-55 kg)	IV infusion	500 mg	500 mg	Before procedure and 3 doses every 8 h	1 d	500 mg+ (500 × 3 = 1500)	4 vials	• Quantity is exactly equal to 4 infusion packs.	Appropriate

Abbreviations: IV, intravenous.

Table 4. Amoxicillin Calculation.

Age (Weight)	Dosage Form	Dose	Strength	Dosing Frequency	Duration of Therapy	Dose/Day and Dose/Day × No. of Days	Quantity of Dosage Form to Be Used	Calculation	Result
Indication: Sinusitis									
7-28 d (3.7-4.3 kg)	Suspension	30 mg/kg max 125 mg (111-125 mg)	125 mg /5 mL	3 times a day	7 d	333-375 mg 333-375 mg × 7 = 2331-2625 mg	93.24-105 mL	• 3.24 mL less in maximum available pack size of suspension, ie, 90 mL	Inappropriate
1-5 y (9-18 kg)	Suspension	250 mg	250 mg /5 mL	3 times a day	7 d	750 mg 750 mg × 7 = 5250 mg	105 mL	• 15 mL less in maximum pack size of suspension, ie, 90 mL	Inappropriate
1-5 y (9-18 kg)	IV injection	20-30 mg/kg max 500 mg (180-270 to 360-540 mg)	500 mg /10 mL	3 times a day	7 d	540-1620 mg 540-1620 mg × 7 = 3780-11 340 mg	75.6-226.8 mL	• Quantity is exactly equivalent to pack size for upper dose range, ie, 500 mg/10 mL	Appropriate
5-12 y (18-39 kg)	Suspension	500 mg	250 mg /5 mL	3 times a day	7 d	1500 mg 150 mg × 7 = 1050 mg	210 mL	• Quantity is exactly equivalent if 3 packs of suspension are dispensed 1 × 90 mL and 2 × 60 mL	Appropriate
5-12 y (18-39 kg)	IV injection	20-30 mg/kg max 500 mg (360-540 to 780-1170 mg)	500 mg	3 times a day	7 d	1080-3510 mg 1080-3510 mg × 7 = 7560-24,570 mg	21 vials	• 140 mg extra for lower dose range for dose strength of 500 mg per dose. • 420 mg extra for lower dose range for dose strength of 500 mg per day. • 2940 mg extra for lower dose range for dose strength of 500 mg for whole duration. • Quantity is exactly equivalent to pack size for upper dose range, ie, 500 mg	Inappropriate Appropriate
Indication: Acute otitis media									
1 mo to 1 y (4.3-9 kg)	Suspension	125 mg	125 mg /5 mL	3 times a day	5 d	375 mg 375 mg × 5 = 1875 mg	75 mL	• 15 mL less in minimum pack size of suspension, ie, 60 mL • 15 mL extra in maximum pack size of suspension, ie, 90 mL	Inappropriate
1 mo to 1 y (4.3-9 kg)	Suspension	125 mg	125 mg /5 mL	3 times a day	7 d	375 mg 375 mg × 7 = 2625 mg	105 mL	• 15 mL less in maximum pack size of suspension, ie, 90 mL	Inappropriate
1 mo to 1 y (4.3-9 kg)	IV injection or IV infusion	20-30 mg/kg max 500 mg (86-129 to 180-270 mg)	500 mg	3 times a day	7 d	258-810 mg 258-810 mg × 7 = 1806-5670 mg	21 vials	• 330 mg extra per dose. • 990 mg extra per day. • 6390 mg extra for whole duration.	Inappropriate
1-5 y (9-18 kg)	IV Injection	20-30 mg/kg max 500 mg (180-270 to 360-540 mg)	250 mg	3 times a day	5 d	540-1620 mg 540-1620 mg × 5 = 2700-8100 mg	15 vials	• Quantity is exactly equivalent to pack size for upper dose range, ie, 500 mg	Inappropriate
5-12 y (18-39 kg)	Suspension	500 mg	250 mg /5 mL	3 times a day	3 d	1500 mg 1500 mg × 3 = 4500 mg	90 mL	• Quantity is exactly equivalent to available pack size, ie, 90 mL	Appropriate

(continued)

Table 4. (continued)

Age (Weight)	Dosage Form	Dose	Strength	Dosing Frequency	Duration of Therapy	Dose/Day and Dose/Day × No. of Days	Quantity of Dosage Form to Be Used	Calculation	Result
5 to 12 y (18-39 kg)	IV Injection	20-30 mg/kg Max.500 mg (360-540 to 780-1170 mg)	500 mg	3 times a day	3 d	1080-3510 mg 1080-3510 mg × 3 = 3240-10 530 mg	15 vials	• 140 mg extra for lower dose range for dose strength of 500 mg per dose. • 420 mg extra for lower dose range for dose strength of 500 mg per day. • 1260 mg extra for lower dose range for dose strength of 500 mg for whole duration. • Quantity is exactly equivalent to pack size for upper dose range for upper dose range, ie, 500 mg	Inappropriate Appropriate
5 to 12 y (18-39 kg)	Suspension	500 mg	250 mg /5 mL	3 times a day	5 d	1500 mg 1500 mg × 5 = 7500 mg	150 mL	• Quantity is exactly equivalent if 2 packs of suspension are dispensed 1 × 60 mL and 1 × 90 mL	Appropriate
5-12 y (18-39 kg)	IV injection	20-30 mg/kg max 500 mg (360-540 to 780-1170 mg)	500 mg	3 times a day	5 d	1080-3510 mg 1080-3510 mg × 5 = 5400-17,550 mg	15 vials	• 140 mg extra for lower dose range for dose strength of 500 mg per dose. • 420 mg extra for lower dose range for dose strength of 500 mg per day. • 2100 mg extra for lower dose range for dose strength of 500 mg for whole duration. • Quantity is exactly equivalent to pack size for upper dose range, ie, 500 mg	Inappropriate Appropriate
Indication: Pharyngitis, uncomplicated pneumonia, UTIs, cystic fibrosis									
1-5 y (9-18 kg)	IV injection	20-30 mg/kg max 500 mg (180-270 to 360-540 mg)	500 mg	3 times a day	3 d	540-1620 mg 540-1620 mg × 3 = 1620-4860 mg	9 vials	• Quantity is exactly equivalent to pack size for upper dose range, ie, 500 mg.	Appropriate
Indication: Meningitis									
1-5 y (9-18 kg)	IV infusion	100 mg/kg (900-1800 mg)	1 g	3 times a day	14 d	2700-5400 mg 2700-5400 mg × 14 = 37,800-75,600 mg	42 vials	• 100 mg extra for lower dose range for dose strength of 1000 mg per dose. • 300 mg extra for lower dose range for dose strength of 1000 mg/100 mL per day. • 4200 mg extra for lower dose range for dose strength of 1000 mg for whole duration. • 200 mg extra for upper dose range for dose strength of 2 × pack of 1000 mg per dose. • 600 mg extra for upper dose range for dose strength of 2 × pack of 1000 mg per day. • 8400 mg extra for upper dose range for dose strength of 2 × pack of 1000 mg for whole duration.	Inappropriate

(continued)

Table 4. (continued)

Age (Weight)	Dosage Form	Dose	Strength	Dosing Frequency	Duration of Therapy	Dose/Day and Dose/Day × No. of Days	Quantity of Dosage Form to Be Used	Calculation	Result
12-18 y (39-54 kg)	IV infusion	100 mg/kg (3900-5400 mg)	1 g	3 times a day	11,700-16,200 mg 11,700-16,200 mg × 14 = 163,800-226,800 mg	14 d	42 vials	• 100 mg extra per lower dose range for 4 × dose strength of 1 g. • 300 mg extra for lower dose range for 4 × dose strength of 1 g per day. • 4200 mg extra for lower dose range for 4 × dose strength of 1 g for whole duration. • 600 mg extra per higher dose range for 6 × dose strength of 1 g. • 1800 mg extra for higher dose range for 6 × dose strength of 1 g per day. • 25,200 mg extra for higher dose range for 6 × dose strength of 1 g for whole duration.	Inappropriate
Indication: Group B Streptococcus infections									
12-18 y (39-54 kg)	IV infusion	50 mg/kg (1950-2700 mg)	1 g	4 times a day	14 d	7800-10,800 mg 780-10,800 mg × 14 = 109,200-151,200 mg	56 vials	• 50 mg extra for lower dose range for 2 × dose strength of 1 g per dose. • 200 mg extra for lower dose range for 2 × dose strength of 1 g per day. • 2800 mg extra for lower dose range for dose strength of 1 g for whole duration. • 300 mg extra for upper dose range for 3 packs of strength of 1 g per dose. • 1200 mg extra for upper dose range for 3 packs of strength of 1 g per day. • 16,800 mg extra for upper dose range for 3 packs of strength of 1 g for whole duration.	Inappropriate

Abbreviation: IV, intravenous.

Table 5. Gentamicin Calculations.

Age (Weight)	Dosage Form	Dose	Strength	Dosing Frequency	Duration of Therapy	Dose/Day and Dose/Day × No. of Days	Quantity of Dosage Form to Be Used	Calculation	Result
Indication: Septicemia, meningitis, biliary tract infections, acute pyelonephritis, endocarditis, pneumonia, listeria meningitis									
5-12 y (18-39 kg)	IM or IV injection or IV Infusion	2.5 mg/kg (45-97.5 mg)	160 mg	3 times a day	14 d	135-292.5 mg 135-292.5 mg × 14 = 1890-4095 mg	42 vials	• 62.55 mg extra dose. 187.5 mg extra per day. • 2625 mg extra for whole duration.	Inappropriate
Indication: Pseudomonas lung infection in cystic fibrosis									
5-12 y (18- 39 kg)	IV injection or IV infusion	3 mg/kg (54-117 mg)	160 mg	3 times a day	14 d	162-351 mg 162-351 mg × 14 = 2268-4914 mg	42 vials	• 43 mg extra per dose. • 129 mg extra per day. • 1806 mg extra for whole duration.	Inappropriate
12-18 y (39-55 kg)	IM or IV injection or IV infusion	3 mg/kg (117-165 mg)	160 mg	3 times a day	14 d	351-495 mg 351-495 mg × 14 = 4914-6930 mg	42 vials	• 43 mg extra for lower dose range per dose. • 129 mg extra for lower dose range per day. • 1806 mg extra for lower dose range per day. • 155 mg extra for upper dose range for 2 × pack per dose. • 465 mg extra for upper dose range for 2 × pack per dose. • 6510 mg extra for upper dose range for 2 × pack per dose.	Inappropriate

Abbreviations: IM, intramuscular; IV, intravenous.

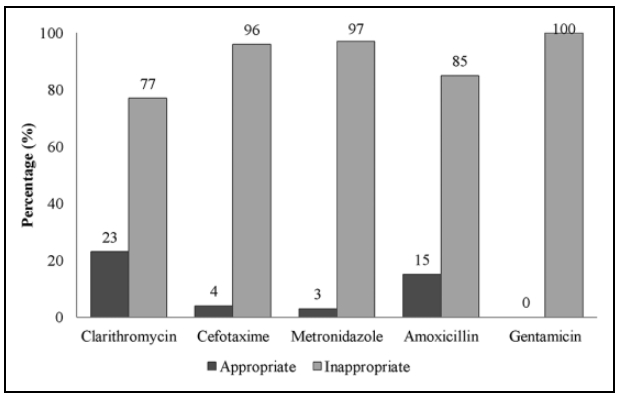

Figure 1. Extent of appropriateness and inappropriateness of the available pack sizes of the selected antibiotics.

The findings of this study also showed that the available antibiotic pack sizes contained a small quantity of product. An Indian and Australian study also indicated that the antibiotic formulations contained an inadequate volume of product intended to be used in pediatrics.[8,14] The insufficient volume of product may lead to a suboptimal dose of antibiotic followed by development of antimicrobial resistance.[8] While on the other hand, the purchase of another pack of medicine to complete the treatment regimen may result in increased social visits, higher treatment costs, greater financial burden, and leftover medicines.[14,38]

Our findings showed that highly inappropriate dosage forms in terms of packaging sizes were IV infusions and oral suspensions, which were mostly available in powder form and used after reconstitution. It is very critical to maintain stability, compliance, and proper usage of these dosage forms by the patients, caregivers, and health care professionals.[51] These reconstituted liquid dosage forms are highly prone to degradation and need to be stored in the refrigerator in order to gain the required benefits.[52] But many patients fail to fulfil the specified storage conditions because of many reasons like unavailability of refrigerator and/or interrupted electric power supply. Previous studies have reported difficulties for resource-limited settings to meet antibiotic refrigeration requirements, consequently creating a high-risk environment for toxicity and adverse events.[52,53] Misuse of inadequately stored leftover reconstituted liquid preparations is very common among pediatric facilities.[54,55] A study from Jordan reported that the use of reconstituted leftover suspension from one child to another was frequently practiced by the mothers.[54] Moreover, use of leftover parenteral product contributes to risk of administration errors and increased health care costs.[56,57] According to a published study, if one vial contained 10 times extra product in the pack, then there was 10 times more probability of occurrence of administration errors among pediatrics.[57]

In Pakistan, acute respiratory tract infections (ARTIs) are the chief pediatric complaints for which antibiotics are prescribed.[58] Penicillins (amoxicillin, ampicillin) are the preferred drug of choice for lower respiratory tract infections while macrolides (clarithromycin) and cephalosporins (cefotaxime) are preferred for upper respiratory tract infections.[59] Our findings revealed that most of the packaging sizes of selected antibiotics did not supply the medicine required to complete the recommended treatment duration in pediatrics for common indications. This could result in a high rate of medication errors and subsequent irrational use of antibiotics among pediatric patients in Pakistan. To add strength to this notion, a Pakistani study reported that merely 29.1% of neonates, 30% of infants, and 36.8% of children had received rational antibiotic dose.[24] Moreover, according to the Pakistan Society of Health System Pharmacists (PSHP), medication errors caused mortality of about 400,000 to 500,000 residents annually,[59,60] and among all the errors, pediatrics were more prone to dosing errors.[61]

Like every study, this study also has few limitations. First, only 5 antibiotics were investigated while there is a need to study a complete range of antibiotics available for pediatrics and other age groups. Second, the appropriateness of antibiotic pack size was studied using only 1 set of recommendation (ie, BNFC) while the results could be slightly different with regard to other international treatment guidelines for pediatrics. We used BNFC because it is trusted by the health care professionals worldwide and is used as a primary source of information to minimize medication errors in pediatrics.

Besides novel contributions to the academic literature, this study has important implications for policy and practice. The evidence-based insight gained from this study is expected to draw the attention of the health policy makers and regulatory authorities toward unavailability of age-appropriate antibiotic pack sizes in the country. The study emphasized the need to strengthen the pharmaceutical packaging of antibiotics through strict regulation and compulsion on pharmaceutical industries to manufacture age-appropriate pack sizes regardless of their low profit and demand. This study also provides a foundation for future research, and it is strongly recommended to further explore the issue of inappropriate pack sizes for all essential and lifesaving medicines at the national and international level.

Conclusion

The findings of this study point to a mismatch between antibiotic packaging sizes and the recommended duration of treatment in pediatric patients for common indications. Among the selected antibiotics, clarithromycin had the most appropriate packaging sizes, while none of the packaging sizes for gentamicin was found appropriate. Highly inappropriate dosage forms containing excess or shortfall of antibiotics per pack were IV infusions and oral suspensions.

Declaration of Conflicting Interests

No potential conflicts were declared.

Funding

No financial support of the research, authorship, and/or publication of this article was declared.

ORCID iD

Iram Malik https://orcid.org/0000-0001-8029-7163
Muhammad Atif https://orcid.org/0000-0001-6866-8152

Supplemental Material

Supplemental material for this article is available online.

References

1. World Health Organization. *Promoting Safety of Medicines for Children*. Geneva: World Health Organization; 2007.
2. Nunn T, Williams J. Formulation of medicines for children. *Br J Clin Pharmacol*. 2005;59(6):674-676.
3. Ivanovska V, Rademaker CM, van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: a review of challenges and progress. *Pediatr*. 2014;134(2):361-372.
4. European Medicines Agency. Guidelines on Pharmaceutical development of Medicines for Paediatric Use. 2013.
5. Le Doare K, Barker CIS, Sharland AIM. Improving antibiotic prescribing for children in the resource-poor setting. *Br J Clin Pharmacol*. 2015;79(3):446-455.
6. Hoppu K, Ranganathan SS, Dodoo AN. Realities of paediatric pharmacotherapy in the developing world. *Arch Dis Child*. 2011;96(8):764-768.
7. Standing JF, Tuleu C. Paediatric formulations—getting to the heart of the problem. *Int J Pharm*. 2005;300(1-2):56-66.
8. McGuire TM, Smith J, Del Mar C. The match between common antibiotics packaging and guidelines for their use in Australia. *Aust N Z J Public Health*. 2015;39(6):569-572.
9. Kaplan W, Mathers C. *The World Medicines Situation* 2011. Geneva: World Health Organization; 2011.
10. Rogawski ET, Platts-Mills JA, Seidman JC, et al. Use of antibiotics in children younger than two years in eight countries: a prospective cohort study. *Bull World Health Organ*. 2017;95(1):49.
11. Schirm E, Tobi H, de Vries TW, Choonara I, De Jong-van den Berg LT. Lack of appropriate formulations of medicines for children in the community. *Acta Paediatr*. 2003;92(12):1486-1489.
12. Ekins-Daukes S, McLay JS, Taylor MW, Simpson CR, Helms PJ. Antibiotic prescribing for children. Too much and too little? Retrospective observational study in primary care. *Br J Clin Pharmacol*. 2003;56(1):92-95.
13. Fredericks I, Hollingworth S, Pudmenzky A, Rossato L, Kairuz T. "Repeat" prescriptions and antibiotic resistance: findings from Australian community pharmacy. *Int J Pharm Pract*. 2017;25(1):50-58.
14. Naik PP, Mehta CD, Srivastava SK. Analysis of commonly used pediatric systemic antibacterial liquid formulations for rational drug therapy. *Natl J Physiol Pharm Pharmacol*. 2017;7(4):348.
15. Benjamin L, Frush K, Shaw K, et al. Pediatric medication safety in the emergency department. *Pediatrics*. 2018;141(3):e20174066.
16. Girma S, Sisay M, Mengistu G, Amare F, Edessa D. Antimicrobial utilization pattern in pediatric patients in tertiary care hospital, eastern Ethiopia: the need for antimicrobial stewardship. *Hosp Pharm*. 2018;53(1):44-54.
17. McCague P, McElnay J, Donnelly R. What are your views on specials and extemporaneous medicines preparation? *Stroke*. 2018;13:57.
18. Pai V, Nahata M. Need for extemporaneous formulations in pediatric patients. *J Pediatr Pharmacol Ther*. 2001;6:107-121.
19. Pawar S, Kumar A. Issues in the formulation of drugs for oral use in children. *Paediatr Drugs*. 2002;4(6):371-379.
20. Shankar P, Upadhyay D, Subish P, Dubey A, Mishra P. Prescribing patterns among paediatric inpatients in a teaching hospital in western Nepal. *Singapore Med J*. 2006;47(4):261.
21. Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. *Expert Opin Drug Deliv*. 2007;4(1):37-45.
22. Qindeel S, Kashif M. *The state of children in Pakistan* 2015.
23. World Health Organization. *Framework for Health Information Systems and Core Indicators for Monitoring Health Situation and Health System Performance* 2016. Geneva: World Health Organization; 2016.
24. Tasawer Baig M, Akbar Sial A, Huma A, Ahmed M, Shahid U, Syed N. Irrational antibiotic prescribing practice among children in critical care of tertiary hospitals. *Pak J Pharm Sci*. 2017;30(4)(suppl):1483-1489.
25. Khan IA, Hasnain F, Yasoob M, Qamar S, Chaudry K, Hussain M. Use of antibiotics within the Integrated Management of Childhood Illness (IMCI): guidelines in pediatric outpatient settings. Paper presented at: APMC 2016.
26. Abera B, Kibret M, Mulu W. Knowledge and beliefs on antimicrobial resistance among physicians and nurses in hospitals in Amhara Region, Ethiopia. *BMC Pharmacol Toxicol*. 2014;15(1):26.
27. Chang J, Ye D, Lv B, et al. Sale of antibiotics without a prescription at community pharmacies in urban China: a multicentre cross-sectional survey. *J Antimicrob Chemother*. 2017;72(4):1235-1242.
28. Atif M, Azeem M, Sarwar MR, et al. WHO/INRUD prescribing indicators and prescribing trends of antibiotics in the Accident and Emergency Department of Bahawal Victoria Hospital, Pakistan. *SpringerPlus*. 2016;5(1):1928.
29. Essack S, Bell J, Shephard A. Community pharmacists—leaders for antibiotic stewardship in respiratory tract infection. *J Clin Pharm Ther*. 2018;43(2):302-307.
30. Mason T, Trochez C, Thomas R, Babar M, Hesso I, Kayyali R. Knowledge and awareness of the general public and perception of pharmacists about antibiotic resistance. *BMC Public Health*. 2018;18(1):711.
31. Ali I, Khan TM. Potential for community pharmacies to promote rational drug use in Pakistan. *Res Social Adm Pharm*. 2016;12(1):167-168.
32. Atif M, Ahmad M, Saleem Q, Curley L, Qamar-uz-Zaman M, Babar Z-U-D. Pharmaceutical policy in Pakistan. In: Babar Z-U-D, ed. *Pharmaceutical Policy in Countries with Developing Healthcare Systems*. Cham: Springer International Publishing; 2017:25-44.
33. Atif M, Azeem M, Sarwar MR, et al. Evaluation of prescription errors and prescribing indicators in the private practices in Bahawalpur, Pakistan. *J Chin Med Assoc*. 2018;81(5):444-449.

34. Pakistan Bureau of Statistics. *Province wise provisional results of census—2017*. Islamabad: Pakistan Bureau of Statistics, 2017.
35. Paediatric Formulary Committee. *British National Formulary for Children (BNFC)*. London: Pharmaceutical Press; 2016-2017. http://www.medicinescomplete.com. Accessed December 25, 2018.
36. Qureshi Y, Dayo A, Ghoto M, et al. Evaluation of prescriptions containing antibiotics in pediatrics, suffering from respiratory tract infections at selected Hospitals of Jamshoro and Hyderabad, Pakistan. *B55 Pediatr Clin Stud*. 2018;197:A3656.
37. Neeshat M, ed. *PharmaGuide*. 24th ed. Karachi, Pakistan: PharmaGuide Publishing Co; 2016.
38. Mukherjee S, Saha N. Correlation of recommendations of treatment guidelines and frequently prescribed antibiotics: evaluation of their pharmaceutical pack size. *Basic Clin Pharmacol Toxicol*. 2017;122(3):317-321.
39. World Health Organization. Efforts on child-appropriate medicines intensify. http://www.who.int/mediacentre/news/releases/2007/pr63/en/. Published 2007.
40. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet*. 2009; 373(9659):240-249.
41. Chen W, Tang S, Sun J, Ross-Degnan D, Wagner AK. Availability and use of essential medicines in China: manufacturing, supply, and prescribing in Shandong and Gansu provinces. *BMC Health Serv Res*. 2010;10(1):211.
42. Le Doare K, Barker CI, Irwin A, Sharland M. Improving antibiotic prescribing for children in the resource-poor setting. *Br J Clin Pharmacol*. 2015;79(3):446-455.
43. Duncan JC, Orubu S, Tuleu C, Turner M, Nunn AJ. Age-appropriate evaluation and availability of enteral drug formulations in WHO essential medicines list for children. Paper presented at: 4th Conference of the European Paediatric Formulation Initiative (EuPFI); 2012; Prague.
44. Batchelor HK, Marriott JF. Formulations for children: problems and solutions. *Br J Clin Pharmacol*. 2015;79(3):405-418.
45. Venables R, Marriott J, Stirling H. FIND OUT: key problems with children's medicines formulations . . . It's a taste issue. *Int J Pharm Pract*. 2012;20(suppl 2):23.
46. Karamikhah R, Firouzabadi D, Bahmani S, Vazin A. Cost estimation related to drug waste in two major pediatric referral centers and one adult hospital in southern Iran: comparative cross-sectional study. *Trends Pharma Sci*. 2018;4(1).
47. Nepal G, Bhatta S. Self-medication with antibiotics in WHO Southeast Asian Region: a systematic review. *Cureus*. 2018; 10(4):e2428.
48. Okeke IN, Adebayo L. Export of antimicrobial drugs by West African Travelers. *J Travel Med*. 2003;10(2):133-135.
49. Parimi N, Pinto Pereira LM, Prabhakar P. The general public's perceptions and use of antimicrobials in Trinidad and Tobago. *Rev Panam Salud Publica*. 2002;12(1):11-18.
50. Desai AJ, Gayathri G, Mehta D. Public's perception, knowledge, attitude and behaviour on antibiotic resistance—a survey in Davangere City, India. *J Prev Med Holistic Health*. 2016;2(1): 17-23.
51. Campbell GA, Vallejo E. Primary packaging considerations in developing medicines for children: oral liquid and powder for constitution. *J Pharma Sci*. 2015;104(1):52-62.
52. Jassim AM.In-home drug storage and self-medication with antimicrobial drugs in Basrah, Iraq. *Oman Med J*. 2010; 25(2):79.
53. Peace N, Olubukola O, Moshood A. Stability of reconstituted amoxicillin clavulanate potassium under simulated in-home storage conditions. *J Appl Pharm Sci*. 2012;2(1):28-31.
54. Romman HAHA. Patterns of antibiotic use among children. *Int J Med Sci*. 2013;5(6):264-272.
55. Chan GC, Tang SF. Parental knowledge, attitudes and antibiotic use for acute upper respiratory tract infection in children attending a primary healthcare clinic in Malaysia. *Singapore Med J*. 2006; 47(4):266-270.
56. Chaves CMP, Bezerra CM, Lima FET, Cardoso MVLML, Fonseca SGDC, Silva VMD. Residual volume in vials of antibiotics used in pediatrics. *Rev Esc Enferm USP*. 2017;51:e03234.
57. Koren G, Barzilay Z, Greenwald M. Tenfold errors in administration of drug doses: a neglected iatrogenic disease in pediatrics. *Pediatrics*. 1986;77(6):848-849.
58. Taufiq M, Zuberi RW. Overuse of antibiotics in children for upper respiratory infections (URIs): a dilemma. *J Coll Physicians Surg Pak*. 2011;21(1):60.
59. Iftikhar S, Sarwar MR, Saqib A, Sarfraz M. Antibiotic prescribing practices and errors among hospitalized pediatric patients suffering from acute respiratory tract infections: a multicenter, cross-sectional study in Pakistan. *Medicina*. 2019;55(2):44.
60. Medication errors cause half a million deaths in Pakistan, say pharmacists. *Dawn*, October 11, 2017.
61. Kozer E. Medication errors in children. *Paediatr Drugs*. 2009; 11(1):52-54.