

COMPARATIVE ANALYSIS OF APPROPRIATENESS OF DRUG INFORMATION GIVEN IN PEDIATRIC FORMULARIES AVAILABLE IN INDIA

Running title: ANALYSIS OF PEDIATRIC FORMULARIES AVAILABLE IN INDIA

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ABSTRACT: *Objective:* This study was done to assess the appropriateness of drug information on prescribing in Pediatric age group given in a popular formulary, CIMS and IAP.

Methods and Material: We collected detailed information of 51 drugs (Anti-infectives, NSAIDs, Drugs acting on respiratory system and Vitamins) which are commonly prescribed in pediatric age group from Current Index of Medical specialties (CIMS) (April-July 2012) and Indian Academy of Pediatrics (IAP) Drug formulary (2013) 30th edition. WHO model formulary for children 2010, was used as standard reference. We compared appropriateness of drug information which is given in CIMS and IAP with WHO model formulary for children.

Results: In our study, it was found that indication was inappropriate for 52% drugs in IAP and 73% drugs in CIMS, regarding contraindication 36% drugs in IAP and 43% drugs in CIMS was inappropriate, Precautions was inappropriate for 77% drugs in IAP and 88% in CIMS, Drug dosage was not mentioned appropriately for 75% drugs in IAP and 85% drugs in CIMS, Relevant information in pediatric patients in presence of renal and hepatic impairment was not mentioned for 86% drugs in IAP and 100% drugs in CIMS, adverse effects were not mentioned properly for 77% drugs in IAP and 95% in CIMS, interactions were not mentioned properly for 75% drugs in IAP and 83% in CIMS and ancillary information was inappropriate for 39% drugs in IAP and 70% in CIMS.

Conclusions: This study highlights the inadequacy of popular Indian formularies CIMS and IAP in context of pediatric prescribing. Thus, there is imminent need of a pediatric national formulary with due focus on guidelines for pediatric prescribing.

KEYWORDS: Appropriateness, Drug formulary, Pediatrics.

KEY MESSAGES: *There is ample scope of improvement in existing pediatric formularies. Hence we suggest there is need to establish a national pediatric formulary to provide therapeutic guidelines to prescribers.*

1 INTRODUCTION

Pediatric patients comprise a large proportion of the patient population, but concern about their medication safety has been neglected for a long time. Drug prescribing for pediatric patients offers special challenge. ^[1] They are the most vulnerable group of population suffering from frequent but usually non-serious illness. Most of these are self-limiting and treated not only inappropriately but also report to polypharmacy. ^[2] In 2007, the World Health Assembly passed a Resolution titled 'Better Medicines for Children'. ^[1] This resolution recognized the need for research and development into medicines for children, including better dosage forms, better evidence and better information about how to ensure that medicines for treating the common childhood diseases are given at the right dose for children of all ages. Compared to adult medicines, drug use in pediatrics is not extensively researched and range of licensed drug in appropriate dose form is limited. ^[3] Unfortunately, nowadays, 50% of the medicines used in children may not have been studied in this age group. ^[4] Children

have therapeutic needs which probably cannot be met if medicines representing major therapeutic advances in adults are not tested and labeled for pediatric use. Prelicensure studies on safety and efficacy of a drug are generally carried out in adult subjects.^[5] In majority of times their safety and tolerability are extrapolated from such adult studies. Once a medicine becomes available in the market for adults, it is possible to use it in children in an off-label way. Thus, the use of unlicensed and off-label medicines for children has been a common practice for decades; this does not offer children the same quality, safety and efficacy of medicines as in adults. Approximately 75% of the prescription medications listed in the Physician's Desk Reference lack pediatric labelling.

Inappropriate prescribing (IP) is a major public health problem and screening for IP is highly desirable since detection and correction are easy and worthwhile.^[6] Most developed nations have formularies to provide therapeutic guidelines to prescribers and enhance rational use of drugs. Most prescribers look upon other sources of drug information like Current Index of Medical Specialties (CIMS), Drug Formulary, Monthly Index of Medical Specialities (MIMS), Drug Index, Drugs Today etc., for guidance on drug information. These proprietary formularies may have shortcomings in terms of authenticity, accuracy of drug information in general, and a specific age group of patients, in particular. Promotion of appropriate and safe use of drugs in children is the need of the hour. Hence there is a need to quantify these errors and look for possible solutions.

Thus, this study was done with the objective to assess the appropriateness of drug information on prescribing in pediatric age group given in a popular formulary, CIMS-India (April-July 2012) and IAP drug formulary (2013) 30th edition.

2 MATERIALS AND METHODS

We collected detailed information of 51 drugs which are commonly prescribed in pediatric age group. List of drugs included are anti-infective, non-steroidal anti-inflammatory drugs (NSAIDs), drugs acting on respiratory system and vitamins. WHO model formulary for children 2010 was taken as a standard reference and given information of drugs considered appropriate. Detailed information about the drug groups was taken from Current Index of Medical specialties (CIMS-India) (April-July 2012) and Indian Academy of Pediatrics (IAP) Drug formulary (2013) 30th edition (which is published by Indian Pediatrics Association). Appropriateness was checked regarding indications, contraindications, precautions, dosage, renal and hepatic impairment, adverse effects, interactions and ancillary information. We compared the appropriateness of drug information which is given in CIMS and IAP with WHO model formulary for children. Comparison of drug information was also done between IAP and CIMS.

3 RESULTS

The study results showed that out of the selected 51 drugs from WHO Model formulary for children, informations were lacking for 11 drugs in CIMS which include Niclosamide, Benzathine Benzyl Penicillin, Benzyl Penicillin, Procaine Benzyl Penicillin, Trimethoprim, Epinephrine, Diloxanide furoate, Ferrous salt, Vit K, Riboflavin and Thiamine. As compared to WHO Model Formulary for children appropriate informations were not mentioned, for all of the rest 40 drugs in CIMS (fig.1)

In CIMS, 29 drugs had inappropriate information regarding indications and the remaining drugs with appropriate information were Levamisole, Praziquantal, Ivermectin, Cefalexin, Erythromycin, Nitrofurantoin, Gentamicin, Ibuprofen, Paracetamol, Budesonide and Salbutamol.

Considering contraindications, informations were inappropriate for 17 drugs which included Amoxicillin, Amoxicillin + Clavulanic Acid, Ceftriaxone, Imipenem+ Cilastin, Azithromycin, Chloramphenicol, Ciprofloxacin, Doxycycline, Erythromycin, Nitrofurantoin, Gentamicin, Sulfamethoxazole+Trimethoprim, Clindamycin, Ibuprofen, Folic acid, Vit C and Colecalciferol.

Details regarding precautions were inappropriate for 35 drugs and the informations were appropriate for Folic acid, Vit C, Colecalciferol, Pyridoxine and Retinol. Dosages were inappropriate (age-wise, weight-wise, dose, duration) for 34 drugs while it was appropriate for Levamisole, Ampicillin, Chloramphenicol, Sulfamethoxazole+ Trimethoprim, Budesonide and Vit C.

Relevant information in presence of renal and hepatic impairment (Modifications, Severity and consequences), were not mentioned for all the 40 drugs. Adverse effects were not properly mentioned for 38 drugs, while for Pyrantel and Paracetamol it was mentioned properly.

WHO model formulary for children 2010 has put asterisk mark (*) for some of the potentially hazardous interactions. These interactions were not mentioned for 33 drugs while it was mentioned properly for Albendazole, Ivermectin, Paracetamol, Colecalciferol, Pyridoxine, Retinol and Hydroxycobalamine.

WHO Model Formulary has mentioned ancillary information where ever applicable such as administration instructions, patient advice and storage information; while in CIMS the same was lacking for 28 drugs and the remaining 12 drugs which had the ancillary information are Pyrantel, Amoxicillin, Ampicillin, Cefalexin, Cefazolin, Doxycycline, Acetylsalicylic acid, Ibuprofen, Paracetamol, Salbutamol, Folic acid and Hydroxycobalamine.

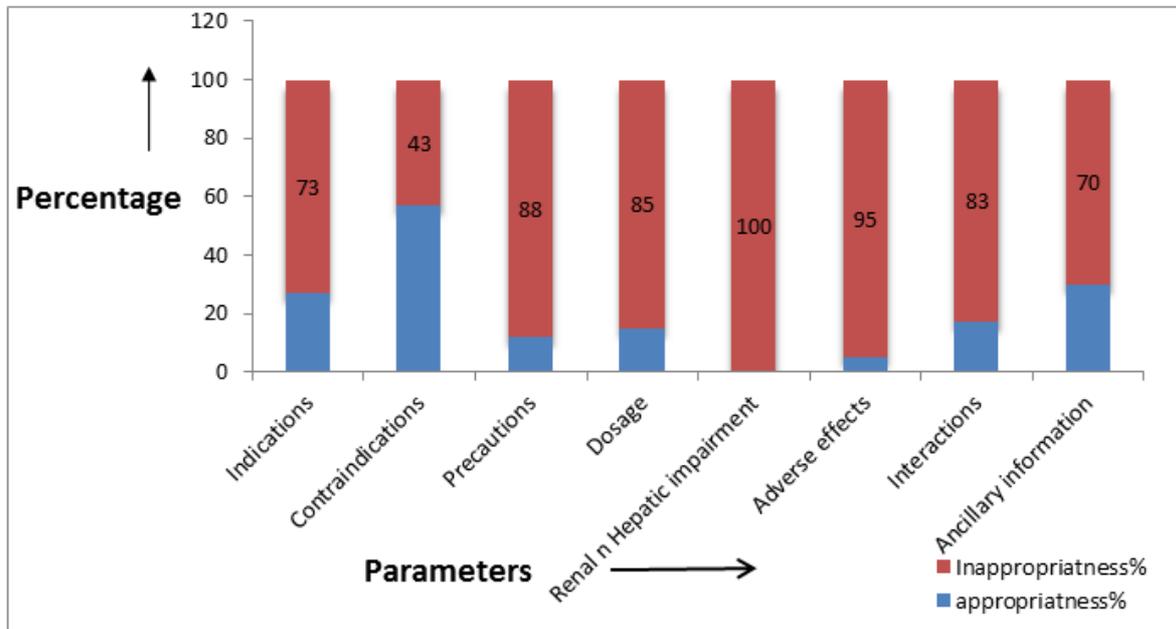


Figure 1: Qualitative comparative analysis between WHO model formulary and CIMS

When we compared IAP drug formulary with WHO Model formulary for children, study results showed that out of the selected 51 drugs, informations were lacking for 7 drugs in IAP which include Amoxicillin+Clavulanic acid, Cefazolin, Procaine Benzyl Penicillin, Doxycycline, Sulfamethoxazole+trimethoprim, Trimethoprim and Epinephrine. Considering all parameters, appropriate information was not mentioned for all of the rest 44 drugs in IAP as compared to WHO Model Formulary for children (Fig.2). Inappropriate information regarding indications were present in 23 drugs and remaining drugs had appropriate information which include Albendazole, Niclosamide, Ivermectin, DEC, Ibuprofen, Paracetamol, Cloxacillin, Imipenam + Cilastin, Chloramphenicol, Erythromycin, Gentamicin, Metronidazole, Nitrofurantoin, Clindamycin, Budesonide, Diloxanide furoate, Amphotericin B, Ferrous salt, Folic acid, Vit K and Hydroxycobalamine. Considering contraindications information of 28 drugs were appropriate and the rest had inappropriate informations which include Albendazole, Amoxicillin, Benzathine benzyl Penicillin, Ceftriaxone, Cefotaxime, Imipenam+Cilastin, Chloramphenicol, Ciprofloxacin, Erythromycin, Nitrofurantoin, Clindamycin, Vancomycin, Diloxanide furoate, Ferrous salt, Vit C and Colecalciferol. Details regarding precautions were inappropriate for 34 drugs and the remaining 10 drugs which include Levamisole, Diloxanidefuroate, Amphotericin B, Folic acid, Vit C, Pyridoxine, Retinol, Riboflavin, Thiamine and Hydroxycobalamine had appropriate information. Dosage were inappropriate (age-wise, weight-wise, dose, duration) for 33 drugs, rest of the drugs which include Abendazole, Levamisole, Ibuprofen, Ampicillin, Cephalexin, Cloxacillin, Imipenam + Cilastin, Chloramphenicol, Budesonide, Diloxanide furoate and Folic acid had appropriate information. Relevant information in presence of renal and hepatic impairment (Modifications, Severity and consequences), were not mentioned for 38 drugs, remaining drugs with appropriate information were Levamisole, Ceftazidime, Ciprofloxacin, Metronidazole, Thiamine and Colecalciferol. Adverse effects were not mentioned properly for 34 drugs, while for the remaining 10 drugs (Pyrantel, Acetylsalicylic acid, Budesonide, Diloxanide furoate, Amphotericin B, Vit K, Colecalciferol, Retinol, Riboflavin and Thiamine) it was mentioned properly. WHO model formulary for children 2010 has put asterisk mark (*) for some of the potentially hazardous interactions. These interactions were not mentioned in 33 drugs while it was mentioned properly for Albendazole, Niclosamide, Pyrantel, DEC, Paracetamol, Diloxanidefuroate, Colecalciferol, Pyridoxine, Retinol, Riboflavin and Thiamine. WHO Model Formulary has mentioned ancillary information where ever applicable such as administration instructions, patient advice and storage information which was lacking for 17 drugs which include Levamisole, Pyrantel, Ivermectin, DEC, Cefotaxime, Ciprofloxacin, Erythromycin, Gentamicin, Metronidazole, Nitrofurantoin, Ferrous salt, Vit K, Vit C, Colecalciferol, Pyridoxine, Retinol and Thiamine.

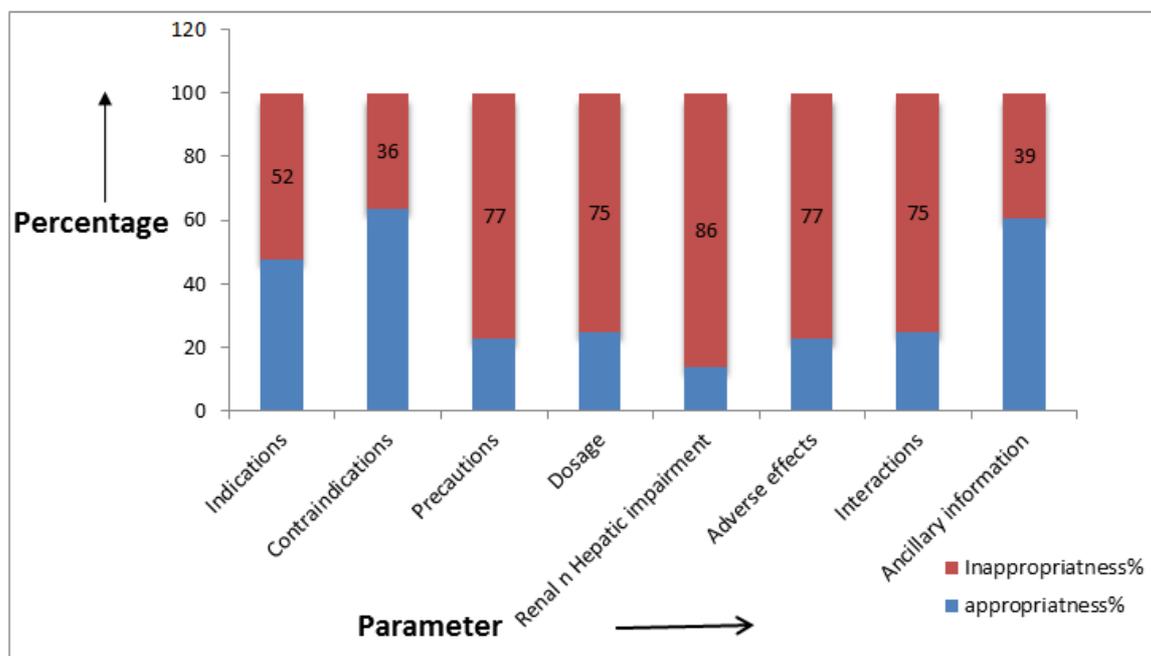


Figure2: Qualitative comparative analysis between WHO model formulary and IAP

There are additional 39 drugs as shown in Table 3, with related information mentioned in IAP under sections of antimicrobial, antiprotozoal, antihelminthic, NSAIDS, drugs acting on respiratory tract and vitamins which are absent in WHO list of essential medicines 17th ed. and Indian list of essential medicines.

Table 3: Additional drugs mentioned in IAP

SECTIONS	DRUG LIST
Antimicrobial	Aztreonam, Carbapenems, Cefaclor, Cefadroxil, Cefdinir, Cefepime, Cefprozane, Cefpodoxime, Cefuroxime, Furazolidone, Linezolid, Meropenem, Minocycline, Netilmicin, Oxytertracyclin, Piperacillin with tazobactam Roxithromycin, Spiramycin, Teicoplanin and Tobramycin.
Antiprotozoal	Gamma Benzene Hexachloride, Nitazoxanide, Furazolidone, Nitazoxanide and Tinidazole.
NSAIDS	Indomethacin, Meloxicam, Naproxen, Nimesulide and Piroxicam.
Drug acting on respiratory system	Aminophylline, Theophylline and Pholcodine.
Vitamins	Alphacalcidol, Biotin, Ergocalciferol, MVI pediatric, Vitamin B complex and Vitamin E.

When we compared CIMS with IAP study results showed that out of the selected 51 drugs from IAP, information were lacking for 9 drugs in CIMS. Considering all parameters, appropriate information was not mentioned for all of the rest 42 drugs in CIMS as compared to IAP (Fig.3). Appropriate information regarding indications was lacking in 38 drugs and contraindications were inappropriate for 24 drugs. Details regarding precautions were not appropriate for 9 drugs. Dosage were not appropriate (age-wise, weight-wise, dose, duration) in paediatric patients for 32 drugs. Relevant information in paediatric patients in presence of renal and hepatic impairment (Modifications, Severity and consequences), were not mentioned for 14 drugs. Adverse effects were not mentioned properly for 27 drugs. Interactions were not mentioned properly in 28 drugs. Ancillary information where ever applicable such as administration instructions, patient advice and storage information were lacking for 5 drugs.

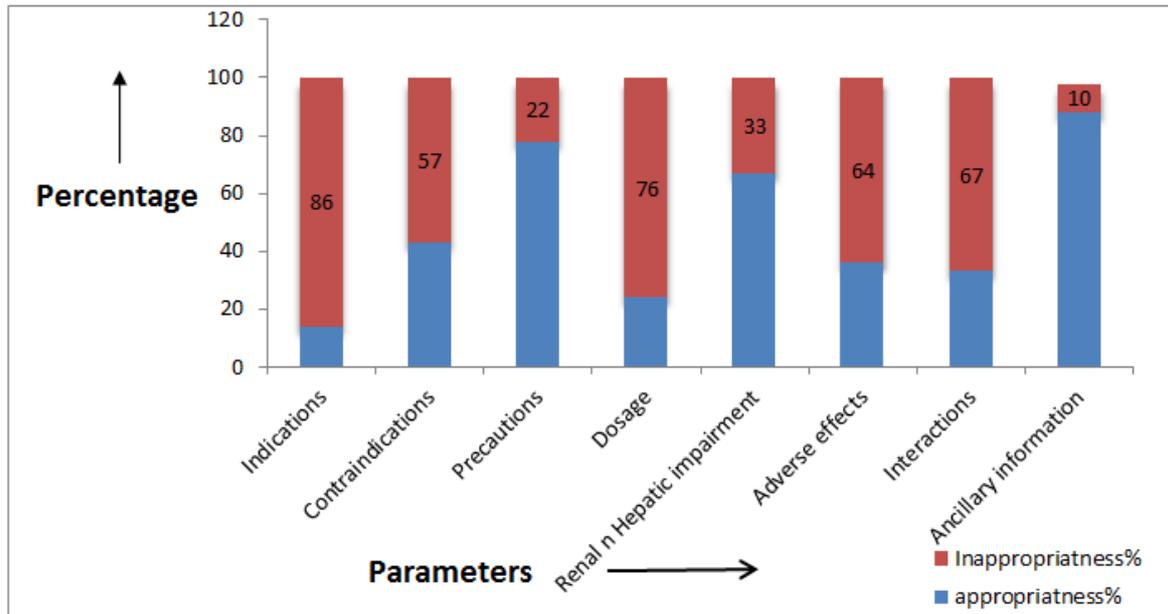


Figure 4: Qualitative comparative analysis between IAP and CIMS

4 DISCUSSION

Children form one of the largest groups of patients consulting general practitioners.^[7] It is estimated that every year 18% of all general practitioners consultations concern children <16 years. Treating pediatric patients requires specialized knowledge and skills and must consider the unique physiological, emotional and social characteristics of this population subset.^[8] Health care practitioners must pay close attention to a child's age, weight, medication dosing frequencies, allergies and other factors to ensure safety of medication therapy. Inappropriate prescription not only increases the cost of medical treatment but also increases the morbidity and mortality.^[3] Third world population spends 30-40% of their total health budget on drugs many of which are prescribed irrationally.

Individual prescribers are always responsible for ensuring that there is adequate information to support the quality, efficacy, safety and intended use of a drug before prescribing it.^[7] Doctors themselves report that they often use promotional drug literature as a source of information about new drugs.^[9] Doctors in private practice or who graduated long ago report the highest use of promotional drug literature as a source of drug information. Physicians should be aware of the limitations of these sources of information for daily practice in this vulnerable group.

In the present study, selection of drugs was based on various studies: Ajapuje et.al stated that antibiotics (78%) are the most prescribing drug in paediatrics followed by NSAIDS (19%), Multivitamins (14%) and Bronchodilators(12%).^[3] Similar results were found in another two studies by Mothilol M et.al^[10] and Shamsy K et.al.^[11] VenKateswaramurthy N et.al stated anti infective and anti-inflammatory comprises of total (75%) of prescription.^[12] Of the anti infective agents, antibiotics were most commonly prescribed. So, in our study we have selected 51 drugs which include anti infective, anti-inflammatory, drugs acting on respiratory system and vitamins.

Indication parameter illustrate the official use of the drugs and while prescribing drugs to pediatric patients physicians must stick to it thus for curbing off-label usage of drugs and problems regarding dosing information. In our study, considering indication, inappropriate information was present in 78% and 58% of drugs in CIMS and IAP respectively. Spectrum of medication error can be further narrowed with adequate information regarding contraindications and precautions for drug usage. In our study considering contraindication, inappropriate information were present in 45% and 51% of drugs in CIMS and IAP, respectively. Considering precaution inappropriate information were present in 84% and 82% of drugs in CIMS and IAP. This implies that the prescribers would have to look for more information of these drugs elsewhere which is often tedious and time consuming. All drugs have a therapeutic range below which they do not work and above which they are toxic.^[4] Wrong dosage causes toxicity or treatment failures.^[13] Drugs (age-wise, weight-wise) need to be used in utmost rational manner in the correct dosage and for correct duration. The road to pediatric drug testing has been a rocky one.^[14] Nobody wants to use children as guinea pigs, but the problem remains that drugs are being given to children in potentially unsafe doses. The FDA understands that giving medications to children for which there is only adult data available could be

harmful, considering that children have dosing concerns and side-effect risks that differ from adults. In our study, dosage was inappropriate for 88% and 76% of drugs in CIMS and IAP respectively.

Children may have unique disease states and immature organ development that may impact the elimination of a drug from their bodies or create unique needs for drug elimination.^[15] Information relevant in pediatric patients in presence of renal and hepatic impairment (modifications, severity and consequences) is thus equally important. In our study, relevant information in presence of renal and hepatic impairment was not mentioned for 100% and 88% drugs in CIMS and IAP respectively. Children are more likely to experience adverse events as a result of errors because of their physiology and limited defences.^[16] Reference to drug formularies for prescribing information has been reported as an important step to prevent ADRs. Prescribing doctors should monitor specifically adverse reaction of prescribing drugs to pediatric age group thus; more classified emphasis of adverse effect is required. Our results showed that adverse effects were not mentioned properly for 94% and 80% drugs in CIMS and IAP respectively. Polypharmacy and overprescribing is common in India.^[3] More medicines increase the risk of drug interactions, adversely affect the patient compliance and hike cost of treatment. In our study, interactions were not mentioned properly in 78% and 68% of drugs in CIMS and IAP respectively.

Further it was found that, some of the drugs mentioned in IAP (Table 3) are lacking in WHO list of essential medicines, 17th ed. and Indian list of essential medicines. When IAP and CIMS are compared with each other (Table 4), IAP seems to be superior to CIMS. In our setup presence of formulary like IAP is of due importance.

Children cannot evaluate and articulate their response to medications.^[8] Drugs on the market approved for use in children may not have been tested in clinical trials on children.^[17] High-profile incidents of heparin overdoses in California, Indiana and Texas and cardiovascular medication errors have shed light on the unique safety challenges associated with the medications to the pediatric population.^[18] Reducing pediatric medication errors is topmost priority nationwide. The latest examples are the ban of drugs like nimesulide and phenylpropanolamine in anticold formulation.^[5]

Oshikoya Kazeem A et.al states that there is reduced level of confidence among prescribers (Interns) while prescribing drugs to pediatric age group.^[19] This signifies pitfalls in traditional teaching of pharmacology, medical students are not formally taught pediatric dose calculation either in pharmacology or pediatrics; they have demonstrated difficulty in calculating pediatric doses. Deficiency in the knowledge and basic skills of prescribing are also responsible for significant number of medication errors. Thus, there is a need to improve the undergraduate teaching methods so that it encompasses more knowledge and practice directed towards rational prescribing.

When compared with WHO Model Formulary, both IAP and CIMS formularies give widely different dosing guidelines for drug prescription in pediatric age group. This study highlights the inadequacy of popular Indian formularies CIMS and IAP for pediatric prescribing. The respondents are likely to prescribe drugs that are more expensive and unavailable locally at that time; this totally negates the WHO's guidelines for rational prescribing. Thus, there is an imminent need of a pediatric national formulary with due focus on guidelines for pediatric prescribing. Buck MarciaL et.al also stated need of pediatric formulary for drug evaluation, selection and therapeutic use.^[20] Similar results are found in other two studies by Elora Hilmas et.al.^[18] and Yewala Vijay N et.al.^[5]

5 CONCLUSION

As the pediatric population continues to rise, the need for improving the healthcare of these patients should be a priority of all nations. There is ample scope of improvement in existing pediatric formularies. Hence we suggest there is need to establish a national pediatric formulary to provide therapeutic guidelines to prescribers.

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