Original Research

Potential drug-drug interactions in paediatric outpatient prescriptions in Nigeria and implications for the future.

Kazeem Adeola Oshikoya[1], Ibrahim Adekunle Oreagba[2], *Brian Godman[3,4], Fisayo Solomon Oguntayo[2], Joseph Fadare[5], Samuel Orubu[6], Amos Massele[7], Idowu Odunayo Senbanjo[8]

[1]Pharmacology Department, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria. Email: kazeemoshikoya@ymail.com
[2]Pharmacology, Therapeutic and Toxicology Department, College of Medicine, University of Lagos, Idiaraba, Lagos, Nigeria. Email: oreagbai@yahoo.com, solomonoguntayo@yahoo.com
[3]Division of Clinical Pharmacology, Karolinska Institute, Stockholm, Sweden. Email: Brian.Godman@ki.se
[4]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, United Kingdom. Email: Brian.godman@strath.ac.uk
[5]Department of Pharmacology, Ekiti State University, Ado-Ekiti, Nigeria. Email: jofadare@gmail.com
[6]Faculty of Pharmacy, Niger Delta University, Bayelsa State, Nigeria. Email:samuelorubu@lycos.com
[7]Department of Clinical Pharmacology, School of Medicine, University of Botswana, Gaborone, Botswana. Email: amos.massele@mopipi.ub.bw
[8]Paediatric Department, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria. Email: senabjo001@yahoo.com

*Author for correspondence: Brian Godman, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom. Email: brian.godman@strath.ac.uk. Telephone: 0141 548 3825. Fax: 0141 552 2562 and Division of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden. Email: Brian.Godman@ki.se. Telephone + 46 8 58581068. Fax + 46 8 59581070

(Accepted for publication Expert Review of Clincal Pharmacology – Please keep CONFIDENTIAL).

Abstract
Background: Information regarding incidence of drug-drug interactions (DDIs) and adverse drug events (ADEs) among paediatric patients in Nigeria is limited. *Methods:* Prospective clinical audit among paediatric outpatients in four general hospitals in Nigeria over a 3-month period. ADEs documented in case files extracted. *Results:* Among 1233 eligible patients, 208 (16.9%) received prescriptions with at least one potential DDI. Seven drug classes were implicated with antimalarial combination therapies predominating. Exposure mostly to a single potential DDI, commonly involved promethazine, artemether/lumefantrine, ciprofloxacin and artemether/lumefantrine. Exposure mostly to major and serious, and moderate and clinically significant, potential DDIs. Overall exposure similar across all age groups and across genders. A significant association between severity of potential DDIs and age. Only 48 (23.1%) of patients presented at follow-up clinics with only 15 reporting ADEs. *Conclusion:* There was exposure to potential DDIs in this population. However, potential DDIs were associated with only a few reported ADEs.

Key words: Drug: drug interactions, pediatrics, Nigeria, adverse drug events, clinical audit

1. Introduction

The intent of a prescribing doctor is to prescribe a medicine that is beneficial to the patients they treat, cure their disease or, at least, try and treat their symptoms, without causing harm. [1] However, poor knowledge of pharmacology of the medicines prescribed and prescribing errors can undermine this. [2] Safe prescribing is a decision-making process whereby potentially hazardous drug-drug interactions (DDIs) and drug-disease interactions (contraindications) are avoided where possible. [3]

Theoretically, DDIs are defined as a phenomenon of two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered. [4] Drug interactions can occur at the level of many physiological processes in the body and can result in an increased effect of the interacting drugs (potential cause of an adverse drug event), or a decreased effect (potential loss of efficacy). [1] Interactions during drug absorption, distribution, hepatic metabolism, or renal excretion, resulting in an increased or a decreased plasma concentration that consequently alters the pharmacological effects, are termed pharmacokinetic interactions; while synergistic or antagonistic effects of two or more co-administered drugs, occurring at their sites of action, are termed pharmacodynamic interactions. [1, 5] Pharmaceutical interactions, otherwise called drug incompatibilities, can also occur when two or more drugs are mixed in the same device before administration, and are evidenced by reduced or interrupted activity of one or both drugs or formation of a new compound. [5]

The theoretical definition of drug interactions was based on the known pharmacological properties of the administered drugs, but in practice clinically relevant adverse events may rarely occur. The term potential DDIs are frequently used in clinical practice and refers to the prescription of potentially hazardous or contraindicated drug combinations. [1, 3] This phenomenon encompasses not only potential DDIs, but also some drug- disease interactions that are identified by drug combinations in which one of the drugs is contraindicated in a patient with a particular disease condition. [3] Thus, potential DDIs may far outnumber actual drug interactions in clinical practice. [1]

Patient harms from drug interactions are common and include adverse drug events (ADEs), prolonged hospitalization, increased treatment costs, morbidity and mortality. [1, 6] Average treatment costs for a single ADR in Germany have been estimated at approximately €2250. [7] The costs of emergency related admissions due to ADRs have been estimated at GB£2billion annually in the UK[8], with the cost of drug-related morbidity and mortality exceeding US$177.4billion in the United States in 2000[9]. Among 520 adult medical patients, Fokter and his colleagues observed potential DDIs in the prescriptions for 51% of patients on admission and 63% on discharge, of which 13% and 18%, respectively were identified as major. [10] Among a population of hospitalized pediatric patients in Brazil, potential DDIs were observed in 61% of prescriptions, resulting in 1.9 interactions per prescription and approximately seven interactions per patient. Of these potential DDIs, 24% were clinically significant and ranged from severe (8%) and moderate (48.9%) to mild (3.2%). [11] A study conducted among elderly hypertensive patients in South-west Nigeria also identified at least one potential DDI in 47.6% of the patients. [12]

Pediatric patients are at a high risk of adverse drug interactions as they handle drugs differently from adults. For example, the concentration of metabolizing enzymes and maturation of the organ-system for drug disposition differ in children and adults, resulting in altered drug disposition in children. [13] The concomitant and extensive utilization of more than two drugs for children is common in Nigeria [14], potentially enhanced by a greater prevalence of HIV and malaria among the population in Nigeria versus for instance Western countries. [15] Overall, a quarter of the malaria burden in Africa is found in Nigeria. [16, 17] Polypharmacy has been identified as a risk factor for potential DDIs in adults.[18, 19] As the policies guiding drug development and clinical trial studies in children have been reviewed [20, 21], the number of drugs, as well as multiple drug therapies, for children is likely to increase. As a result, the frequency of potential DDIs is likely to increase, which may be accompanied by a proportionate increase in major DDIs.

Although it may be impossible to recognise every potential DDI in clinical practice, electronic prescribing systems software programmes have been introduced to prevent adverse drug interactions through identifying potential DDIs in many developed countries.[22-25] For example, SFINX (a drug-drug interaction database) was designed and integrated into clinical decision support systems in Sweden and Findland.[23] SFINX has also been used in website solutions for clinical evaluation of drug interactions.[23] In 2009, over 31,000 physicians and pharmacists received interaction alerts through SFINX and feedback from the users is continuously collected for regular improvement of the content of the database. [23] In the United States, Tatonetti *et al.* developed two novel signal detection algorithms and used them to generate databases for identifying off-target effects of individual drugs as well as drug-drug interactions. [24,25] While one algorithm uses machine learning techniques to identify common secondary effects and infer adverse

events without explicit reporting[24], the other uses automated cohort matching to correct for biases inherent in large adverse events databases.[25] Overall, the software package allows more robust and accurate drug safety surveillance. Furthermore, the databases for drug effects also serve as a resource to understand the pharmacology of small molecules needed for new drug development; an important concept in drug discovery and design.Such systems and resources, however, are currently lacking in developing countries. During the drug discovery processes, various algorithms and computational methods have been developed to predict drug interaction with nuclear receptors and enzymes catalysing most chemical reactions in cells.[26, 27] The prediction tools are available to the public via a user-friendly server, enabling those working in a similar field to obtain data on drug-cell interactions. [27,28] It is hoped that development of such predicting tools for drug-drug interactions in clinical practice, and their availablity to the public domain, can help minimise the prescribing of potentially interacting drugs, especially in the developing countries. These, however, will be developments for the future.

Currently available literature on potential DDIs are typically based on studies performed in developed countries and among adult populations.[3, 7] Drug interactions have not been explored among pediatric population, particularly in developing countries where drug utilization for children is high. [14] The few studies evaluating potential DDI in pediatric populations have been focused on inpatients, retrospective in nature and rarely identified the potential adverse events that may be associated with the interactions. [6, 29-32] We aimed to rectify this by investigating the frequency of potential DDIs in the medications prescribed for pediatric outpatients attending hospitals in Nigeria. Potential adverse events associated with potential DDIs were also documented to provide future guidance to prescribers in Nigeria as well as wider African and other developing countries with similar populations. We believe this is the first study of its kind undertaken in Nigeria.

2. Methods

2.1 Study design

We prospectively analyzed the clinical records of children who presented consecutively to the pediatric outpatient clinics at four General Hospitals (Mushin, Gbagada, Isolo and Surulere) in Lagos, Nigeria, between April 1 and June 30, 2015. These hospitals were chosen for the study since they are all situated in densely populated Local Government Areas and are likely to experience a very high patient load during clinic days. Outpatient clinics are held at each of the hospitals every Monday through Friday, between 8 am and 4 pm. Lagos was chosen as this is the former capital of Nigeria and the most populous city .[33] It should, therefore, provide a reflection of potential prescribing habits across Nigeria.

The pediatric outpatient clinic in each of the hospitals is run by between 3-5 medical officers. On average, about 30 patients are seen each day at each of the outpatient clinics in the hospitals. All outpatient children who met the inclusion criteria were included in this study. These included children younger than 18 years old that do not require hospital admission. Patients must have completely documented demographic information and prescribed medicines in the case files to be enrolled. We excluded neonates since they attend special baby clinics, which differ from the pediatric outpatient clinic. Patients prescribed topical preparations for application to the skin such as emollient, lotion, cream, or ointments; ear, eye and nasal drops; patches; inhalers; or on multivitamins and herbal supplements only were excluded since these are rarely evaluated in drug-drug interaction studies. If any of these drugs were prescribed along with other enteral and parenteral drugs, they were excluded from the list of drugs evaluated for potential interactions since the potential interactions associated with them are rarely documented in the databases to check.

During the study, adolescents and parents or caregivers of young children were required to come for follow-up every week for 6 weeks and to take note of any untoward events that may occur while their child/ward took the prescribed medicines at home. In this study, children were classified into infants (1- 12 months old), young children (1- 6 years old), children (6- 12 years old) and adolescents (12- 17 years old) according to the methods of Knoppert *et al.* [34] The attending physicians informed adolescent patients and caregivers of young children about the likely adverse effects of each drug prescribed according to their

documentation in the British National Formulary (BNF) for Children. [35] Such adverse events were reported at the clinic during follow-up and documented in the case file of the patients.

2.2 Data abstraction

Eligible cases were identified prospectively through the main register obtained from the medical record of each outpatient clinic after 4 pm throughout the study period. These are case files returned from the pediatric outpatient clinic each day to the medical record office. Four registered nurses, trained for this research, one per study center, reviewed each case file on a daily basis, and - using a standardized form purposively designed for the study - extracted data on age and gender of the patient, prescribed medicines and their route of administration.

2.3 Identification of potential interactions between paired co-prescribed drugs

The co-prescribed drugs were screened in pairs for potential interactions using reference books[9, 35] as well as online references such as Medscape Reference Drug Interaction Checker[36]. This electronic resource had been validated in our previous study where clinically-significant drug interactions in HIV-infected children were profiled. [37] The potential DDIs not identified by the two reference books or those with the severity rated as contraindicated (category X) or unknown (category A) by the online database were searched from a second database - drugs.com. [38] This was to ensure that important DDIs were not missed out of the total potential DDIs. The lack of access to other electronic resources for potential DDI checks in our environment restricted us to use the reference books and the two freely available online resources.

2.4 Classification of potential interactions between paired co-prescribed drugs

The severity and category of potential DDIs were based on the classifications used in our previous study. [39] The details of the severity rating scale (A to D and X) are presented in Table 1.

Insert Table 1

We excluded from our analysis the drug pairs that yielded no or unknown interactions (A rating). If a given drug interaction was listed more than once with different risk ratings, the most severe risk rating was used to determine the severity grade. The mechanism of action of the interactions, and their management, were as documented in the interaction checkers. Evidence for documentation of the potential DDI in the literature is classified according to the method of Feinstein *et al.* as excellent (existence of the drug interaction is clearly established by randomized controlled trial studies), good (reports in the literature strongly suggests that the interaction exists, but not supported by well-controlled studies), fair (the interaction is scarcely documented in the literature; however, the interaction is suspected based on some pharmacologic considerations of the interacting drugs), poor (only few studies and limited reported cases support the existence of the interaction), or unlikely (insufficient documentation of the interaction in the literature and no pharmacological basis). [29]

2.5 Identification of potential adverse events associated with the interactions

Only adverse events associated with contraindicated, major and moderate interactions reported in the interaction checkers are listed in this study. Since minor interactions typically have no clinical significance, no adverse event is attributed. Patients or their caregivers were advised to report immediately any observed adverse event. They were also interviewed by the attending physicians for suspected adverse events during their weekly follow-up visits. The nurses reviewed the case file of each patient prospectively during follow-up visit, weekly for six weeks to specifically look for documentation of any potential adverse event known to be associated with the interactions that was documented by the attending physicians. We classified adverse events that are related to the drug-drug interactions according to the Medscape interaction checker. [36] Patients who experienced moderate to severe ADEs were admitted and treated as such, while those who experienced mild ADEs were observed closely.

2.6 Statistical Analysis

The demography of the patients and pattern of medicines prescribed in the study cohort are described by frequencies and percentages. To describe the prevalence of potential DDIs, the frequencies and

percentages of specific potential DDIs were calculated per patient. We then determined the exposure per patient exposed as the ratio of percentage potential DDI exposure to the percentage of patients exposed.

The potential DDI patterns are also described according to the age group of the patients. For each potential DDI, we determined the frequencies and percentages of the implicated drug pairs, the severity of the interaction, and the level of scientific evidence for the interaction. Finally, we also determined the frequency and percentage of all potential DDIs associated with each of the different categories of potential ADEs. Each potential DDI could be associated with one or more potential ADE.

Statistical analyses were performed with SPSS version 17. The association between severity of the potential DDI and age group of the patients or gender was determined with Yates' chi-square test (if any expected frequency is below 1 or if the expected frequency is less than 5 in more than 20% of the cells), otherwise a Pearson Chi-square test was used, at a significant p-value of <0.05.

3. Results

Over the three-month study period, 2535 patients were seen at the pediatric outpatient clinics. At least one prescription was received by 2000 (78.9%) patients but only 1233 (61.6%) patients who met the inclusion criteria were included and analyzed in this study. More males (705; 57.2 %) than females (528; 42.8%) were recorded in this study. Their mean age was 3.73 ± 0.16 years.

3.1 Pattern of drugs prescribed

Of the eligible patients, 208 (16.9%) received prescriptions with at least one potential DDI. These patients were prescribed a total of 480 drugs with potential for interactions. Table 2 shows the classes of drugs implicated for potential DDI in this study.

Insert Table 2

Among the seven classes of drugs implicated, antimalarials, predominantly the Artemisinin-based Combination Therapies (ACTs), were the most implicated (179; 37.3%), followed by antiemetics/antihistamines (126; 26.3%), and antimicrobials (103; 21.5%). The ACTs (artemether/lumenfantrine and artemether/amodiaquine) (179; 37.3%) and promethazine (118; 24.6%) were the two specific drugs most commonly implicated in the potential DDIs.

3.2 Profile of the drug-drug interactions

Altogether, 240 potential DDIs were identified; majority of which were a single DDI (188; 78.3%). Ten patients were exposed to three potential DDIs (30; 12.5%), nine were exposed to two potential DDIs (18; 7.5%) and only one patient was exposed to four potential DDIs.

The co-prescribed drug pairs with potential for interaction, to which the patients were exposed, as well as the profile of the interactions are presented in Table 3.

Insert Table 3

The patients were most exposed to promethazine and artemether/lumefantrine (111; 46.2%) and ciprofloxacin and artemether/lumefantrine (39; 16.2%) drug pairs with potential for interactions. The most identified potential DDI, based on the severity, was major and serious (141; 58.8%), followed by moderate and clinically significant (83; 34.5%), minor (12; 5.0%) and contraindicated (4; 1.7%) types (Table 3). Excellent (33; 13.8%) and good (9; 3.8%) scientific evidence for the potential DDIs were documented in the literature (Table 3).

Furthermore, the severity of the potential DDI was compared with the age and gender of the patients in Table 4.

Insert Table 4

The overall exposure to potential DDIs was highest among infants (106; 44.1%) and higher for male patients (138; 57.5%). There was a significant association between the severity of potential DDIs and patients' ages (p= 0.046) but not with their gender (p= 0.631). However, there was a slight differenece in the exposure per exposed patients across all age groups and across both genders.
The exposure per exposed patient ratio differs slightly among all the interacting drug pairs prescribed to patients (Table 5). The possible adverse events that may result from the potential DDIs and how these interactions can be prevented are presented in Table 5.

Insert Table 5

Of the 208 patients who received prescriptions for drugs with potential for interactions, only a few (48; 23.1%) presented to the follow-up clinic over the six weeks' period. Among the 48 patients seen at the follow-up clinic, 15 reported ADEs of which 8 (53%) were to promethazine and artemether/lumefantrine (fainting spells-3, dizziness- 3, and palpitations-2), 4 (27%) to promethazine and metoclopramide (tongue protrusion- 1, lip smacking-1, restlessness- 1, and abnormal movement of the neck-1), and 3 (20%) to ciprofloxacin and artemether/lumefantrine (fainting spell-1, dizziness- 1 and palpitation-1) (Figure 1). None of the ADEs required medical intervention since they lasted for less than 24 hours. Furthermore, none of the patients presented to the emergency room because of the ADEs.

Insert Figure 1

4. Discussion

Among the cohort of pediatric outpatients treated in Nigeria, less than a quarter (16.9%) were exposed to at least one potential DDI. Studies evaluating drug-drug interactions in pediatric population are few and focused on inpatients. [6, 29-32] Among a large cohort of pediatric patients treated at 42 children's hospitals in the United States, Feinstein *et al* reported a much higher exposure (49%) of the patients to potential DDI during their admission. [29] Higher exposures than observed in our study were reported among hospitalized children in Yugoslavia (24.6%) and Pakistan (25.8%). [31, 32] However, a very low exposure (3.83%) was reported among hospitalized children in Czech Republic. [30] Variation in the disease pattern necessitating the varied prescription pattern, age groups of the children included in the studies, settings of the studies, samples sizes, and duration of the studies may have resulted in the differences in the potential DDIs reported in all the studies.

Our study, like the American study, excluded neonates while this class of children was involved in other studies. We also only evaluated outpatient prescriptions while other studies evaluated prescriptions for hospitalized children. The sample sizes for all, but the American study, was small and varied from ours. In addition, we identified potential DDIs from the BNF for Children, Stockley's Drug Interaction reference book, free online Medscape interaction and drugs.com databases, while Micromedex Drug-Reax® or INFOPHARM Drug Interactions Compendium® Software were widely used in other studies[4, 27,29, 32] However, the Yugoslavian study did not document the assessment tool for identifying potential DDIs.[31] The lack of a standardized assessment tool for potential DDI studies may also have contributed to the varied potential DDI exposures in the different studies. Previous studies have reported discrepancies in potential DDI listings in various databases for drug interaction checks. [37, 61]

Artemisinin-based Combination Therapy (ACT) for malaria predominates (37%) the list of drugs responsible for the potential DDIs in our study, which underscores the burden of malaria in pediatric outpatients in Nigeria. By contrast, opioids (25%) were the drugs most involved in potential DDIs in hospitalized children in the United States.[29] This further highlights the effects of disease and prescription patterns on exposure of children to potential DDI. Many of the antimalarial and antiemetic drugs, which were implicated in most of the potential DDIs, were prescribed for intramuscular administration. Other medicines, including amikacin, gentamicin, and some of the analgesics, were also prescribed for intramuscular administration. This is contrary to all guidelines, including the standard treatment guideline in Nigeria, for routine pediatric outpatient treatment where the practice was discouraged because of

potential complications such as abscess and hematoma formation, infection transmission and allergic reactions.[62]

Contraindicated (1.7%) as well as major and significant (58.8%) potential DDIs occurred in our patients. Varying results were, however, reported for contraindicated (5%) and major (41%) potential DDIs among hospitalized children in the United States. [29] Within the confines of our study, only a single drug pair (phenobarbital and artemether/amodiaquine) were implicated in the contraindicated potential DDI, whilst 10 different drug pairs (ibuprofen and ketorolac, fluconazole and ondansetron, calcium chloride and ceftriaxone, aspirin and ketorolac, glycopyrrolate and potassium chloride, calcium gluconate and ceftriaxone, metoclopramide and promethazine, ketorolac and naproxen, epinephrine and linezolid, and atropine and potassium chloride) were implicated in the larger American cohort. [29] Potential explanations for the differences seen include diseases and health conditions necessitating hospitalization that are likely to be more severe than among outpatients. Consequently, more medicines may be utilized by pediatric inpatients versus outpatients.

Among the interacting drug pairs in our study and others, some are avoidable by replacing one of the pairs with another medicine in the same pharmacological group based on the mechanism of drug interactions. However, some of the interacting drug pairs are unavoidable because of their high therapeutic benefit versus minor consequences of the interactions. Unfortunately, the likely drug substitution among the interacting pairs to avert the potentially avoidable interactions, without necessarily affecting disease treatment , has not been addressed. For those interacting drug pairs (promethazine and artemether/lumefantrine; ciprofloxacin and artemether/lumefantrine; and promethazine and metoclopramide) that resulted in reported adverse events, we believe chlorpheniramine, diphenhydramine, cetirizine, and metoclopramide are good substitutes for promethazine co-prescribed with artemether/lumenfantrine since these combinations would not produce adverse interactions.[36,38] Cefepime can be substituted for ciprfloxacin in combination with artemether/lumefantrine since they have a similar wide spectrum for bacterial infections.[35,38] Both promethazine and metoclopramide are antihistamines with similar mechanism of action. It will be prudent to use just one from the same class or combine one with another from a different class and mechanism of action. Ondansetron could be substituted for either promethazine or metoclopramide since their combinations do not interact adversely.[35,36,38] For contraindicated interacting pairs (phenobartital and artemether/amodiaquine), lorazepam could be substituted for phenobarbital since this new pair rarely interact adversely.[36,38]

Increased drug prescription is an identified risk for potential DDI. [32] Based on the type of electronic database used for interaction checks in our study, metoclopramide and promethazine drug pair would result in major and serious interaction, while Micromedex Drug-Reax® rated the interaction as contraindicated. [29] We may have, therefore, underestimated the proportion of contraindicated interactions in our study or this may have been overestimated in a previous study. [29] This further underscores the significance of developing a uniform assessment tool for future drug interaction studies. Discrepancies in the rating of severity of potential DDIs by the information sources used in the present and previous studies may have also resulted in the variety of drug pairs implicated in the contraindicated interactions reported in the American study.

Only a few potential DDIs have an excellent (13.6%) and good (3.8%) scientific evidence in the literature. Other studies have documented higher levels (60%-80%) of evidence for assignment of severity to a potential DDI as good to excellent. [29, 31, 32] This suggests that majority of the potential DDIs observed in our study may only occur in theory and may not be very significant clinically. Clinicians may tend not to prescribe many of the drug pairs responsible for the majority of the potential DDIs in this study, when indeed the interactions are clinically not significant. Such practice may cause an unnecessarily avoidance of useful therapy options for patients thereby denying them optimal treatments. It has been documented previously that many interactions rated moderate and clinically significant by Micromedex and Lexicomp databases were found to be clinically insignificant by doctors and pharmacists. [61] This needs to be borne in mind in the future.

The high prevalence of potential DDI exposures in our study could have resulted in a wide range of potential ADEs (Table 5). This, however, did not correspond with the rates of actual ADEs reported by patients during their follow-up. This may have resulted from the low follow-up rates (23%) in our study. Alternatively, it could be possible that ADEs did occur but were unrecognized by the patients, their caregivers or the attending physicians. Recognizing ADEs from exposure to potential DDIs could be challenging to healthcare professionals and even more challenging to patients and their caregivers. [63, 64] This will be followed-up in future studies along with other means of following up patients such as the use of mobile phone calls or home visits to potentially identify additional patients who may be experiencing adverse events, and this will be the subject of future studies to confirm or dispute our findings.

There was a significant association between the age of the patients and the severity of the interaction exposures in this study. Infants and young children are more exposed to potential DDIs than older children and adolescents. By contrast, older children and adolescents were more exposed than young children to potential DDIs among hospitalized children in the United States [29] and Czech Republic. [31] Ismail *et al* reported a significant association between potential DDI and female gender [32], while no significant association was observed in our study and among hospitalized children in Czech Republic. [30] Variation in age group classification and settings of the studies, as well as methodological and sample size differences, may have accounted for the differences seen between the findings in ours versus other published studies.

We acknowledge several limitations with our study. A major limitation is that we did not assess the doses of interacting drug pairs prescribed for patients. Since children are often prescribed medicines based on their body weight or body surface area; overdosing of one of the interacting drug pairs can impact on potential adverse interactions. The potential interaction of drugs such as isoniazid with other co-formulated drugs (pyrazimnamide, ethambutol and rifampicin) is dose dependent and results in adverse toxicity (peripheral neuropathy) when the administered dose exceeds 300 mg/day.[65] At a recommended dose of 5mg/kg/day, prophylactic or therapeutic use of isoniazid rarely causes adverse toxicity.[65] Ciprofloxacin is known to increase the exposure of cyclosporine when both drugs are co-administered. This beneficial potential DDI, following timely dosage adjustment of cyclosporine, increases immunosuppresive serum levels in patients with bone marrow aplasia without experiencing any adverse toxicity.[66]

Other limitations include conducting the study in only four general hospitals in Lagos, and only actively following up a minority of patients. We also accept our data was based only on the evaluation of prescriptions as we did not have direct information about those patients who actually used the prescribed medicines. Consequently, adherence to the medications prescribed cannot be ascertained among those who used the prescribed interacting drugs. In addition, in a country battling with an epidemic of adulterated, counterfeit and fake medicines [67], we accept it may also be necessary to directly measure the plasma levels of each drug exposure. Doing this would enable us to know the extent to which the medicines prescribed are involved in clinically significant interactions. Rational prescribing is based on the risk-benefit ratio of a medicine to patients. It is, however, believed that the benefits of co-prescribing potentially interacting drugs might have outweighed the risks for the condition being treated. Despite these limitations, we believe our findings are valid but may require further studies involving all six geo-political zones before they could be generalized for Nigeria as a whole. We also accept future studies should consider including both public and private hospitals across the six geo-political zones in Nigeria. The use of electronic medical recording systems could also improve the quality of data generated in future studies. These are consdierations for the future building on our initial study.

Finally, as shown in a series of recent publications demonstrating new approaches to predicting drug-cell, drug-disease, and drug-drug interactions, using user-friendly and publicly accessible web-servers [23,27,28,68-72], as well as freely available online databases such as the Medscape Reference Drug Interaction Checker[36] used in our study, would significantly reduce adverse drug interactions in resource limited countries such as Nigeria.

5. Conclusions and recommendations

Outpatient children are frequently exposed to potential DDIs in Nigeria and may be at risk of adverse drug events. Continuing education of prescribers and regular use of freely available online information resources on potential drug interactions could be beneficial towards inproving rational prescribing and minimizing adverse drug interactions among this population in the future. However, tempered by the fact that these can highlight potential ADEs that are not clinically significant and result in sub-optimal treatment of patients.

Overall, we recommend that clinicians are discouraged, through educational and other programs, to reduce the administration of intramuscular injections where oral formulations are just as effective. Clinicians should also be well grounded in the pathophysiology of pediatric diseases and the mechanism of action of the drug combinations prescribed, as well as the risk-benefit of the drugs, while monitoring for their potential adverse interactions. Collaboration between prescribers and pharmacists could further promote rational medicine use for children and reduce potential DDIs and any consequent ADEs. Careful consideration of medicines contraindicated or without indications in specific age-groups, for instance the use of promethazine in children under the age of two years, and the use of a handbook of medicines for children are other potential means of promoting rational medicine for children that should be embraced by the prescribers in Nigeria. This will be followed up.

6. Five-year review

We expect over the next five years that continuing education of prescribers, greater collaboration between prescribers and pharmacists, as well as greater availability of freely available online information sources, will further improve rational rescribing and mimimse potential drug-drug interactions. This will include greater recognition that some potential ADEs are not clinically significant; consequently, care should be taken in order not to result in sub-optimal treatment.

There will also be continued educational and other programmes to reduce the use of intramusvular injections where oral formulations are just as effective. This will be helped by strengthening regulations regarding the supply of medicines in Nigeria including reducing the extent of self-purchasing of medicines through a variety of sources.

7. Key Points

- Pediatric patients are at a high risk of adverse drug interactions as they handle drugs differently from adults. However available literature on potential DDIs are typically based on studies performed in developed countries and among adult populations
- Outpatient prescriptions among paediatric outpatients in Nigeria were associated with exposure to potential drug-drug interactions, which resulted in some adverse drug events
- Antimalarial drug class, particularly the artemisinin combination therapies (ACTs), were the most implicated drugs in potential drug-drug interactions. This suggests that disease patterns, which dictate drug utilization pattern, play a pivotal role in exposure to drug-drug interactions
- Potential drug-drug interactions due to prescription of contraindicated drugs were few; infants and young children being those at risk
- The use of freely available online drug information resources on potential drug-drug interaction is feasible in developing countries, particularly Nigeria. Encouraging prescribers to use this tool could prevent avoidable and unnecessary exposures to potential drug-drug interaction in children
- Interventions are required to avoid prescription of two or more similar drugs, such as promethazine and metoclopramide, with the potential for additive adverse events. Interventions are also needed to reduce the administration of intramuscular injections where oral formulations are just as effective

Acknowledgements and financial disclosure

There are no conflicts of interest from any author and there was no writing assistance with the production of this paper.

The write up of this publication was in part supported by a VR-Link grant (Vetenskapsrådet) from Swedish Research Council (VR-Link 2013-6710) granted to Amos Massele.

References

1. Pirmohammed M. Drug-drug interactions and adverse drug reactions: separating the wheat from the chaff. Wien Klin Wochenschr 2010; 122: 62-64.

2. Al Khaja KAJ, Al-Ansari TM Sequeira RP. An evaluation of prescribing errors in primary care in Bahrain. Int J Clin Pharmacol Ther. 2005; 43: 294-301.

3. Chen Y, Avery AJ, Neil KE, Johnson C, Dewey ME, Stockley IH. Incidence and possible causes of prescribing potential hazardous/contraindicated drug combinations in general practice. Drug Saf. 2005; 28: 67-80.

4. Baxter K. Stockley's Drug interactions. 8th ed. London: Pharmaceutical press, 2008.

5. Tatro DS. Drug interaction facts. St. Louis: Facts and Comparisons, 2006.

6. Godman B, Finlayson AE, Cheema PK, Zebedin-Brandl E, Gutierrez-Ibarluzea I, Jones J, et al. Personalizing health care: feasibility and future implications. BMC Med. 2013; 11: 179.

7. Rottenkolber D, Schmiedl S, Rottenkolber M, Farker K, Salje K, Mueller S, et al. Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations. Pharmacoepidemiol Drug saf. 2011; 20: 626-634.

8. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ . 2004; 329: 15-19.

9. Kim MM, Metlay J, Cohen A, et al. Hospitalization costs associated with warfarin-related bleeding events among older community-dwelling adults. Pharmacoepidemiol Drug Saf. 2010; 19: 731-736.

10. Fokter N, Mozina M, Brvar M. Potential drug-drug interactions in patients treated in medical departments. Wien Klin Wochenschr 2010; 122: 81-88.

11. Martinbiancho J, Zukermann J, Dos Santos L, Silva MM. Profile of drug interactions in hospitalised children. Pharm Pract. 2007; 5: 157-161.

12. Fadare JO, Ajayi AE, Adeoti AO, Desalu OO, Obimakinde AM, Agboola SM. Potential drug-drug interactions among elderly patients on anti-hypertensive medications in two tertiary healthcare facilities in Ekiti State, South-West Nigeria. Sahel Med J. 2016; 19: 32-37.

13. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Cytochrome 2450 3A: ontogeny and drug disposition. Clin Pharmacokinet. 1999; 36: 439-452.

14. Oshikoya KA, Chukwura HA, Njokanma OF, Ojo IO. Adverse drug reactions in Nigerian children. Paediatr Perinat Drug Ther. 2007; 8: 81-88.

15. UNAIDS. Fact Sheet 2016. Global Statistics 2015. Available t URL: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf.

16. World Health Organization: The World Malaria Report. Geneva: WHO; 2012. Available at URL: http://www.who.int/malaria/publications/world_malaria_report_2012/en/

17. Olasehinde GI, Ojurongbe OD, Akinjogunla OJ, Egwari LO, Adeyeba AO. Prevalence of malaria and predisposing factors to antimalarial drug resistance in Southwestern Nigeria. Res J Parasitol. 2015;10: 92-100.

18. Gagne JJ, Maio V, Rabinowitz C. Prevalence and predictors of potential drug-drug interactions in Regione Emilia-Romagna, Italy. J Clin Pharm Ther 2008; 33: 141-51.

19. Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy for older people. The Cochrane Database of Systematic Reviews. 2014; 10: Cd008165.

20. United States Government Printing Office. 2015. Food and Drug Administration Safety and Innovation Act. Available at: http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf

21. European Medicines Agency. The EU Paediatric Regulation, 2007. Available at http://www.emea.europa.eu/htms/human/paediatrcs/regulation.htm

22. Yeh YT, Hsu MH, Chen CY, Lo YS, Liu CT. Detection of potential drug-drug interactions for outpatients across hospitals. Int J Environ Res Public Health. 2014; 11:1369-1383.

23. Böttiger Y, Laine K, Andersson ML, Korhonen T, Molin B, Ovesjö ML, Tirkkonen T, Rane A, Gustafsson LL, Eiermann B. SFINX-a drug-drug interaction database designed for clinical decision support systems. Eur J Clin Pharmacol. 2009; 65:627-633.

24. Min JL, Xiao X, Chou KC. iEzy-Drug: A web server for identifying the interaction between enzymes and drugs in cellular networking. BioMed Res Int. 2013, 2013, 701317

25. Tatonetti NP, Fernald GH, Altman RB. A novel signal detection algorithm for identifying hidden drug-drug interactions in adverse event reports. J Am Med Inform Assoc. 2012; 19: 79-85.

26. Tatonetti NP, Denny JC, Murphy SN, Fernald GH, Krishnan G, Castro V, Yue P, Tsao PS, Kohane I, Roden DM, Altman RB. Detecting drug interactions from adverse-event reports: interaction between paroxetine and pravastatin increases blood glucose levels. Clin Pharmacol Ther. 2011; 90: 133-142.

27. Fan YN, Xiao X, Min JL, Chou KC. iNR-Drug: Predicting the interaction of drugs with nuclear receptors in cellular networking. Int J Mol Sci. 2014; 15: 4915-4937.

28. Xu Y. Recent progress in predicting post-translational modification sites in proteins. Curr Top Med Chem. 2016; 16: 591-603.

29. Feinstein J, Dai D, Zhong W, Freedman J, Feudtner C. Potential drug-drug interactions in infant, child, and adolescent patients in children's hospitals. Pediatrics 2015; 135: e99-108.

30. Langerová P, Prokeš M, Konvalinka M, Fürstová J, Urbánek K. Incidence of potential drug interactions in medication prescriptions for children and adolescents in the University Hospital Olomouc, Czech Republic. Eur J Pediatr 2013; 172: 631-638.

31. Qorraj-Bytyqi H, Hoxha R, Krasniqi S, Bahtiri E, Kransiqi V. The incidence and clinical relevance of drug interactions in pediatrics. J Pharmacol Pharmacother 2012; 3: 304-307.

32. Ismail M, Iqbal Z, Khan MI, Javaid A, Arsalan H, et al. Frequency, levels and predictors of potential drug-drug interactions in a paediatric ward of a teaching hospital in Pakistan. Trop J Pharm Res 2013; 12: 401-406.

33. World Population Review. Lagos population. Available at: http://worldpopulationreview.com/world-cities/lagos-population/

34. Knoppert D, Reed M, Benavides S, Joyce Totton J, Hoff D, Moffett B, Norris K, Vaillancourt R, Aucoin R, Worthington M. Position paper: Paediatric age categories to be used in differentiating between listing on a model essential medicines list for children. The World Health Organization. Available at http://archives.who.int/eml/expcom/children/Items/PositionPaperAgeGroups.pdf

35. British National Formulary for Children (BNFC) 2014-2015, September 2014-2015.

36. Medscape Reference Online Drug Interaction Checker [database on the Internet]. New York, NY, USA: WebMD LLC; 2013. Available from: http://reference.medscape.com/drug-interactionchecker

37. Oshikoya KA, Oreagba IA, Ogunleye OO, Lawal S, Senbanjo IO. Clinically significant interactions between antiretroviral and co-prescribed drugs for HIV-infected children: profiling and comparison of two drug databases. Ther Clin Risk Manag 2013; 9: 215-221.

38. Drugs.com. Drug interactions checker. Available at http://www.drugs.com/drug_interactions.php

39. Armahizer M, Kane-Gill SL, Smithburger PL, Anthes AM, Seybert AL. Comparing drug-drug interaction severity for clinician opinion to proprietary databases. Adv Pharmacoepidemiol Drug Saf 2012; 1: 115.

40. Simkó J, Csilek A, Karász Ai, Lorincz I. Proarrhythmic potential of antimicrobial agents. Infection 2008; 36: 194- 206.

41. Malik M, Camm AJ. Evaluation of drug-induced QT interval prolongation: Implications for drug approval and labelling. Drug Safety 2001; 24: 323-351.

42. Bates DE, Beaumont SJ, Baylis BW. Ototoxicity induced by gentamicin and furosemide. Ann Pharmacother 2003; 36: 446-51.

43. Smith CR, Lietman PS. Effect of furosemide on aminoglycoside-induced nephrotoxicity and auditory toxicity in humans. Antimicrob Agents Chemother 1983 Jan; 23: 133–137.

44. O'Reilly RA, Motley CH. Racemic warfarin and trimethoprim-sulfamethoxazole interaction in humans. Ann Intern Med 1979; 91: 34-36.

45. Ho JM, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. CMAJ 2011; 183: 1851-1858.

46. Youssef AS, Parkman HP, Nagar S. Drug-drug interactions in pharmacologic management of gastroparesis. Neurogastroenterol Motil 2015; 27:1528-41.

47. Zhang Q, Simoneau G, Verstuyft C, Drouet L, Bal dit Sollier C, Alvarez J, Rizzo-Padoin N, Bergmann JF, Becquemont L, Mouly S. Amoxicillin/clavulanic acid-warfarin drug interaction: a randomized controlled trial. Br J Clin Pharmacol. 2011; 71: 232–236.

48. Davydov L, Yermolnik M, Cuni LJ. Warfarin and amoxicillin/clavulanate drug interaction. Ann Pharmacother. 2003; 37: 367-70.

49. Rice PJ, Perry RJ, Afzal Z, Stockley IH. Antibacterial prescribing and warfarin: a review. Br Dent J 2003; 194: 411-5.

50. Shek KL, Chan LN, Nutescu E. Warfarin-acetaminophen drug interaction revisited. Pharmacotherapy. 1999; 19: 1153-1158.
51. Hughes GJ, Patel PN, Saxena N. Effect of acetaminophen on international normalized ratio in patients receiving warfarin therapy. Pharmacotherapy. 2011; 31: 591-597.
52. Zhang Q, Bal-dit-Sollier C, Drouet L, Simoneau G, Alvarez JC, Pruvot S, Aubourg R, Berge N, Bergmann JF, Mouly S, Mahé I. Interaction between acetaminophen and warfarin in adults receiving long-term oral anticoagulants: a randomized controlled trial. Eur J Clin Pharmacol. 2011; 67: 309-14.
53. Mahé I, Bertrand N, Drouet L, Bal Dit Sollier C, Simoneau G, Mazoyer E, Caulin C, Bergmann JF. Interaction between paracetamol and warfarin in patients: a double-blind, placebo-controlled, randomized study. Haematologica 2006; 91: 1621-7.
54. van Dijk KN, Plat AW, van Dijk AA, Piersma-Wichers M, de Vries-Bots AM, Slomp J, de Jong-van den Berg LT, Brouwers JR. Potential interaction between acenocoumarol and diclofenac, naproxen and ibuprofen and role of CYP2C9 genotype. Thromb Haemost 2004; 91: 95-101.
55. Choi KH, Kim AJ, Son IJ, Kim K, Kim K, Ahn H, Lee EB. Risk Factors of drug interaction between warfarin and nonsteroidal anti-inflammatory drugs in practical setting. J Korean Med Sci 2010; 25: 337–341.
56. Sancilio LF, Taylor MA, Mathur PP, Crowe JT. Interaction between warfarin and nonsteroidal anti-inflammatory drugs (NSAIDs) in rats. Life Sci 1985; 36: 1041-1050.
57. Schulman S, Henriksson K. Interaction of ibuprofen and warfarin on primary haemostasis. Br J Rheumatol 1989; 28: 46-9.
58. Shrivastava MP, Makde SD, Paranjpe BD. Interaction of ciprofloxacin with diclofenac and paracetamol in relation to its epileptogenic effect. Indian J Physiol Pharmacol. 1997; 41: 164-6.
59. Iqbal Z, Khan A, Naz A, Khan JA, Khan GS. Pharmacokinetic interaction of ciprofloxacin with diclofenac: a single-dose, two-period crossover study in healthy adult volunteers. Clin Drug Investig 2009; 29: 275-81.
60. Kumar N, Singh SD, Jayachandran C. Pharmacokinetics of enrofloxacin and its active metabolite ciprofloxacin and its interaction with diclofenac after intravenous administration in buffalo calves. Vet J 2003; 165: 302-6.
61. Smithburger PL, Kane-Gill SL, Benedict NJ, Falcione BA, Seybert AL. Grading the severity of drug-drug interactions in the intensive care unit: a comparison between clinician assessment and proprietary database severity rankings. Ann Pharmacother 2010; 44: 1718-1724.
62. The Federal Ministry of Health, Nigeria. Standard Treatment Guidelines, Nigeria, 2008. Available at URL: http://apps.who.int/medicinedocs/documents/s17035e/s17035e. pdf

63. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. Pharmacoepidemiol Drug Saf 2010; 19: 901-910.

64. Magro L, Moretti U, Leone R. Epidemiology and characteristics of adverse drug reactions caused by drug-drug interactions. Expert Opin Drug Saf 2012; 11: 83-94.

65. Arbex MA, VarellaII MDL, de Siqueira HR, de Mello FAF. Antituberculosis drugs: drug interactions, adverse effects, and use in special situations. Part 1: first-line drugs. J Bras Pneumol. 2010; 36: 626-640

66. Borras-Blasco J, Conesa-Garcia V, Navarro-Ruiz A, Marín-Jiménez F, González-Delgado M, Gomez-Corrons A. Ciprofloxacin, but not levofloxacin, affects cyclosporine levels in a patient with pure red blood cell aplasia. Am J Med Sci. 2005; 330: 144-146.

67. Oshikoya KA. Treating children for malaria fever in the face of counterfeit and fake medicines. Int J Med Med Sci 2010; 2: 1-2.

68. Chen W, Ding H, Feng P, Lin H, Chou KC. iACP: a sequence-based tool for identifying anticancer peptides. Oncotarget. 2016; 7:16895-16909.

69. Jia J, Liu Z, Xiao X, Liu B, Chou KC. iCar-PseCp: identify carbonylation sites in proteins by Monto Carlo sampling and incorporating sequence coupled effects into general PseAAC. Oncotarget. 2016 May 2. doi: 10.18632/oncotarget.9148. [Epub ahead of print]

70. Qiu WR, Sun BQ, Xiao X, Xu ZC, Chou KC. iHyd-PseCp: Identify hydroxyproline and hydroxylysine in proteins by incorporating sequence-coupled effects into general PseAAC. Oncotarget. 2016 Jun 14. doi: 10.18632/oncotarget.10027. [Epub ahead of print]

71. Qiu WR, Xiao X, Xu ZC, Chou KC. iPhos-PseEn: Identifying phosphorylation sites in proteins by fusing different pseudo components into an ensemble classifier. Oncotarget. 2016 Jun 13. doi: 10.18632/oncotarget.9987. [Epub ahead of print].

72. Xiao X, Ye HX, Liu Z4, Jia JH, Chou KC. iROS-gPseKNC: Predicting replication origin sites in DNA by incorporating dinucleotide position-specific propensity into general pseudo nucleotide composition. Oncotarget. 2016 Apr 27. doi: 10.18632/oncotarget.9057. [Epub ahead of print].

Tables

Table 1: Drug–drug interaction rating scale

Rating	Category	Action	Explanation
X	Contraindicated	Avoid combination	The drugs are contraindicated for concurrent use
D	Major	Consider therapy modification	The interaction may be life threatening and/or require medical intervention to minimize or prevent serious adverse events
C	Moderate	Monitor therapy	The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy
B	Minor	No action needed	The interaction would have limited clinical effects. May include an increase in the frequency or severity of side effects but generally would not require a major alteration in therapy
A	Unknown	No known interaction	Unknown

Table 2: The pattern of drugs with potential for interactions prescribed for patients attending general peadiatric outpatient clinics of four general hospitals in Lagos, Nigeria

	Frequency of prescription (%)
Drug class	
Antimalarial	
Artemether/lumenfantrine	171(35.6)
Artemether/amodiaquine	8(1.7)
Antiemetic/antihistamine	
Promethazine	118(24.6)
Metoclopramide	8(1.7)
Antimicrobial	
Ciprofloxacin	44(9.2)
Erythromycin	13(2.7)
Cotrimoxazole	12(2.5)
Azithromycin	11(2.3)
Amoxicillin	10(2.1)
Gentamicin	5(1.0)
Amikacin	4(0.8)
Metronidazole	4(0.8)
Analgesic	
Ibuprofen	13(2.7)
Paracetamol	9(1.9)
Diclofenac	9(1.9)
Anticoagulants	
Warfarin	28(5.3%)
Anticonvulsant	
Phenobarbital	4(0.8)
Total	**480(100.0)**

Table 3: The pattern of interacting drug pairs and their profiles

Interacting drug pairs	Frequency of prescription (%)	Severity	Rating	Documentation of evidence for Potential DDI in the literature
Phenobarbital and artemether/amodiaquine	4(1.7)	Contraindicated	X	Fair [36, 38]
Promethazine and artemether/lumefantrine	111(46.2)	Major and serious	D	Fair [36, 38]
Erythromycin base and artemether/lumefantrine	13(5.4)	Major and serious	D	Fair [40, 41]
Furosemide and gentamicin	5(2.1)	Major and serious	D	Excellent [42, 43]
Furosemide and amikacin	4(1.7)	Major and serious	D	Excellent [42, 43]
sulfamethoxazole (septrin) and warfarin	4(1.7)	Major and serious	D	Good [44, 45]
Promethazine and metoclopramide	4(1.7)	Major and serious	D	Fair [46]
Ciprofloxacin and artemether/lumefantrine	39(16.2)	Moderate and clinically significant	C	Fair [36, 38]
Amoxicillin and warfarin	10(4.2)	Moderate and clinically significant	C	Excellent [47-49]
Paracetamol (acetaminophen) and warfarin	9(3.7)	Moderate and clinically significant	C	Excellent [50-53]
Azithromycin and artemether/lumefantrine	8(3.3)	Moderate and clinically significant	C	Fair[36, 38]
Ibuprofen and warfarin	5(2.1)	Moderate and clinically significant	C	Excellent [54-57]
Diclofenac and ciprofloxacin	5(2.1)	Moderate and clinically significant	C	Good [58-60]
Metronidazole and artemether/amodiaquine	4(1.7)	Moderate and clinically significant	C	Fair [36, 38]
Promethazine and azithromycin	3(1.2)	Moderate and clinically significant	C	Fair[36, 38]
sulfamethoxazole (septrin) and ibuprofen	8(3.3)	Minor	B	Fair[36, 38]
Diclofenac and metronidazole	4(1.7)	Minor	B	Fair[36, 38]

Table 4: Comparing the age and gender of the patients with the severity of potential drug-drug interaction exposures

Characteristics	Frequency (%)	Severity and prevalence of potential drug-drug interaction (%)					*P*- value	Exposure/exposed ratio
		Contraindicated	Major	Moderate	Minor	Overall		
Age								
Infants	87 (41.8)	2 (0.8)	73 (30.4)	29 (12.1)	2 (0.8)	106 (44.1)	0.046*¶	1.06
Young children	65 (31.3)	2 (0.8)	29 (12.1)	30 (12.5)	5 (2.1)	66 (27.5)		0.88
Older Children	52 (25.0)	0 (0.0)	32 (13.3)	28 (11.7)	5 (2.1)	65 (27.1)		1.08
Adolescent	4 (1.9)	0 (0.0)	3 (1.3)	0 (0.0)	0 (0.0)	3 (1.3)		0.68
Gender								
Male	122 (58.6)	2 (0.8)	84 (35.0)	45 (20.8)	7 (2.9)	138 (57.5)	0.631¶	0.98
Female	86 (41.4)	2 (0.8)	53 (22.1)	42 (17.5)	5 (2.1)	102 (42.5)		1.03

*significant p value, ¶Yates' chi-square test

Table 5: The mechanism of action of the interacting drug pairs, proportion of exposure to the event and the exposed children, associated adverse events and their management

Interacting drug pairs	Mechanism of action	Overall exposure (%)	Number of patient exposed (%)	Exposure per exposed patient ratio (Percentage exposure/percentage exposed)	Potential adverse event	Management
Promethazine and artemether/lumefantrine*	Both increase QTc interval	111(46.2)	96(46.2)	1.00	Sudden dizziness**, lightheadedness, fainting**, shortness of breath, or palpitations**	Combination is strongly discouraged unless benefits outweigh risks or no alternatives available. Use alternative drugs to either of the drugs.
Ciprofloxacin and artemether/lumefantrine*	Both prolong QT interval and cause torsades de pointes (TdP). However, ciprofloxacin elicits minimal effects on QT interval	39(16.2)	34(16.3)	0.99	Sudden dizziness**, lightheadedness, fainting**, shortness of breath, or palpitations**	Monitor patient closely.
Erythromycin base and artemether/lumefantrine	Both prolong QTc interval and may result in serious or life-threatening interaction. Artemether/lumefantrine decreases the level or effect of erythromycin base by affecting hepatic and/or intestinal enzyme CYP3A4 metabolism.	13(5.4)	13(6.2)	0.87	Sudden dizziness, lightheadedness, fainting, shortness of breath, or heart palpitations	Combination is strongly discouraged unless benefits outweigh risks and no alternatives available. Use alternatives to either of the drugs
Amoxicillin and warfarin	Amoxicillin increases the effects of warfarin by	10(4.2)	8(3.8)	1.11	Unusual bleeding or	Monitor patient closely.

	either interference with the CYP2C9-dependent liver metabolism of warfarin or alterations in normal gut flora resulting in reduced intestinal vitamin K synthesis. Amoxicillin may enhance anticoagulant effect of vitamin K antagonists					bruising, swelling, vomiting, blood in the urine or stools, headache, dizziness, or weakness	
Paracetamol (acetaminophen) and warfarin	Paracetamol increases the effects of warfarin by an unknown mechanism	9(3.7)	5(2.4)	1.54		Unusual bleeding or bruising, swelling, vomiting, blood in the urine or stools, headache, dizziness, or weakness	Monitor patient closely.
Azithromycin and artemether/lumefantrine	Both drugs increase QTc interval	8(3.3)	5(2.4)	1.38		Sudden dizziness, lightheadedness, fainting, shortness of breath, or palpitations	Monitor patient closely.
sulfamethoxazole (septrin) and ibuprofen	Sulfamethoxazole will increase the level or effect of ibuprofen by affecting hepatic enzyme CYP2C9/10 metabolism	8(3.3)	5(2.4)	1.38			No action suggested.
Ibuprofen and warfarin	High protein binding and the cytochrome P450 (CYP)-dependent clearance mechanisms of NSAIDs can affect the	5(2.1)	5(2.4)	0.88		Unusual bleeding or bruising, vomiting, blood in urine or	Use with caution and monitor patient closely.

	serum levels of warfarin				stools, headache, dizziness, or weakness	
Diclofenac and ciprofloxacin	Mechanism of the interaction is unknown but there is increased risk of CNS stimulation and seizures with high doses of fluoroquinolones	5(2.1)	5(2.4)	0.88	Tremors, involuntary muscle movements, hallucinations, or seizures	Use with caution and monitor patient closely
Furosemide and gentamicin	Either increases nephrotoxicity or ototoxicity of the other by pharmacodynamic synergism.	5(2.1)	5(2.4)	0.88	Hearing loss, dizziness, numbness, skin tingling, muscle twitching, or seizures which may be signs of nerve damage	Monitor patient very closely. Use alternatives to either of the drugs.
Phenobarbital and artemether/amodiaquine	Phenobarbital decreases the level or effect of artemether/amodiaquine by affecting hepatic/intestinal enzyme CYP3A4 metabolism	4(1.7)	4(1.9)	0.89	Prolonged malaria symptoms	Contraindicated and never use the combination. Use alternatives to either of the drugs
Furosemide and amikacin	Either increases nephrotoxicity or ototoxicity of the other by pharmacodynamics synergism.	4(1.7)	4(1.9)	0.89	Hearing loss, dizziness, numbness, skin tingling, muscle twitching, or seizures which may be signs of nerve damage	Monitor patient very closely. Use alternatives to either of the drugs.
sulfamethoxazole (septrin) and warfarin	Sulfamethoxazole increases effects of warfarin by decreasing metabolism. Sulfamethoxazole increases effects of	4(1.7)	4(1.9)	0.89	Dizziness; lightheadedness; red or black, tarry stools; coughing up or vomiting fresh or	Monitor patient very closely. Use alternatives to either of the drugs.

	warfarin by plasma protein binding competition. Trimethoprim-sulfamethoxazole interacts with racemic warfarin, possibly at a receptor-site locus.					dried blood that looks like coffee grounds; severe headache; weakness; morbilliform rash; and generalized pruritus.	
Metronidazole and artemether/amodiaquine	Metronidazole increases the level or effect of artemether/amodiaquine by affecting hepatic and/or intestinal enzyme CYP3A4 metabolism	4(1.7)	4(1.9)	0.89		Sudden dizziness, lightheadedness, fainting, shortness of breath, or palpitations	Monitor patient closely.
Promethazine and metoclopramide*	Both increase antidopaminergic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome	4(1.7)	4(1.9)	0.89		Abnormal muscle movements, especially of the face and limbs**. Other adverse events include lip smacking**, chewing, puckering, frowning or scowling, tongue thrusting**, teeth clenching, jaw twitching, blinking, eye rolling, shaking or jerking of arms and legs, tremor, jitteriness, restlessness**, pacing, and foot	Monitor patient closely.

					tapping.	
Diclofenac and metronidazole	Metronidazole increases the level or effect of diclofenac by affecting hepatic enzyme CYP2C9/10 metabolism	4(1.7)	4(1.9)	0.89		No action suggested.
Promethazine and azithromycin	Promethazine and azithromycin both prolong QTc interval	3(1.2)	3(1.4)	0.86	Sudden dizziness, lightheadedness, fainting, shortness of breath, or palpitations	Monitor patient closely.

Note: *represents the drug pair that produced the adverse events reported by patients; ** represents the specific adverse events reported by the patients after exposure to the corresponding interacting drug pairs

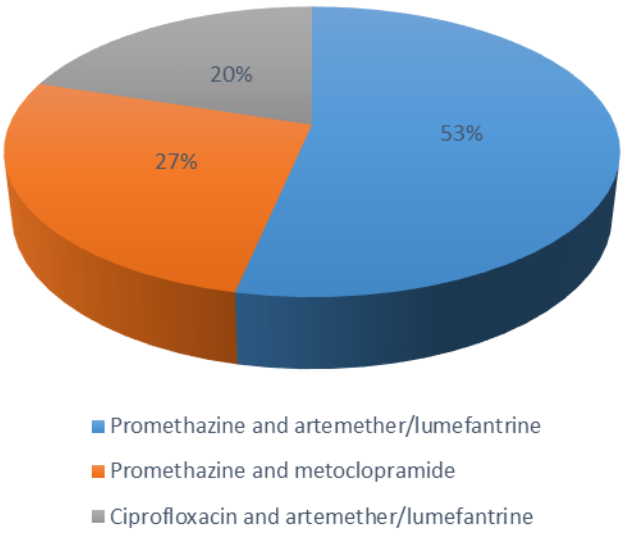

Figure 1. The 15 reported adverse events (ADEs) among 48 patients presenting at the follow-up clinic