# Adverse drug reactions in Nigerian children

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***Aims*: Children constitute a vulnerable group with regard to rational drug prescribing since many new drugs are marketed for their use without evidence from clinical trials. The paucity of information about the incidence of adverse drug reactions (ADRs) in developing countries, especially Nigeria has necessitated this study. The study was therefore aimed at documenting the types of ADRs in children admitted to the Lagos State University Teaching Hospital, Ikeja.**

***Methods*: It was both a retrospective and prospective study. The retrospective study was performed from January 2004 to June 2006. The prospective study involved all patients admitted to the children's ward for various forms of paediatric medical conditions over a 6 month period between July and December 2006. Suspected ADRs noted in the hospital records were used for the retrospective study. For the prospective study pharmacovigilance by a multi-disciplinary team was performed.**

***Results*: 3139 children were admitted to the children's ward over the 30 month retrospective study and 682 children were admitted over the 6 month prospective study. Altogether, 17 children (0.4%) were admitted due to ADRs and 27 children (0.7%) experienced an ADR in hospital. Antibiotics were the group of drugs most likely to be associated with an ADR. Skin reactions were the most frequent ADR. Two children died as a result of their ADR.**

***Conclusion*: ADRs are a significant problem in children in Nigeria. We conclude that a functional monitoring and reporting system for ADRs in children needs to be put in place for early detection. Such a scheme will hopefully result in increased awareness amongst health professionals and parents about reducing the risk of an ADR.**

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## Introduction

Globally physicians are faced everyday with problems of adverse drug reactions (ADRs)[1-3] and about 95% of such cases go unreported worldwide[4,5]. All drugs have the potential to cause ADRs. Some medicines, such as antibiotics[6-9], immunosuppressive agents[7] and anticonvulsants[10-12] are more likely to be associated with ADRs in children. In Nigeria, a high rate of antibiotic prescription and misuse and polypharmacy has been reported in both urban and rural health facilities[13-15], thus placing Nigerian children at a high risk of ADRs.

The actual reported incidence of ADRs varies according to the population described and the case definition used[16-18], the method used, the vigour with which ADRs are sought, as well as the number of concomitantly administered drugs to produce drug interactions[17-20].

Febrile illnesses in children constitute a common presentation in Nigeria and other countries in sub-Saharan Africa[21,22], the major cause being malaria and respiratory tract infections. The majority of these children are usually treated at home either with antimalarials alone[23,24] or in combination with antibiotics when upper respiratory tract infections were suspected by the parents[13]. Antibiotic utilisation in upper respiratory tract infections is not peculiar only to self medications by Nigerian mothers, but is a common practice amongst general practitioners[25,26], primary health care workers[27,28], tertiary and teaching hospitals physicians[14,15]. The irrational use of antimalarials and antibiotics not only predisposes patients to drug resistance, but also places them at risk of ADRs[15,29]. Co-trimoxazole and ampicillin are two commonly prescribed antibiotics in the Nigerian primary health care centres[28] and are associated with ADRs manifesting as morbilliform rash[30]. Other identified risk factors to developing ADRs in Nigerian children include environmental factors, polypharmacy, pre-existing diseases, previous ADRs, medication errors, inappropriate prescribing and long periods of hospitalisation[31].

ADRs are ranked as one of the top leading causes of death and illness in the developed world[17]. However, there is a paucity of information about its incidence in developing countries, especially Nigeria. This study was therefore aimed at documenting ADRs in children admitted to Lagos State University Teaching Hospital (LASUTH), Ikeja, Nigeria. An ADR monitoring committee was established in this hospital and became effective shortly before we commenced the prospective study. In addition to reporting incidences of ADRs, we also wished to compare detection of ADRs before and after the inception of the monitoring committee.

## Methods

The study was both retrospective and prospective. The retrospective study was performed through the hospital's admission records. The admission records for the period from January 2004 to June 2006 were used to identify children with an ADR (either on admission or as an inpatient). The prospective study involved all patients admitted to the children's ward for various paediatric medical conditions over a six month period between July and December 2006. For both studies, patients admitted for less than 24 hours and those with repeated admissions were excluded from the study.

For the prospective study, on each day of the study period, a specific questionnaire was completed for all children newly admitted. All children were evaluated daily for the presence of ADRs by the research team (clinical pharmacologist, paediatrician and pharmacists) and were observed until discharge to ascertain the final diagnosis. The evaluation was usually carried out about two hours before the normal ward rounds. The evaluation consisted of examining medical and nursing records, reviewing prescription charts and attending clinical rounds. All the paediatricians and junior doctors were asked to participate in the study and to record any suspected ADRs.

If a suspected ADR was reported, data on that particular suspected drug and reaction were collected and documented in a suitably designed ADR documentation form. All relevant data, including all drugs the patient had received before the onset of the reaction, their respective doses, the routes of administration with their frequency, laboratory test results present in medical records, clinical details (system–organ class involvement), and the treatment (pharmacological or non-pharmacological) were noted. In addition, when the documented drug history was unclear, the patient's medication history was taken from the patients or parents/guardians or the attending physicians, and co-morbidity was identified to assess the causal relationship between the suspected drug and the reaction. In the retrospective study, the same documentation form was completed for the patients who experienced an ADR. Therefore, this study was done on three separate populations: those admitted to the hospital because of an ADR in the prospective study; those who experienced an ADR in the hospital in the prospective study; and those admitted for, or who developed, an ADR in the retrospective study.

For the prospective study, information regarding previous drug use was obtained by interviewing parents, relatives, nurses, or others, as necessary.

ADRs were defined in accordance with the WHO definition of an ADR[32]. A pharmacist, pharmacologist and paediatric dermatologist acted as a final source of confirming an ADR. The ADRs and drugs were classified according to the WHO classification[33]. The causality relationship in the prospective study between the ADR and the suspected drug therapy was assessed case by case using the method of Jones[34]. To ensure that patients with ADRs had not been missed out in the retrospective study, we analysed 200 random case notes of patients categorised as not having had an ADR. Severity was classified according to the following scheme: fatal; severe (directly life-threatening and/or more than one month in duration, associated with organ-system dysfunction, reduced life expectancy); moderate (some but not all of the mild criteria and none of the severe criteria); and mild (uncomplicated primary disease, no treatment required, and drug discontinuation not necessary)[35-38].

The ethical committee of LASUTH approved the study. All data from the questionnaires and medical records were coded and statistical analysis of the results was performed using SPSS version 13. Continuous data were analysed using Student's *t*-test at a significance level of $P < 0.05$.

## Results

3139 children were admitted to the children's ward of LASUTH during the 30 month retrospective study, of whom 1844 (59%) were males. 682 children were admitted during the six month prospective study, of whom 386 (57%) were males. The admission rate per month remained relatively constant in both the retrospective and prospective studies (105/month vs 114/month).

During the retrospective study period, 13 children were admitted due to ADRs and 17 inpatients developed ADRs. The mean age of the patients admitted with ADRs was 7.2 years (age range, 6 months–12 years) and was significantly higher than the mean age (3.9 years; range, 2 days–12 years) for the inpatients that developed ADRs ($P = 0.017$).

During the prospective study, four children (0.6%) were admitted following ADRs and 10 (1.5%) inpatients developed ADRs. The mean age of the patients admitted with ADRs was 6.7 years (age range, 3–10 years) and was not significantly different from the mean age 3.1 years (range, 2 days–10 years) for the inpatients that developed ADRs ($P = 0.11$).

The patients admitted for the prospective study had a wide variety of diseases. The main reason for admission was malaria ($n = 247$, 36%), followed by meningitis ($n = 77$, 11%). The 682 patients received a total of 3032 drugs during hospitalisation (4.5 drugs per patient; range, 2–10). The most commonly used drugs were cefuroxime and gentamicin. The 10 inpatients from the prospective study that developed ADRs were prescribed a total of 51 drugs (mean 5.1 drugs per patient, range 4–10).

*Combined data*

The incidence of ADRs resulting in admission was 0.45% and during hospitalisation was 0.71%. Overall, 44 children (1.15%) experienced ADRs. Among the patients with ADRs, five children had a previous history of ADRs but not to the suspected drugs.

**Table 1** Systemic-organ classes of adverse drug reactions and the suspected drugs

| Types of reaction | Suspected drugs | *n* |
|---|---|---|
| **Cutaneous manifestation** | | |
| Erythema multiforme | Cotrimoxazole (5), Phenobarbitone (4), Ampicillin (5), Sulphadoxine/Pyrimethamine (4) | 14 |
| Pustular rash | Baby oil (8), Vancomycin (2) | 10 |
| Fixed drug eruption | Sulphadoxine/Pyrimethamine (1), Cotrimoxazole (1) | 2 |
| Stevens Johnson syndrome | Cotrimoxazole (1), Sulphadoxine/Pyrimethamine (1), Ampicillin (1), Phenobarbitone (1) | 2 |
| Macular and morbiliform rash | Ampicillin | 1 |
| Urticaria rash | Ceftriaxone | 1 |
| Papulo-nodular rash | Isoniazid | 1 |
| **Systemic manifestation** | | |
| Fever | Ceftriaxone (1), Ceftazidime (1) | 2 |
| Red Man syndrome | Vancomycin (2) | 2 |
| Anaphylactic shock | Ceftriaxone | 1 |
| Hyperbilirubinaemia | Ceftriaxone | 1 |
| **CNS manifestation** | | |
| Dystonia | Promethazine (1), Metroclopramide (1) | 2 |
| Transient loss of vision | Quinine (2) | 2 |
| Hepatic encephalopathy | Herbal drug | 1 |
| Convulsion | Herbal concoction | 1 |
| Irrational behaviour | Halofantrine | 1 |
| **Total** | | **44** |

Twenty eight ADRs were considered to be definite, 12 probable and four possible. Most ADRs (*n* = 34) shown in this study were classified as type A ADRs, according to the classification of Rawlins and Thompson[16]. Forty three were judged to be preventable. Eleven ADRs were directly responsible for the prolongation of the hospital stay (range, 18–30 days).

Table 1 summarises the ADRs detected according to the organ-system affected. The most common clinical manifestation of an ADR during the study period was erythema multiforme rash (14 cases), followed by pustular rash (10 cases). In total, 50 drugs were incriminated in the occurrence of the 44 ADRs (Table 1). The 50 drugs consisted of the following types of drugs: antibiotics 24, antimalarials nine, baby oil eight, anticonvulsants five, herbal drugs and others four.

Twenty two of the ADRs were severe, of which two resulted in death, 18 were moderate, and four mild (Tables 2 and 3). Most of the survivors recovered without long-term sequelae. One child died from liver failure due to the use of herbal medicines and another died from Stevens Johnson Syndrome (SJS) due to antibiotics. The most frequent severe ADR was erythema multiforme. The erythema multiforme was characterised by multiple and extensive complex skin rashes that involved the mucous membrane. Exfoliation and peeling of the skin resulted in the debility and prolonged hospitalisation of the patients. Most of the skin lesions healed with permanent hyper-pigmentations. The two cases of SJS had a similar presentation to erythema multiforme, except for greater mucocutaneous involvement, associated perineal and oral mucosal peeling, hyphaemia and alopecia. One patient later developed unioccular blindness.

The anaphylaxis to ceftriaxone and ceftazidime (two children) was similar to the Red Man syndrome (shock) induced by vancomycin (two children). The patients developed difficulty in breathing, excessive sweating, palpitations, chest pain, cold and clammy extremities, and weak thready pulse following rapid administration of

**Table 2** Adverse drug reactions in admitted cases

| ADR | Co-morbidity | Drug | Parental presumed diagnosis | Age (years) | Sex | Severity | Duration of ADR before presentation (days) | Duration of admission (days) |
|---|---|---|---|---|---|---|---|---|
| **Prospective** | | | | | | | | |
| Erythema M. | Epilepsy | ***Phenobarbitone | Nil | 6 | M | Severe | 2 | 8 |
| Erythema M. | Nil | *Sulphadoxime / Pyrimethamine | URTI, Malaria | 10 | M | Severe | 2 | 21 |
| Erythema M. | Malnutrition | *Co-trimoxazole | URTI | 12 | M | Severe | 5 | 28 |
| Macular and morbiliform rash | Nil | *Ampicillin | Diarrhoea | 2 | F | Moderate | 2 | 7 |
| **Retrospective** | | | | | | | | |
| Erythema M. | Epilepsy | ***Phenobarbitone<br>*Ampiclox<br>*Multivitamine<br>*Calamine lotion | Measles | 10 | M | Severe | 4 | 22 |
| Erythema M. | Nil | **Ampicillin<br>**Gentamicin<br>*Cefuroxime | Tonsillitis | 4 | M | Severe | 1 | 9 |
| Erythema M. | Nil | *Sulphadoxime / Pyrimethamine | Malaria | 7 | F | Severe | 7 | 21 |
| Erythema M. | HIV infection | ***Co-trimoxazole | - | 10 | M | Severe | 2 | 10 |
| Erythema M. | Epilepsy | ***Phenobarbitone<br>*Ampicillin | URTI | 6 | F | Severe | 2 | 30 |
| Erythema M. | Nil | *Ampicillin<br>*Sulphadoxime / Pyrimethamine | Malaria, URTI | 4 | M | Severe | 7 | 30 |
| Erythema M. | Nil | ***Sulphadoxime / Pyrimethamine | Malaria | 6 | F | Severe | 3 | 20 |
| Erythema M. | Malnutrition | *Co-trimoxazole | URTI | 6 | M | Severe | 3 | 30 |
| Erythema M. | Nil | *Ampicillin<br>*Co-trimoxazole | URTI | 5 | F | Severe | 7 | 18 |
| SJS | Nil | +Cotrimoxazole<br>+Sulphadoxime / Pyrimethamine<br>++Chloramphenicol<br>++Procaine penicillin<br>++Ampicillin | Malaria, Typhoid | 8 | M | Severe | 3 | Died 3 days later |
| Hepatic failure | Nil | *Herbal drug | Haemorrhoids | 0.5 | M | Severe | 3 | Died 5 days later |
| Irrational behaviour | Nil | ++Halofanthrine | Malaria | 7 | M | Moderate | 1 | 5 |
| Convulsion | Nil | *Herbal concoction | Malaria | 3 | F | Moderate | 30 mins | 5 |

Erythema M. = Erythema multiforme
URTI = Upper respiratory tract infection
SJS = Stevens Johnson syndrome
*Self medication (non-prescribed drug)
**Prescribed at primary health care centre
***Prescribed at LASUTH outpatient clinic
+Prescribed by trained unregistered nurse
++Prescribed by general practitioners in private clinics/hospitals

**Table 3** Adverse drug reactions in in-patients who developed ADRs

| ADR | Co-morbidity | Diagnosis on admission | Age | Sex | Severity | Duration of treatment prior to ADR | Suspected drugs | Other drugs |
|---|---|---|---|---|---|---|---|---|
| **Prospective** | | | | | | | | |
| Erythema M. | Nil | Cerebral abscess | 6 months | M | Severe | 6 days | Ampicillin, Phenobarbitone | Ceftriaxone |
| Red Man syndrome | Nil | Osteomyelitis | 3 years | M | Severe | 10 mins | Vancomycin | Chloramphenicol |
| Red Man syndrome | Nil | Osteomyelitis | 6 years | F | Severe | 2 days | Vancomycin | Chloramphenicol |
| Dystonia | Nil | Malaria | 12 years | M | Moderate | 8 hours | Promethazine | Chloroquine, Paracetamol |
| Dystonia | Nil | Gastroenteritis | 2 years | F | Moderate | 6 hours | Metoclopramide | Artesunate |
| Pustular rash | Neonate | Sepsis | 3 days | M | Moderate | 2 days | Baby oil | Cefuroxime, Gentamicin |
| Pustular rash | Neonate | Sepsis | 3 days | F | Moderate | 3 days | Baby oil | Cefuroxime, Gentamicin |
| Pustular rash | Prematurity | Sepsis | 2 days | F | Moderate | 2 days | Vancomycin | Gentamicin |
| Pustular rash | Prematurity | Sepsis | 2 days | F | Moderate | 2 days | Vancomycin | Gentamicin |
| **Retrospective** | | | | | | | | |
| SJS | Nil | Meningitis | 6 years | M | Severe | 7 days | Ampicillin, Phenobarbitone | Chloramphenicol |
| Erythema M. | HIV | Gastroenteritis | 8 years | F | Severe | 3 days | Co-trimoxazole | |
| Pustular rash | Neonate | Sepsis | 2 days | M | Moderate | 2 days | Baby oil | Cefuroxime, Gentamicin |
| Pustular rash | Neonate | Sepsis | 4 days | M | Moderate | 3 days | Baby oil | Cefuroxime, Gentamicin |
| Pustular rash | Neonate | Sepsis | 2 days | F | Moderate | 3 days | Baby oil | Cefuroxime, Gentamicin |
| Pustular rash | Prematurity | Sepsis | 3 days | F | Moderate | 2 days | Baby oil | Cefuroxime, Gentamicin |
| Pustular rash | Prematurity | Sepsis | 2 days | M | Moderate | 2 days | Baby oil | Cefuroxime, Gentamicin |
| Pustular rash | Prematurity | Sepsis | 4 days | M | Moderate | 3 days | Baby oil | Cefuroxime, Gentamicin |
| Jaundice | Hyperbilirubinaemia | Birth asphyxia, sepsis | 4 days | M | Severe | 3 days | Ceftriaxone | Gentamicin |
| Anaphylaxis | Nil | Septicaemia | 11 years | F | Severe | 20 mins | Ceftriaxone | |
| Urticaria | Nil | Septicaemia | 8 years | M | Severe | 10 mins | Ceftriaxone | |
| Fixed drug eruption | Nil | Shigellosis | 12 years | M | Mild | 4 days | Cotrimoxazole | |
| Fixed drug eruption | Nil | Malaria | 10 years | F | Mild | 3 days | Sulphadoxime / Pyrimethamine | Artesunate |
| Papulo-nodular rash | Nil | TB meningitis | 6 months | M | Moderate | 5 days | Isoniazid | Rifampicin, Pyrazinamide |
| Fever | Nil | Septicaemia | 4 months | F | Mild | 3 days | Ceftazidime | |
| Fever | Nil | Septicaemia | 6 months | F | Mild | 7 days | Ceftriaxone | |
| Transient blindness | Nil | Cerebral malaria | 4 years | M | Moderate | 6 days | Quinine | Dexamethasone |
| Transient blindness | Nil | Cerebral malaria | 6 years | M | Moderate | 7 days | Quinine | Dexamethasone |

Erythema M. = Erythema multiforme

SJS = Stevens Johnson syndrome

the drugs intravenously. They were revived by active resuscitation and rehydration. The infant with hyperbilirubinaemia required an urgent exchange blood transfusion and phototherapy.

The 18 moderate ADRs included 10 cases of pustular rash to adulterated baby oil and vancomycin, two cases of dystonia, and two cases of transient loss of vision from quinine. There was no permanent deformity or debility to the patients, except the papulo-nodular skin rashes from isoniazid that remained permanent. The pustular rash required treatment with corticosteroids. The irrational behaviour and dystonia were treated with benztropine, and the convulsion controlled with rectal diazepam.

Of the 17 children admitted due to ADRs (Table 2), nine cases resulted from the use of non-prescribed drugs, i.e. self-medicated drugs from the parents, three cases from the use of drugs prescribed in the community, four cases from the use of prescribed drugs from LASUTH paediatric outpatient clinic, and one case from the use of a prescribed drug at LASUTH that interacted with a self-medicated drug. Antibiotics, used alone or in combination, resulted in ADRs in 10 children admitted following ADRs and 14 inpatients.

## Discussion

The data resulting from this study offer an insight for health professionals into the impact of ADRs in a developing country in the setting of a Nigerian paediatric population. The overall incidence of ADRs leading to admission was 0.45% and 0.71% patients following admission developed an ADR. These rates were low when compared with results (2.1% and 9.5% respectively) from developed countries[7,9], thus suggesting that ADRs are under-reported in developing countries. Under-reporting may have resulted from a lack of awareness of ADRs and a lack of facilities for their proper monitoring. Similarly, when the incidence rates were compared with the results (5.1% and 10.9% respectively) from adult settings in developed countries[17,39-41], they were also very low thus suggesting that ADRs are less common in children than adults[9,17,18]. The higher incidence rates obtained from the prospective study over the retrospective study may be explained by the daily monitoring for ADRs. A proactive ADR monitoring and reporting system, focusing on paediatric patients in developing countries appears to be successful.

The most commonly affected organ system was the skin (over 50% of ADRs). The most frequently reported ADR was a rash which was similar to the findings of other studies[35,42-44]. The group of drugs most frequently involved in ADRs in our study was antibiotics. Infectious diseases were, however, the commonest cause for admission to hospital and hence antibiotics were frequently prescribed. Erythema multiforme, the most common ADR in this study, was caused by antibiotics (ampicillin and cotrimoxazole), antimalarials (sulfadoxime/pyrimethamine) and anticonvulsants (phenobarbitone). These drugs are well known for this type of ADR[30,45]. The high increase of erythema multiforme was probably a result of the pattern of self-medicated and prescribed drugs used by the patients (Tables 2 and 3). In those patients who developed ADRs from a combination of two or more drugs, the skin manifestation was either erythema multiforme or its severe form, SJS, and they were hospitalised for over two weeks.

ADRs are of significant concern in that two children died during the course of this study. It was, however, difficult to determine from this study the fatality rate of the ADRs because of the small population studied. This is therefore one of the limitations of this study. One of the deaths resulted from use of herbal medicine containing naphthalene tablets as one of the ingredients. Renal failure complicating the use of herbal medicines has been previously reported in Africa[46]. Severe jaundice, anaemia, haemolysis, hepatic encephalopathy and renal failure, as manifested by this patient, are a few of the manifestations of chronic toxicity of naphthalene[47]. It can be concluded that ADRs are a significant public health problem in children.

Self-medication was a common finding among the patients hospitalised for ADRs and this involved the use of drugs that have the potential for adverse interactions. The use of 5.1 drugs per patient on admission that developed ADRs in the prospective study was consistent with the reports of other studies[48,49]. This high drug use is termed polypharmacy. An association between the number of drugs received by children and the risk of ADRs has been previously reported[9,42,49,50].

## Conclusion

We conclude that ADRs are not a rare problem in Nigeria. Even though they are under-reported worldwide, they are much more under-reported in Nigeria. A functional monitoring and reporting system for ADRs in children therefore needs to be put in place for early detection. A public enlightenment programme is advised in order to stem the tide of self-medications amongst Nigerian mothers since many of these drugs have the potential for adverse interactions that could cause unwanted drug reactions. The Government should regulate the sales and use of herbal medicines for children.

Physicians should familiarise themselves with the pharmacology of the commonly used drugs in children and weigh the benefit–risk ratio before prescribing.

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