PHARMACOVIGILANCE - POST MARKETING SURVEILLANCE NEWS

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Editor's Note

We wish to thank all our numerous stakeholders who have been working tirelessly with the National Pharmacovigilance Centre (NPC) to ensure the safe use of medicines in Nigeria. The NPC is committed to sending out quarterly newsletter to its stakeholders. The objectives of the Newsletter are to disseminate information on Pharmacovigilance activities nationally and globally, to educate stakeholders on medicine safety issues, to promote rational use of drugs and to promote spontaneous reporting. This second quarter newsletter focuses on paediatric Pharmacovigilance.

We encourage Health care Professionals and other stakeholders to continue to report all adverse drug reactions. Your valued comments and acknowledgement of receipt of this issue through our email addresses (nafdac_npc@yahoo.com; pharmacovigilance@nafdac.gov.ng) would be most appreciated.

Thank you for your relentless efforts in strengthening Pharmacovigilance System in Nigeria

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Text any DRUG RELATED PROBLEM to the **SHORT CODE 20543 (***For* **free** *on* **MTN, Glo and Etisalat)** *for action by the Pharmacovigilance Centre*

Review of Pediatric Pharmacovigilance

Introduction

The 2010 vol. 4, No. 2 edition of the Pharmacovigilance Newsletter was focused on reported Adverse Drug Reactions (ADRs) attributable to medicines used in the paediatric population. This current issue is more or less a review of that edition. The review covers all reported events in children ages 0-17. The paeditric population subgroups used are: Neonates (0-30days) infants (1month-2years), young child (2-6years), child (6-12 years) and adolescents (12-17years).[1]
The aim of the review is to bring an update on pediatric ADRs since received at the National Centre. Secondly, to remind health professionals about the importance of their contribution towards the process of paediatric pharmacovigilance, credit to their role in reporting of ADRs.

Pediatric Pharmacovigilance: Rationale and Principle

The WHO defines Pharmacovigilance (PV) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. These drug related problems include Adverse Drug Reactions (ADR), Medication Errors and therapeutic failure. PV is a necessary tool in ensuring the safe use of medicines.

The concern over safety of medicines used in the paediatric populations has increasingly gained prominence over the past decades. There is a general lack of information and appropriate pharmaceutical formulations to support the administration of many medicines in children. This exposes them to unwanted side effects as well as under dosing without the expected efficacy. ADRs in children are associated with over-the-counter (OTC), as well as prescription medicine use. Even commonly used pediatric medicines have potential to cause serious adverse effects.

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[1] http://archives.who.int/eml/expcom/children/Items/PositionPaperAgeGroups.pdf accessed 02/02/2016

Medicines regulatory authorities around the world in concerted efforts to check this trend are advocating for the integration of Paediatric aspects early in the development process of a new drug. In view of this, several Nations have passed Regulatory legislations for drug development in paediatric patients. The US FDA has passed regulations that impose a requirement that pharmaceutical companies test in a paediatric population a new drug likely to be used in children (the Paediatric Research Equity Act (PREA), passed in 2003). While another FDA regulation provides incentives for companies to test drugs in paediatric populations voluntarily (the Best Pharmaceuticals for Children Act (BPCA), passed in 2002).[2] The European Medicines Agency (EMA) has similar legislation governing the development and authorisation of medicines for paediatric use (Regulation (EC) Nº 1901/ 2006). The key objectives of the EMA Regulation are: to ensure high-quality research into the development of medicines for children; to ensure over time, that the majority of medicines used by children are specifically authorised for such use; and to ensure the availability of high-quality information about medicines used by children[3]. In addition, the regulations establish special protections for child research participants that extend beyond those applicable to adults[4]. The result is the dramatically increasing number of drugs tested in and labelled for children. There also has been improvement in rational prescribing for children, including more than 500 labelling changes in the US.[5]

Despite this advances, off-label drug use remains a common and important issue for children and adolescents particularly children under two years and those with chronic and/or rare diseases. Off-label prescribing has been shown to increase the risk of ADR occurrence. The term "off-label" use refers to use of a drug that is not included in the approved labelling for that drug. Many medicines currently used to treat the pediatric population still have no information in the labelling for use in appropriate paediatric age groups. Healthcare professionals are thus posed with the challenge of prescribing medicines off label, to benefit an individual patient[6]. A review of

[2] http://www.ncbi.nlm.nih.gov/books/NBK3997/ accessed 9/5/16
[3] http://ec.europa.eu/health/human-use/paediatric-medicines/index_en.htm accessed 9/5/16
[4] http://www.nap.edu/read/13311/chapter/6#93 accessed 10/5/16
[5] Http://pediatrics.aappublications.org/content/133/3/563 accessed 12/5/16
[6] http://pediatrics.aappublications.org/content/133/3/563 accessed 9/5/16

pediatric studies showed that off-label use ranged between 18 and 65% of prescriptions in hospital and between 11 and 31% in primary care[7]

Another common occurrence with pediatric care is medication error. Errors associated with medications are believed to be the most common type of medical error and are a significant cause of preventable adverse events. Experts agree that medication errors have the potential to cause harm within the paediatric population at a higher rate than in the adult population[8]. A study that retrospectively reviewed 960 randomly selected charts from 12 children's hospitals in the US identified an 11.1% rate of adverse drug events in paediatric patients. The study also showed that 22 percent of those adverse drug events were preventable, 17.8% could have been identified earlier, and 16.8% could have been mitigated more effectively. Only 3.7% were identified by using traditional voluntary reporting methods echoing the challenge of underreporting that is associated with spontaneous reporting[9].

The challenge of off-label prescription and medication errors that are commonly associated with paediatric pharmacotherapy in addition to the limitations of premarketing clinical trials such as secure and protected scientific environment, short-term safety and efficacy testing on a limited number of carefully selected individuals, necessitate pharmacovigilance. Post marketing Pharmacovigilance activity remain the mainstay of safety data generation on effectiveness and safety of paediatric medicines post marketing under real-life conditions such as chronic use, especially in combination with other medicines.

A major aim of PV is to enhance patient care and safety in relation to the use of medicines by identifying drug safety signals as early as possible. This is mainly achieved through spontaneous reporting of ADRs identified during 'real time' use of medicines.

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[7] Kimland E, Odlind V. Off-label drug use in pediatric patients.Clin Pharmacol Ther. 2012;91:796–801
[8] http://www.jointcommission.org/assets/1/18/sea_39.pdf accessed 9/5/16
[9] http://pediatrics.aappublications.org/content/121/4/e927.full accessed 9/5/16

Report on the EMA workshop of pharmacovigilance in the paediatric population in April 2014 specified the action points below for improving the quality of paediatric ADR and paediatric Signal Detection:

- Quality of reported data should be improved: definition of minimum requirements, and common EudraVigilance dataset;
- Age, co-morbidity, and Date of Birth, should be reported/captured fields in ADRs;
- Stratification by age in ICSR should be looked at; in case the implementation is not possible, to have a tick box as "paediatrics", "not paediatrics" or "unknown";
- Age should be retrieved from the Adverse Events narratives when mentioned, so that paediatric Signal Detection can be performed;
- Common methods for Signal Detection in paediatrics should be defined;
- Lack of quality/appropriate formulation in Off-Label Use ADRs should be addressed;
- A MedDRA SMQ for Medication Errors should be developed and Medication Errors reporting encouraged.[10]

PAEDIATRIC ADR REPORTS FROM THE NPC DATA BASE

The percentage of ICSR in the NPC database on children remain low despite the general risk factors predisposing children to develop ADRs. The NPC database for the reporting period of 2004 to February 2016 revealed a total of nine hundred and forty six (946) individual case safety reports involving children one day to 17 years. This constitutes 5.65% of total reports in the database. The distribution of individual case reports based on age groups is given in Table 1.

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[10] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/08/WC500171787.pdf accessed 13/5/16

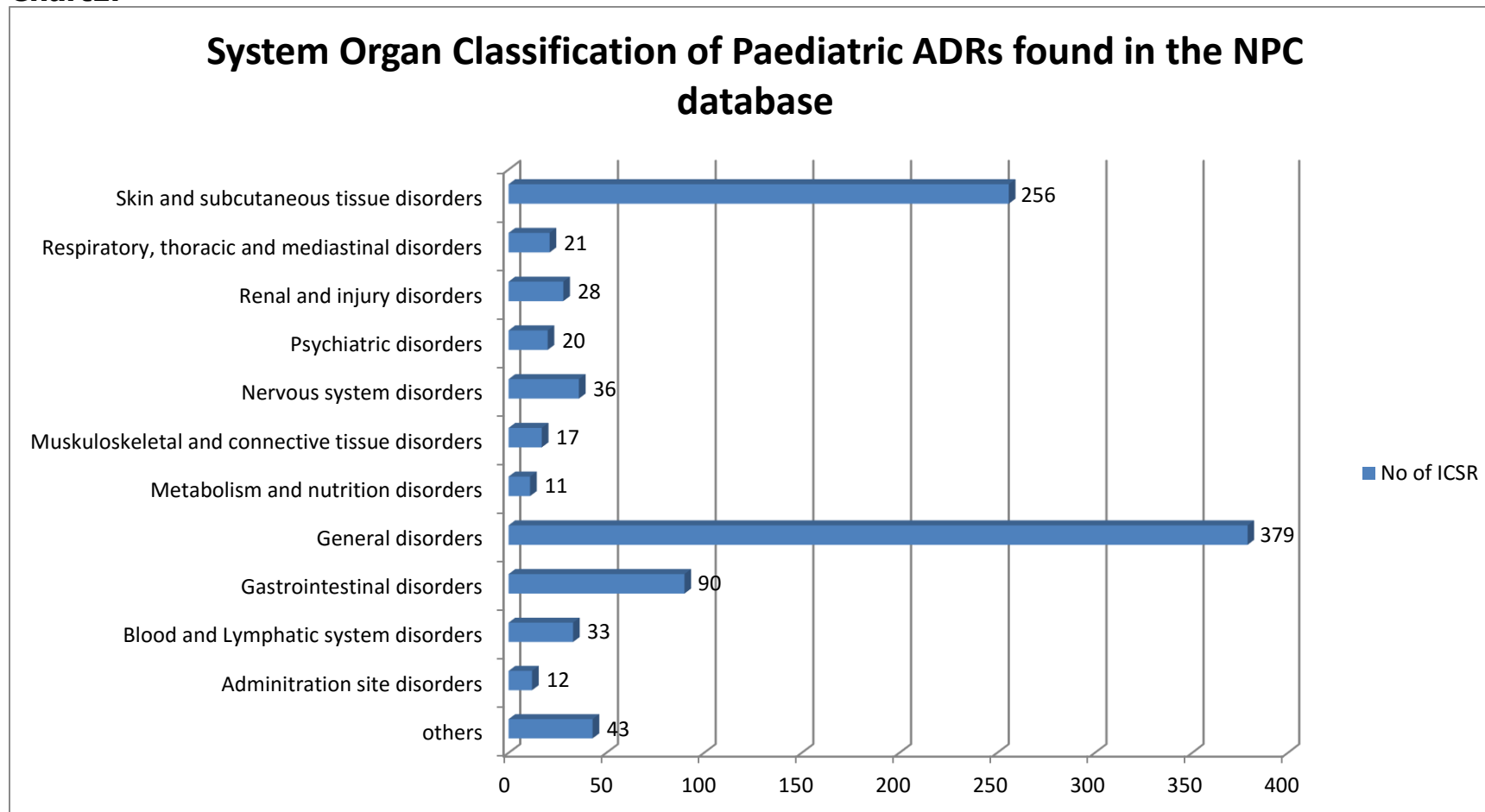**Table1. Pediatric ADR reports according to age sub populations**

Age Class	Age range	No. of reports	Percentage (%)
Neonate	0-30days	14	1.33
Infant	1mnth- 2yrs	253	24.21
Young child	2-6yrs	243	23.25
Child	6-12yrs	233	22.30
Adolescent	12-17yrs	203	21.46
	Total	946	

The system organ classes involved in the majority of the paeditric ADRs in the NPC database were general disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders and nervous system disorders. (chart1). These findings bear some similarities with those from a study done on the European ADR database - EudraVigilance. The study showed that reports of paediatric ADRs in EudraVigilance seemed to be more common under the general and administration site, nervous system, skin and subcutaneous disorders and infections and infestations SOCs.[11]

The highest numbers of pediatric ADRs in the NPC database were however under the SOC, General disorders. Reactions classified in this SOC in the NPC database included classical general disorders like weakness, dizziness body pain etc. The SOC general disorders here also comprised reports that contained two or more reactions pertaining to different organs and systems, so they could not readily fit into any one specific SOC. For instance one such case reported headache, fever, backache, abdominal discomfort, diarrhea, anorexia, nausea, confusion, and delirium; another reported malaise, abdominal pain, palpitation, loss of appetite, and dizziness.

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[11] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2014/05/WC500166901.pdf

Chart1.

System Organ Classification of Paediatric ADRs found in the NPC database

Horizontal bar chart — No of ICSR:

- Skin and subcutaneous tissue disorders: 256
- Respiratory, thoracic and mediastinal disorders: 21
- Renal and injury disorders: 28
- Psychiatric disorders: 20
- Nervous system disorders: 36
- Muskuloskeletal and connective tissue disorders: 17
- Metabolism and nutrition disorders: 11
- General disorders: 379
- Gastrointestinal disorders: 90
- Blood and Lymphatic system disorders: 33
- Adminitration site disorders: 12
- others: 43

Others in chart 1 represents the SOCs that had an incidence of less than 10 such as cardiac disorders, infections and infestations, eye disorders, vascular disorders, ear and labyrinth disorders etc.

In an effort to assess the seriousness of the pediatric ADRs, a search was conducted on the database using the criteria: life threatening, congenital abnormality, recovered/resolved with disability, hospitalization and death. A total of 87 reports, 9.20% of 946 were found to fit into the seriousness criteria. The pharmacological classes of medicines implicated in most of the serious ADRs were analgesics, antimalarial, antibiotics, and ARVs (Table2). Majority of the serious ADRs occurred in the infant subpopulation group with age range of 1month to 2 years (Table 3).

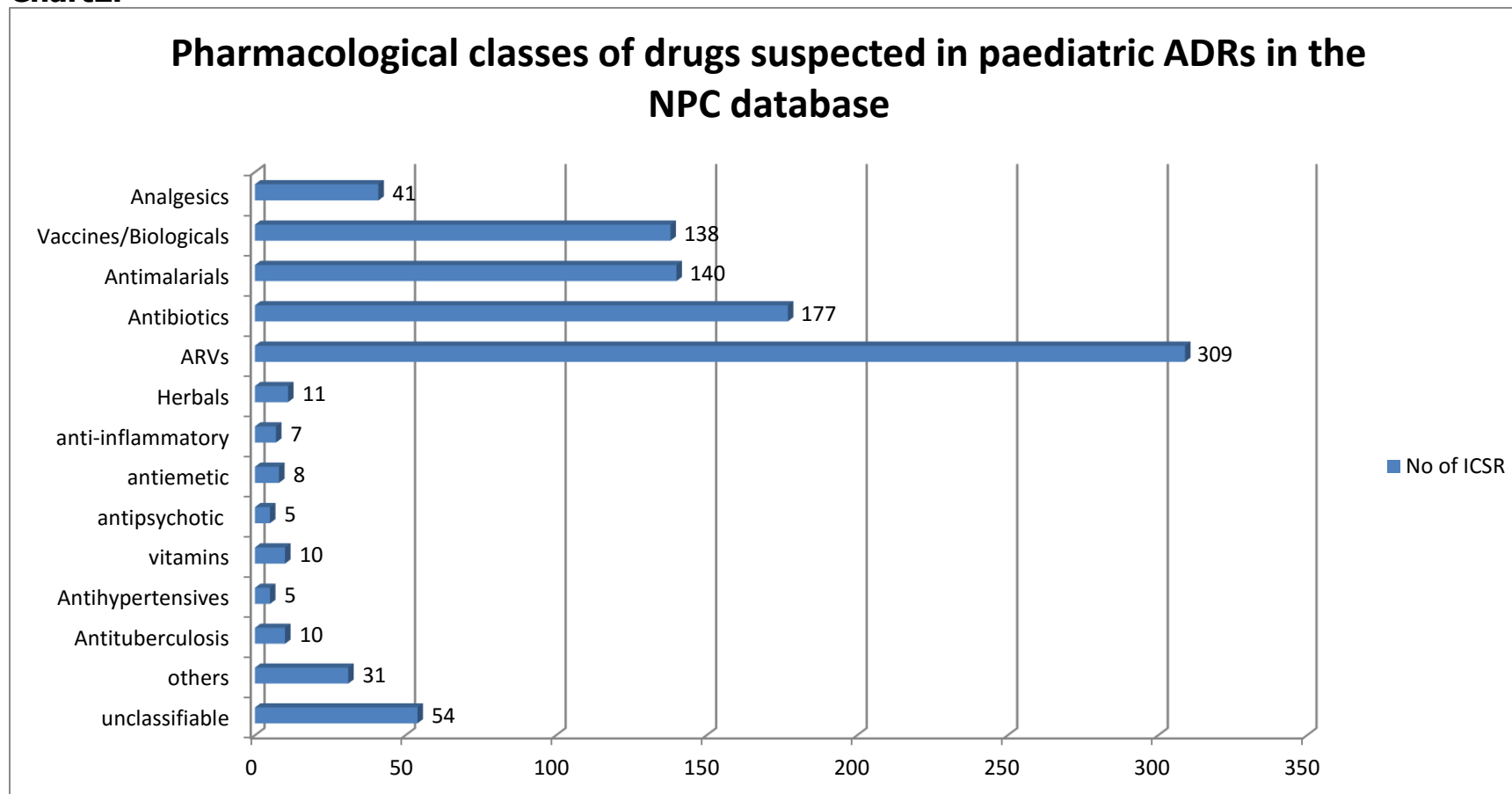**Table 2. Pharmacological classes implicated in serious ADRs**

Pharmacological class	No. of ICSR
Analgesics	17
Antimalarial	11
Antipsychotics	3
Antibiotics	15
ARVs	14
Herbals	4
Vitamins	2
Antiemetic	1

Table3. Serious ADRs according to sub populations

Age class	No. of reports
Neonate	4
Infant	31
Young child	16
Child	22
Adolescent	14

Documented literature show that drugs most frequently associated with pediatric ADRs are generally, those most commonly used among young patients such as vaccines, antibiotics, antipyretics, non- steroidal anti-inflammatory and specific products for colds. The NPC findings as per the pharmacological classes of drugs implicated in the pediatric ADRs were along this pattern. See chart 2. Antibiotics, vaccines and Antimalarial were implicated in a good number of the ADRs. However, the highest cases were observed with ARVs. A number of factors may be considered for this: The high prevalence of HIV/AIDs in Nigeria and consequent wide spread use of ARVs; the potential of ARVs to cause ADRs; the propensity of people living with HIV/AIDS to experience ADRs due to their compromised immunities and polypharmacy influences; and the HIV Programs' commitment to reporting ADRs. This high ADR reporting on ARVs is also reflected in the overall data. Of the 16,738 reports in the NPC database, 11,098 (66.31%) are on ARVs.

Chart2.

Pharmacological classes of drugs suspected in paediatric ADRs in the NPC database

Class	No of ICSR
Analgesics	41
Vaccines/Biologicals	138
Antimalarials	140
Antibiotics	177
ARVs	309
Herbals	11
anti-inflammatory	7
antiemetic	8
antipsychotic	5
vitamins	10
Antihypertensives	5
Antituberculosis	10
others	31
unclassifiable	54

Others in chart 2. Includes the pharmacological classes that had incidence of less than 7 such as anticancer, anti-helminthic, antihistamine, anti-fungi etc.

A significant number of 54 reports were unclassifiable in the pharmacological classes. This included reports of infusions and cosmetics. But very importantly, they also included reports that the drugs thought to be causing the adverse reactions were not stated. The International Conference on harmonization and other Regulatory Agencies have established the minimum criteria for a valid ICSR to include:

- An identifiable patient (initials, age and sex indicated);
- Description of the ADR stating the date it started;
- Brand and generic name of the suspected drug indicating the date it was started and stopped;
- Name and contact of the Reporter in case follow up is needed.[12]

A report that is missing vital information such as the names of the suspected drugs and dates for commencement of therapy and reaction onset cannot be assessed for causality. The WHO uses completeness of report as one of the main tools to assess the quality of reports submitted to the Uppsala Monitoring Centre by member countries.

In conclusion, ADRs can occur in children whether they are in/out patients in a healthcare facility or are being provided medical care in the community, and whether they are taking prescription or OTC medicines. Consequently, Healthcare providers and parents/caregivers alike have responsibility in paediatric ADR identification and reporting.

It is vital for healthcare providers to directly observe patients of this population (particularly infants and children who cannot effectively communicate) for any signs of adverse reactions. Drugs with strong potential to cause ADRs such as vancomycin should also be prospectively appraised.[13]

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[12] NAFDAC Consumer Safety Publication Issue 1, 2014. Pharmacovigilance/ Post Marketing Surveillance

[13] Le, J. et.al. Adverse Drug Reactions Among Children Over a 10-Year Period Pediatrics August 2006, VOLUME 118 / ISSUE 2

A further responsibility is to accurately document and report the ADRs to the National pharmacovigilance Centre at NAFDAC. Studies done on properly documented ADRs will help among other things to determine their 'avoidability' and hence prevent or mitigate future occurrences and also assess the risk/benefit ratio of the marketed medicines. ADR reporting therefore helps to inform regulatory decisions that impact on patient safety. For instance the withdrawal of the infamous "my pikin" teething mixture from the Nigerian market in 2009 was a regulatory decision as a result of reported ADRs.