Adverse drug reactions in Ghanaian children: review of reports from 2000 to 2012 in VigiBase

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Objective: The aim of this article is to describe adverse drug reactions (ADRs) reported for children aged 0 – 17 years in Ghana.

Methods: Paediatric reports submitted by the Ghana National Centre for Pharmacovigilance to the World Health Organisation (WHO) Global ADR database, VigiBase up to December 2012 were extracted. The data were analysed for number of reports per year, types of reporters and suspected ADRs and drugs.

Results: A total of 343 reports for children were received during the period. The drug classes most frequently reported were vaccines (115, 31%), antimalarials (106, 28%) and antibiotics (57, 15%). Of the top 20 individual drugs, 19 were anti-infectives. The most frequently reported ADRs were injection site infection, fever and rash. There were 23 deaths reported, and antimalarials were implicated in 12 cases.

Conclusions: Vaccines, antimalarials and antibiotics are the leading medicines reported to cause ADRs in Ghanaian children. There was a high mortality rate, with many of the deaths due to causes explained in the individual case safety reports.

Keywords: adverse drug reactions, spontaneous reporting system, pharmacovigilance, drug safety, children

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1. Introduction

Adverse drug reactions (ADRs) have been recognised as a major global health concern [1], even though overall reporting of ADRs across the world is generally low [2]. Due to developmental changes taking place during childhood, ADRs in children can be different from those in adults [3]. One in 10 children in hospital will experience an ADR [4]. The majority of studies of ADRs in children have been carried out in prospective observational settings on inpatients and outpatients. In the community, it was suggested that at least 1 in every 500 children experiences an ADR each year [5].

Postmarketing surveillance of drugs by manufacturers plays a vital role in evaluating drug safety [6]. Programmes to promote the reporting of ADRs by healthcare professionals have been established by health authorities in many countries. These are supported by the World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC), Sweden [7], as well as WHO and its Collaborating Centres for pharmacovigilance (Ghana, Morocco, Netherlands). ADRs reported for children worldwide by member states of WHO International Drug Monitoring Programme have been analysed from VigiBase [8]. In addition, paediatric ADRs have been reported...
from national ADR databases of high-income countries in Europe [6,9] and US [10] as well as from Cuba [5,11]. However, there have been no published reports for children in Africa from a national pharmacovigilance database.

The population of Ghana is 25 million, of whom 11 million are children aged 0 – 17 years. Ghana was the first country in West Africa to have a national pharmacovigilance (PV) centre. It joined the WHO Programme for International Drug Monitoring in 2001, and maintained an ADR database. The UMC and WHO then established centres in Ghana in 2009 (the then UMC-Africa as well as the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance), with the responsibility of promoting and supporting ADR reporting in Africa [12]. The national PV centre in Ghana is located within the national drug regulatory agency, the Ghana Food and Drugs Authority (FDA), with active regional centres throughout the country. The reports received are shared globally within the WHO Individual Case Safety Reports database, VigiBase [13], managed by the UMC in Sweden. The aim of this study was to describe the type, frequency and severity of ADRs among Ghanaian children using this database.

2. Methods

The Ghana FDA gave approval for the use of the data, and consent from patients was not required. All the anonymised reports forwarded by the Ghana Food and Drugs Authority between 1999 and December 2012 to the International Drug Monitoring Centre, and entered into the WHO Global Individual Case Safety database, VigiBase, were retrieved. The reports for children aged 0 – 17 years were identified and grouped into neonates, infants, children and adolescents according to ICH guidelines [14]. ADRs were described according to year, sex and age of the child, and notifier of reports. WHO-Adverse Reaction Terminology (WHO-ART) preferred and critical terms were also evaluated. WHO-ART critical terms are reported ADRs which may be indicative of serious disease states, and need quick and decisive action [15]. The suspect drugs were described according to WHO-Drug Dictionary (WHO-DD) preferred base name, and an individual ADR reported with more than one drug in a single case was considered only once.

3. Results

During the 14-year period, 343 reports containing 601 ADRs were received from a total of 1819 reports submitted to UMC by Ghana. This represented an average reporting rate of 2.5 reports per million children per year, and an average of 1.7 ADRs per report. There were no reports received in 1999 and 2001. In the year 2000, and between 2002 and 2007, the number ranged from 1 to 11; thereafter, the number rose steadily from 24 in 2008 to a peak of 130 reports in 2010 (Figure 1).

For the cases where sex was indicated, female reports numbered 164 (48%), and those for males were 167 (49%). Children aged between 2 and 11 years made up just over a third of the reports (Table 1), as did reports for infants aged 28 days to 23 months.

Nurses submitted 172 (50%) of the reports, pharmacists 79 (23%) and physicians 52 (15%). Information on reporter details on 40 (12%) of the cases was not provided.

Of the 601 ADRs reported (Table 2), 25% of these were considered serious. Injection site infection (n = 58), fever (n = 58) and rash (n = 34) were the most frequently reported ADRs. Stevens-Johnson syndrome was the sixth most frequently reported ADR, and was experienced by 27 children. Maculo-papular rash was linked to diclofenac. According to system organ class, infants and children were reported with almost equal proportions of ADRs (35 vs 36%).

Vaccines, antimalarials, antibiotics and anthelmintics were the most frequently reported classes of drugs (Table 3). Vaccines (measles and pentavalent) were the predominant drug class for children 0 – 23 months, followed by antimalarials which were mostly reported for children aged 2 – 11 years.

Three hundred and seventy-seven individual drugs were reported for the 343 children. Tetanus vaccine, measles vaccine, amodiaquine/artesunate and mebendazole were the individual drugs most frequently reported (Table 4). Six antimalarials, five antibiotics, four vaccines and four anthelmintics were within the 20 medicines most frequently reported. Diclofenac was the only drug in the top 20 that was not an anti-infective agent.

There were 23 (6.7%) fatalities recorded for the 343 reports. Anti-infective agents or vaccines were reported for all of the deaths (Table 5). Antimalarials were associated with 12 fatalities, antibiotics with 7 deaths, anthelmintics (4 deaths) and vaccines with 2 deaths. The antimalarial, quinine, was reported for nine fatal cases. The reason for the fatalities was unknown in most cases, and in two cases, quinine was reported as ineffective. Stevens-Johnson syndrome was mostly associated with the reported deaths. Causality assessments were recorded in 16 of the 23 fatalities. The majority (12) were considered possible (Table 5).

An additional 61 children experienced a total of 64 non-fatal critical ADRs (Table 6). Stevens-Johnson syndrome was the most frequent non-fatal critical ADR and was mainly reported with antibiotics and antimalarials.

4. Discussion

Underreporting has been globally acknowledged as a major challenge in pharmacovigilance practice [2], and the ADR reporting rate of 2.5 reports per million children per year recorded is thus not unexpected as observed in a similar study in Nigeria [16]. This may largely be due to the lack of reporting forms, and awareness of ADR reporting procedures from healthcare professionals [17]. However, with the establishment of the WHO Collaborating Centre and the UMC office in...
Ghana in 2009 [18], awareness in pharmacovigilance has improved. The National Centre for Pharmacovigilance has also been active in its advocacy activities leading to increased reporting over the years though the fall in reports between 2011 and 2012 is of concern. Also of importance is the increasing pharmacovigilance activity of the FDA including the appointment of regional pharmacovigilance officers, and close collaboration between the FDA and the Expanded Programme on Immunisation in monitoring safety of vaccines. The high number of nurses’ reports observed may be attributed to their involvement in active monitoring of swine flu (H1N1) pandemic vaccination in Ghana [19] and a unique role in observing patients’ early signs and symptoms of drug reactions [20]. In contrast, pharmacists in Canada [21] and the Netherlands [22] have been seen to report more ADRs for children, as patients consult with them directly at pharmacy outlets. The key to success in ADR reporting is adequate pharmacovigilance education for all healthcare professionals which has been adopted in Cuba, and improved reporting rates [5].

A large proportion of reports in this study concerned children aged 2 – 11 years. This observation was similar, for the same group of children, to a study carried out in Spain [9] but in contrast with the report from Denmark, where majority of cases reported were for infants aged 0 – 2 years [6]. The large number of reports for children aged between 2 and 11 years probably relates to the prevalence of malaria, and hence anti-malarials in this age group.

Anti-infectives, mainly vaccines, constituted the highest number of medical product reported. Their predominance in infancy linked to the immunisation schedule for this age. This observation was consistent with studies conducted in Sweden [23] and UK [24], and contrasted with reports in the US [10] where medicines used to treat paediatric attention deficit hyperactivity disorder were the most frequently reported drugs. The interest shown by the national Expanded Programme on Immunisation in safety monitoring, and its collaboration with the National Pharmacovigilance Centre, may have contributed to the relative large number of reports involving vaccines. The pentavalent vaccine was largely associated with fever and other injection site reactions in children aged between 0 and 2 months. These findings were consistent with previous studies conducted in Sweden and Cuba [5,23].

Malaria is a major contributor of child mortality in sub-Saharan Africa, and chloroquine which was primarily used for its treatment was replaced with artemisinin-amodiaquine as first line of therapy in Ghana in 2005 [25]. The fatality rate reported was much higher than that observed in studies in Europe [26-28]; this could possibly be due to: i) the high prevalence of malaria and hence the widespread use of antimalarials; ii) a predominance for reporting of serious ADRs; or iii) prevalence of sub-standard medicines. The majority of

### Table 1. Age distribution of reports and adverse drug reactions (ADRs).

| Age group               | Reports | n | % |
|-------------------------|---------|---|---|
| Neonates ≤ 27 days      | 5       | 1 | 1 |
| 28 days to 23 months    | 113     | 33| 33|
| 2-11 years              | 133     | 39| 39|
| 12-17 years             | 92      | 27| 27|
| Total                   | 343     | 100| 100|

Figure 1. Number of reports by year.
the fatalities may be due to the disease (severe malaria) itself and not necessarily the antimalarials. In most of the cases, deaths from unknown cause and medicine ineffectiveness were associated with quinine. Quinine is a medicine indicated for the management of severe malaria, a condition which is rapidly fatal in children; thus, there is serious confounding between mortality due to the disease and any drug-associated mortality which in cases like these are difficult to tease out. Other possibilities could be that the drugs used might have been either counterfeit or sub-standard or the diagnosis inaccurate, and the fatalities reported may have resulted from these or could have been due to mis-diagnosis. Root-cause analyses were not carried out; thus, it is impossible to tell the exact cause. The presence of falsified and sub-standard antimalarials, particularly, quinine in sub-Saharan Africa, has been recognised, and in Ghana, sub-standard artemisinin-combination therapy have been sold in the open market. The Ghana FDA has over the past 10 years taken active steps to improve detection of counterfeit medicines circulating in the country, and repeated surveys show that the strong regulatory guidelines applied by the FDA are yielding results. Nonetheless, the FDA has placed measures to curb distribution of such hazardous medicines and alert consumers whenever they are identified.

Three children who were administered the antibiotic, ceftriaxone, also died of an unknown cause. Unexplained sudden death with ceftriaxone has been reported by others in China and Cuba. Three of the four fatalities due to anthelmintics were recorded between 2008 and 2009. The first nationwide programme to deworm children in Ghana was initiated in 2007. However, the programme was derailed due to bad media publicity on rumours of death associated with the drugs used for the programme.

Data incompleteness were a major limitation in this study. A dedicated committee of experts in pharmacovigilance (Technical Advisory/Expert Committee) regularly meet to assess the reports. However, most of the fatal reports did not contain causality assessment and other important information about the drugs such as dosage. This made interpretation of the results difficult.

5. Conclusion

Vaccines, antimalarials and antibiotics are the leading medicines causing reported ADRs in Ghanaian children. There was a high mortality rate among the reports, compared to previous studies in European children. Of the 23 deaths reported, 6 were due to the Stevens–Johnson syndrome which occurred following intake of pyrimethamine/sulfadoxine, mebendazole, albendazole and ivermectin.
Table 5. Death reports and causality assessments.

| ADRs                                      | Suspect drugs                                      | Causality assessment |
|-------------------------------------------|----------------------------------------------------|----------------------|
| Stevens Johnson syndrome (5)              | Mebendazole (1)                                    | Certain              |
|                                           | Benzylpenicillin + pyrimethamine/sulfadoxine (1)    | Possible             |
|                                           | Pyrimethamine/sulfadoxine (1)                       | Probable             |
|                                           | Pyrimethamine/sulfadoxine (1)                       | Possible             |
|                                           | Flucloxacillin (1)                                  | Possible             |
| Stevens Johnson syndrome, acute renal failure and sepsis (1) | Albendazole and ivermectin (1)                     | Possible             |
| Unknown* (9)                              | Quinine (4)                                         | Possible             |
|                                           | Quinine (1)                                         | Unknown              |
|                                           | Quinine + ceftriaxone (2)                           | Possible             |
|                                           | Ceftriaxone (1)                                     | Possible             |
|                                           | Chloroquine (1)                                     | Unknown              |
| Medicine ineffective (2)                  | Quinine (2)                                         | Not provided         |
| Diarrhoea, hyperpyrexia (1)               | Ivermectin (1)                                      | Unlikely             |
| Convulsion (1)                            | Cefuroxime (1)                                      | Unlikely             |
| Erythema multiforme (1)                   | Metronidazole (1)                                   | Not provided         |
| Uncertain* (1)                            | Yellow fever vaccine + measles vaccine (1)          | Possible             |
| Uncertain† (2)                            | Measles vaccine (1)                                 | Not provided         |
|                                           | Tetanus vaccine (1)                                 | Not provided         |

*Death was recorded as the ADR in these cases.
*Recorded with Diarrhoea, fever and vomiting; †Recorded with injection site bleeding, and agitation, constipation, dyspnoea, increased sweating and vomiting respectively, but cause of death unknown.

Table 6. WHO-ART critical ADRs and suspect drugs.

| Critical ADRs            | Number | Suspect drugs                                         |
|--------------------------|--------|-------------------------------------------------------|
| Stevens Johnson syndrome (SJS) | 19     | Antibiotics (7), antimalarials (4), anthelmintics (3), vaccines (3), anti-convulsants (2) |
| Dystonia                 | 8      | Antimalarials (7), propulsives (1)                     |
| Hyperpyrexia             | 8      | Antimalarials (7), anthelmintics (1)                   |
| Face oedema              | 7      | Antimalarials (2), anthelmintics (2), antibiotics (2), immunoglobulins (1) |
| Mouth oedema             | 4      | Antimalarials (2), antibiotics (2)                     |
| Neonatal jaundice        | 3      | Vitamins (3)                                          |
| Dyskinesia               | 2      | Antimalarials (2)                                     |
| Paralysis flaccid        | 2      | Vaccines (2)                                          |
| Anaphylactic reaction    | 2      | Anthelmintics (2)                                     |
| Erythema multiforme      | 2      | Antimalarials (1), antibiotics (1)                     |
| Generalised oedema       | 1      | Antibiotics (1)                                       |
| SJS and generalised oedema| 1     | Vitamins and blood products (1)                       |
| SJS and face oedema      | 1      | Antimalarials (1)                                     |
| Dyskinesia and face oedema| 1     | Antimalarials (1)                                     |

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.

1. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004;329(7456):15-19

2. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006;29(5):385-96

3. Aagard L, Christensen A, Hansen EH. Information about adverse drug reactions reported in children: a qualitative review of empirical studies. Br J Clin Pharmacol 2010;70(4):481-91

4. Clavenna A, Bonati M. Adverse drug reactions in childhood: a review of prospective studies and safety alerts. Arch Dis Child 2009;94(9):724-8

5. Barzaga Arencibia Z, López Leyva A, Mejías Peña Y, et al. Pharmacovigilance in children in Camaguey Province. Cuba. Arch Dis Child 2010;95(6):474-7

- This study is useful for comparison with similar studies in developing countries.

6. Aagard L, Weber CB, Hansen EH. Adverse drug reactions in the paediatric population in Denmark: a retrospective analysis of reports made to the Danish Medicines Agency from 1998 to 2007. Drug Saf 2010;33(4):327-39

- This study is useful for comparison of paediatric ADRs across countries.

7. Venule J, Helling-Borda M. WHO’s International drug monitoring – the formative years, 1968-1975. preparatory, pilot and early operational phases. Drug Saf 2010;33(7):e1-e23

8. Star K, Norcin GN, Nordin K, et al. Suspected adverse drug reactions reported for children worldwide: an exploratory study using Vigibase. Drug Saf 2011;34(5):415-28

- This study is useful for comparison of paediatric ADRs across countries.

9. Aldea A, García Sánchez-Colomer M, Fernández Quintana E, et al. Paediatric adverse drug reactions reported to the Spanish pharmacovigilance system from 2004 to 2009. Eur J Clin Pharmacol 2012;68(9):1329-38

- This study is useful for comparison with similar studies in developing countries.

10. Johann-Liang R, Wyeth J, Chen M, et al. Pediatric drug surveillance and the food and drug administration’s adverse event reporting system: an overview of reports. 2003-2007. Pharmacoepidemiol Drug Saf 2009;18(1):24-7

11. Arencibia ZB, Sotomayor DN, Moliniedo NC, et al. Adverse drug reactions in children in Camaguey Province. Cuba. Arch Dis Child 2010;95(6):474-7

- This study is useful for comparison with similar studies in developing countries.

12. UMC - Africa. 2013. Available from: http://www.who-umc.org/dynpage.aspx?id=98093&mn1=7347&mn2=7252&mn3=7253&mn4=7333

13. Lindquist M. Vigibase, the WHO global ICSR database system: basic facts. Drug Information J 2008;42(5):409-19

14. EMEA. ICH Topic E 11. Clinical investigation of medicinal products in the paediatric population January 2001. CPMP/ICH/2711/99 2001. Available from: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf [Last accessed 17 October 2013]

15. The uppsala monitoring centre critical terms. 2014. Available from: http://www.umc-products.com/DynPage.aspx?id=73559&mn1=1107&mn2=1664&mn3=6044

16. Cliff-Eribo KO, Sammons H, Star K. Adverse drug reactions in Nigerian children: a retrospective review of reports submitted to the Nigerian Pharmacovigilance Centre from 2005 to 2012. Paediatr Int Child Health 2015. [Epub ahead of print]

- This study is useful for comparison of paediatric ADRs across countries.

17. Sabbagh G, Akwoengop D, Darko D, et al. Adverse drug reaction reporting by doctors in a developing country: a case study from ghana. Ghana Med J 2014;48(4):189-93

- This is an essential overview of ADR reporting by healthcare professionals in developing countries.

18. UMC - Africa. What we do? 2014. Available from: http://www.who-umcafrica.org/index.php/what-we-do

19. Nzussouo NT, Michalove J, Diop OM, et al. Delayed 2009 pandemic influenza A virus subtype H1N1 circulation in West Africa, May 2009-April 2010. J Infect Dis 2012;206(Suppl 1):S101-7

20. Backstrom M, Ekman E, Mjorndal T. Adverse drug reaction reporting by nurses in Sweden. Eur J Clin Pharmacol 2007;63(6):613-18

21. Carleton BC, Smith MA, Gelin MN, et al. Paediatric adverse drug reaction reporting: understanding and future directions. Can J Clin Pharmacol 2007;14(1):e45-57

22. Schirm E, Tobi H, van Puijenbroek EP, et al. Reported adverse drug reactions and their determinants in Dutch children outside the hospital. Pharmacoepidemiol Drug Saf 2004;13(3):159-65

23. Kimland E, Rane A, Ufer M, et al. Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. Pharmacoepidemiol Drug Saf 2005;14(7):493-9

24. Hawcutt DB, Mainie P, Riordan A, et al. Reported paediatric adverse drug reactions in the UK 2000-2009. Br J Clin Pharmacol 2012;73(3):437-46

- This study is useful for comparison of paediatric ADRs across countries.

25. Dodoo AN, Fogg C, Asimmwe A, et al. Pattern of drug utilization for treatment of uncomplicated malaria in urban Ghana following national treatment policy change to artemisinin-combination therapy. Malar J 2009;8:2

26. Marques J, Ribeiro-Vaz I, Pereira AC, et al. A survey of spontaneous reporting of adverse drug reactions in 10 years of activity in a pharmacovigilance centre in Portugal. Int J Pharm Pract 2014;22(4):275-82

27. Motola D, Melis M, Lo Bianco S, et al. Ten years of pharmacovigilance in Italy: the experience of Emilia-Romagna region in the monitoring of drug’s safety profile.
McLernon DJ, Bond CM, Hannaford PC, et al. Adverse drug reaction reporting in the UK: A retrospective observational comparison of yellow card reports submitted by patients and healthcare professionals. Drug Saf 2010;33(9):775-88

Nayyar GM, Breman JG, Newton PN, et al. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. Lancet Infect Dis 2012;12(6):488-96

El-Duah M, Ofori-Kwakye K. Substandard artemisinin-based antimalarial medicines in licensed retail pharmaceutical outlets in Ghana. J Vector Borne Dis 2012;49(3):131-9

FDA Cautious Public On Fake Antimalarial.

Yao Y, Zhou R, Wang Y. Fatal adverse effects of injected ceftriaxone sodium in China. Pharmacoepidemiol Drug Saf 2012;21(11):1197-201

Dodoo A, Adjei S, Couper M, et al. When rumours derail a mass deworming exercise. Lancet 2007;370(9586):465-6

Hall A, Hewitt G, Tuffrey V, et al. A review and meta-analysis of the impact of intestinal worms on child growth and nutrition. Matern Child Nutr 2008;4(s1):118-236

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