Systematic review of paediatric studies of adverse drug reactions from pharmacovigilance databases

Kennedy Obebi Cliff-Eribo, Helen Sammons and Imti Choonara

The University of Nottingham, Academic Division of Child Health, Derbyshire Children’s Hospital, Derby, UK

ABSTRACT

Objective: To perform a systematic review of studies describing paediatric adverse drug reactions (ADRs) conducted from national pharmacovigilance databases.

Methods: A systematic literature search of studies describing results for paediatric ADRs from national pharmacovigilance databases was performed. PubMed database, Embase and MEDLINE were searched up to March 2015. The descriptive studies included were analysed for country of origin, reporters, and ADR reporting rate, drugs, ADRs and number of fatalities.

Results: 20 studies were identified. Doctors were the largest group of reporters in all the studies, and with more consumer reports seen in USA. The studies ranged from 3 – 37 years. The highest ADR reporting rate was 1458 reports per year per million children in Cuba. Antibiotics and vaccines were the most frequently reported drugs, in almost all the studies. The most frequent ADRs were skin and nervous system disorders. The highest proportion of fatalities and serious reports was from North America. Drugs used for treating attention deficit hyperactivity disorders (ADHD) and isotretinoin were the most frequently reported drugs for ADRs in North America.

Conclusions: There were geographical differences in drugs responsible for ADRs and their seriousness, especially in North America. Very few studies were conducted in Asia and Latin America, none were found from Africa.

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Adverse drug reactions; paediatric; spontaneous reporting system; pharmacovigilance database

1. Introduction

Adverse drug reactions (ADRs) are a major problem for children in all countries [1]. One in 10 children in hospital in a high-income country (HIC) will experience an ADR [2]. A study in Cuba suggested that at least 1 in 500 children will experience an ADR each year [3]. National pharmacovigilance databases have been useful in detecting signals. They have also been helpful in describing the type of ADRs experienced by children in a country and the drugs responsible [4]. The majority of the published studies describing ADR data for children have originated from HICs in Europe. The most frequently described ADRs in children in Europe are rashes, headache, pyrexia, and gastrointestinal disorders. The medicines responsible were antibiotics and vaccines.

Antibiotics and vaccines are the most widely used medicines in children worldwide. However, there are significant differences in the use of antibiotics in different countries. Additionally, there are major differences in the use of medicines in children, even in Europe [5,6]. Therefore, one may see differences in the types of ADRs experienced. Additionally, the prevalence of diseases will be different in low-income and lower-middle-income countries. One would therefore expect the ADRs to be different. Antimalarials, for example, are infrequently used in children in Europe. Many ADRs are preventable due to inappropriate prescribing. It is only by identifying the drugs responsible for ADRs that one can determine areas where prescribing may be inappropriate. We therefore decided to look at all publications reporting ADRs in children from national pharmacovigilance databases to explore the differences between ADRs and drugs responsible in different countries.

2. Methods

A systematic literature search of published studies describing ADRs from national spontaneous reporting pharmacovigilance databases was performed. In order to capture the relevant articles, the following terms and/or keywords assigned to articles which studied ADRs from databases were used: adverse drug reaction*, adverse effect*, adverse event*, side effect*, pharmacovigilance, spontaneous reporting, ADR reporting system, ADR reporting, drug surveillance program, and adverse event reporting. The databases used were PubMed, Embase, and MEDLINE. The PubMed database was searched from when the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring in Uppsala was established in 1978 to March 2015. The WHO center receives individual case safety reports of suspected ADRs from national pharmacovigilance centers around the world [7]. Embase and MEDLINE were searched from 1980 to March 2015 and 1947 to March 2015, respectively. In addition to these searches, the reference lists of publications were also searched. The search strategy is as shown in Table 1.

Articles which described ADRs from national, international, and regional pharmacovigilance databases were considered.
Eight of the studies excluded vaccines (including all four from North America) (Table 2). The majority of the studies grouped ADRs in system organ class (SOC) and suspect drugs in anatomical therapeutic class (ATC) or drug class, and presented them in percentages of first, second, and third most frequently reported. The type of notifiers and death reports were also presented in percentages.

The period of time data was collected for the studies ranged from 3 to 37 years. The 37-year data described fatal suspected ADRs in UK between 1964 and 2000. For the studies which described seriousness of the events, the percentages of ADRs or reports ranged between 2% and 68% of the total number of ADRs or reports. The highest proportion of serious reports was from North America (42–62%). Four studies described reporting rates. The reporting rates for the other studies were calculated using an estimate of the childhood population for the year of study. The highest ADR reporting rates of 634 and 1458 reports per year per million children were described in regional studies conducted in Cuba in 2010 and 2012, respectively.

Nine studies described notifiers of ADRs (Table 3). Doctors were the largest group of reporters in eight of the studies. Pharmacists and other healthcare professionals (HCPs) (including nurses) also submitted reports in most countries. The largest proportion of reports from consumers was from the USA.

### 3.2. Reported ADRs

The majority of the studies reported skin disorders (rash and urticaria) as the most frequent ADRs (Table 4). Other common ADRs were nervous system disorders (headache, dizziness, and drowsiness) and pyrexia/fever. The less commonly reported ADRs were convulsions, diarrhea, and agitation. One study [19] described only fatal reports, and the most frequent fatal ADR in this study was hepatic failure. The majority of the studies which ranked the frequency of ADRs described them in SOC. Only a few studies described ADRs in lowest level terms.

### 3.3. Reported drugs

The most frequently reported drugs are shown in Table 5. Antibiotics and vaccines were the most frequently reported drugs in almost all the studies identified in Europe, Latin America, and Asia. Amoxicillin was the most frequently reported individual antibiotic (where this was stated) apart from in one Italian study where it was second after amoxicillin/clavulanic acid and in one Chinese study where cefuroxime was the most frequent.

In contrast, in North America, drugs used for treating attention deficit hyperactivity disorders (ADHD) (methylphenidate was named in one study) and isotretinoin were most frequently reported. There was no uniformity in the way frequency of drugs reported were described in the studies. In most studies, ATC was used and in others, specific drugs were described.

### 3. Results

The literature search produced a total of 6720 articles from PubMed, Embase, and MEDLINE. When the inclusion and exclusion criteria were applied, 41 articles were identified, made up of 20 for pediatric studies and 21 for general population studies (Figure 1). Only the 20 pediatric studies were analyzed.

#### 3.1. Summary of findings

The 20 studies reviewed included 3 international, 12 national, and 5 regional studies. The majority of the studies were conducted in Europe. Four were from North America, two from Latin America, one from Asia, and none from Africa.
3.4. Deaths reported

The studies conducted in North America reported the highest fatality rates, which ranged from 3.4% to 13.0% (Table 6). These rates contrasted sharply with the rates reported in Europe, which ranged between 0.1% and 2.2% with a mean rate of 0.8%. In the UK study [19] which described 37-year data, 0.8% fatality was recorded.

4. Discussion

Systemic anti-infectives and vaccines were the group of drugs most frequently associated with ADRs in studies in Europe, Asia, and Latin America. This reflects the widespread use of anti-infectives and vaccines in children [27,28]. Many anti-infectives, however, are prescribed inappropriately [5,6]. Reducing inappropriate prescribing would reduce the number of ADRs. In contrast, in North America [21–23], drugs used for treating ADHD and isotretinoin were most often associated with the ADRs. These findings suggest that the epidemiology of the use of medicines in children in North America may be different to other countries. The diagnosis of ADHD in children visiting outpatient clinics in the USA has been on the rise since 2000 [29]. Interestingly, antiepileptic drugs were the third most frequently reported group of drugs in most countries, including North America.

The most frequently reported ADRs were skin disorders and pyrexia. The proportions of deaths in the reports were higher in North America compared with those in Europe, Asia, and Latin America. This may reflect differences in the use of medicines and also differences in attitudes toward reporting. This is an area open to further research.

The countries which have established programs of ADR reporting in their health-care system are likely to have more reports in national ADR databases. The size of the country, population, and duration of time of data collected for the study may also influence the number of reports in the database. The combination of these factors may have contributed to the higher number of reports or rates of reporting per population observed in the national studies conducted in UK [14,19], Denmark [15], Sweden [16], and USA [21,24]. The high reporting rates recorded from the
Table 2. Type of study and annual reporting frequency.

| Author/continent                  | Country       | Children population (years) | Study duration (years) | Number of reports | Percentage of serious reports/ADRs | Population estimate * | ADR Reporting rate | Source of data/description of reports                                      |
|-----------------------------------|---------------|-----------------------------|------------------------|------------------|-----------------------------------|-----------------------|------------------|--------------------------------------------------------------------------|
| **International**                 |               |                             |                        |                  |                                   |                       |                  |                                                                          |
| Aagaard et al. 2014 [9]           | International | ≤17                         | 5                     | 240              | 68                                | 2.2 billion           | 0.02             | VigiBase (Consumer reports)                                              |
| Star et al. 2011 [7]              | International | ≤17                         | 10                    | 268,145          | –                                 | 2.2 billion           | 12               | VigiBase (Vaccines excluded)                                              |
| **Europe**                        |               |                             |                        |                  |                                   |                       |                  |                                                                          |
| Blake et al. 2014 [10]            | International | <18                         | 18.5                  | 279,359          | –                                 | 742.8 million         | 20               | EudraVigilance (European study)                                          |
| Ferrajolo et al. 2014 [11]        | Italy         | <18                         | 12                    | 8338             | 39                                | 10.3 million          | 67               | National study (Vaccines excluded)                                       |
| Carnovale et al. 2014 [12]        | Italy         | ≤17                         | 4                     | 3539             | 17                                | 10.3 million          | 86               | Regional study                                                            |
| Aldea et al. 2012 [13]            | Spain         | ≤17                         | 6                     | 4279             | 37                                | 8.4 million           | 85               | National study                                                            |
| Hawcutt et al. 2012 [14]          | UK            | <17                         | 10                    | 31,726           | –                                 | 13.3 million          | 238              | National study                                                            |
| Aagaard et al. 2010 [15]          | Denmark       | ≤17                         | 10                    | 2437             | 42                                | 1.1 million**         | 222**            | National study                                                            |
| Kimland et al. 2005 [16]          | Sweden        | ≤15                         | 15                    | 5771             | 13                                | 1.7 million**         | 226**            | National study                                                            |
| Schirm et al. 2004 [17]           | Netherlands   | ≤16                         | 7                     | 773              | 7                                 | 3.6 million           | 31               | National study (Vaccines excluded)                                        |
| Clarkson et al. 2004 [18]         | UK            | ≤16                         | 3                     | 456              | 33                                | 13.2 million          | 11               | Regional study                                                            |
| Clarkson et al. 2002 [19]         | UK            | ≤14                         | 37                    | 43,755           | –                                 | 11.0 million          | 107              | National study (Vaccines excluded) (Fatal ADR reports only)               |
| Morales-Olivas et al. 2000 [20]   | Spain         | ≤14                         | 10                    | 1419             | 27                                | 5.9 million           | 24               | National study                                                            |
| Lee et al. 2014 [21]              | USA           | <18                         | 5.7                   | 78,623           | 42                                | 75.2 million          | 183              | National study (Vaccines excluded)                                        |
| Johann-Liang et al. 2009 [22]     | USA           | <18                         | 5                     | 36,241           | 62                                | 75.1 million          | 97               | National study (Vaccines excluded)                                        |
| Carleton et al. 2007 [23]         | Canada        | ≤19                         | 4.5                   | 1193             | 61                                | 7.0 million           | 38               | National study (Vaccines excluded)                                        |
| Moore et al. 2002 [24]            | USA           | <2                          | 3                     | 5976             | 61                                | 7.8 million           | 255              | National study (Vaccines excluded)                                        |
| Latin America                     |               |                             |                        |                  |                                   |                       |                  |                                                                          |
| Arencibia et al. 2012 [3]         | Cuba          | ≤18                         | 2                     | 533              | 31                                | 183,105**            | 1458**           | Regional study                                                            |
| Arencibia et al. 2010 [25]        | Cuba          | ≤18                         | 1                     | 124              | 15                                | 195,504**            | 634**            | Regional study                                                            |
| Asia                              |               |                             |                        |                  |                                   |                       |                  |                                                                          |
| Li et al. 2014 [26]               | China         | ≤17                         | 1                     | 3848             | 2                                 | 301.2 million         | 13               | Regional study                                                            |

*Population estimates were taken from United Nations Population Division, World Population Prospects: The 2012 Revision [8] to calculate the reporting rates.

**Population and rate as reported in study.

ADR: adverse drug reaction.

Table 3. Notifiers of reports.

| Author/continent                  | Country       | Physicians/doctors (%) | Pharmacists (%) | Nurses and other HCPs (%) | Consumers (%) | Comments                     |
|-----------------------------------|---------------|------------------------|-----------------|---------------------------|---------------|------------------------------|
| Star et al. 2011 [7]              | International | 55                     | 3               | 3                         | 4             | VigiBase reports             |
| Europe                            |               |                        |                 |                           |               |                              |
| Ferrajolo et al. 2014 [11]        | Italy         | 83                     | 10              | 6                         | 1             | National                    |
| Aldea et al. 2012 [13]            | Spain         | 63                     | 11              | 24                        | –             | National                    |
| Hawcutt et al. 2012 [14]          | UK            | 35                     | 5               | 59                        | 1             | National                    |
| Aagaard et al. 2010 [15]          | Denmark       | 89                     | 1               | 7                         | 4             | National                    |
| Latin America                     |               |                        |                 |                           |               |                              |
| Arencibia et al. 2012 [3]         | Cuba          | 73                     | 15              | 10                        | 1             | Regional                    |
| Arencibia et al. 2010 [25]        | Cuba          | 60                     | 16              | 24                        | –             | Regional                    |
| Asia                              |               |                        |                 |                           |               |                              |
| Li et al. 2014 [26]               | China         | 52                     | 24              | 16                        | 3             | Regional                    |
| North America                     |               |                        |                 |                           |               |                              |
| Lee et al. 2014 [21]              | USA           | 31                     | 6               | 22                        | 31            | National                    |
Table 4. Most frequently reported ADRs.

| Author/continent | Country           | 1st most frequent ADR            | 2nd most frequent ADR              | 3rd most frequent ADR             | Comments                  |
|------------------|-------------------|---------------------------------|-----------------------------------|-----------------------------------|---------------------------|
| International    |                   |                                 |                                   |                                   |                           |
| Aagaard et al. 2014 [9] | International | General disorders (20%) | Nervous system disorders (14%) | Injury, poison & procedural complications (7%) | VigiBase data |
| Star et al. 2011 [7] | International | Skin disorders (35%) | General disorders (20%) | Nervous system disorders (19%) | VigiBase data |
| Blake et al. 2014 [10] | International | Pyrexia (13%) | Vomiting (6%) | Convulsion (4%) | EudraVigilance data |
| Ferrajolo et al. 2014 [11] | Italy | Skin disorders (52%) | Gastrointestinal disorders (17%) | Nervous system disorders (12%) |                           |
| Carnovale et al. 2014 [12] | Italy | Skin disorders (26%) | General disorders (24%) | Gastrointestinal disorders (11%) |                           |
| Aldea et al. 2012 [13] | Spain | Pyrexia (7%) | Application site reaction (4%) | Gastrointestinal disorders (11%) |                           |
| Hawcutt et al. 2012 [14] | UK | Headache (10%) | Dizziness (9%) | Pyrexia (7%) |                           |
| Aagaard et al. 2010 [15] | Denmark | General disorders (31%) | Skin disorders (18%) | Nervous system disorders (15%) |                           |
| Kimland et al. 2005 [16] | Sweden | Application site reaction (24%) | Fever (12%) | Rash (exanthema) (7%) |                           |
| Schirmit et al. 2004 [17] | Netherlands | Tooth discoloration (6%) | Rash (5%) | Agitation (3%) |                           |
| Clarkson et al. 2004 [18] | UK | Not reported | Not reported | Not reported |                           |
| Morales-Olivas et al. 2000 [20] | Spain | Not reported | Not reported | Urticaria (6%) |                           |
| North America |                   |                                 |                                   |                                   |                           |
| Lee et al. 2014 [21] | USA | Not reported | Not reported | Not reported |                           |
| Johann-Liang et al. 2009 [22] | USA | Not reported | Not reported | Not reported |                           |
| Carleton et al. 2007 [23] | Canada | Not reported | Not reported | Not reported |                           |
| Moore et al. 2002 [24] | USA | Not reported | Not reported | Not reported |                           |
| Latin America |                   |                                 |                                   |                                   |                           |
| Arencibia et al. 2012 [23] | Cuba | Urticaria/angiodysema (29%) | Drowsiness (11%) | Vomiting (9%) |                           |
| Arencibia et al. 2010 [25] | Cuba | Drowsiness (14%) | Headache (11%) | Respiratory distress/failure (10%) |                           |
| Asia |                   |                                 |                                   |                                   |                           |
| Li et al. 2014 [26] | China | Rash (exanthema) (29%) | Fever (21%) | Application site reaction (9%) |                           |

ADR: adverse drug reaction.

5. Conclusions

The majority of the studies reviewed were from Europe and North America, no study was identified from Africa. ADR reporting rates are higher in Europe, North America, and Latin America compared to Asia. Physicians and doctors reported more ADRs compared to pharmacists and nurses.

Vaccines and anti-infectives were most frequently associated with ADRs in children, with the exception of North America. The reported fatality rate was higher in North America.

6. Expert opinion

ADRs are underreported worldwide. The highest reporting rate was 1458 reports per year per million children in Cuba. Reporting rates in Europe (the continent with most studies) were considerably lower. Education about ADRs and their reporting is needed in Europe. Antibiotics and vaccines were the most frequently reported groups of drugs in most studies. They are also the most frequently prescribed groups of drugs to young children. Antibiotics are often prescribed inappropriately and efforts to improve rational prescribing are needed. In contrast, in North America, drugs for ADHD were the most frequently reported drugs. This may be related to the widespread use of these drugs in North America. More reports of...
| Table 5. Most frequently reported drugs. |
|----------------------------------------|
| Author/continent | Country | 1st most frequent drug | 2nd most frequent drug | 3rd most frequent drug | 4th most frequent drug | 5th most frequent drug | Comments |
|------------------|---------|------------------------|------------------------|------------------------|------------------------|------------------------|----------|
| Aagaard et al. 2014 [9] | International | Anti-infectives and vaccines (36%) | Antineoplastic agents (23%) | Sex hormones (13%) | Nervous system (12%) | Respiratory system (2%) | VigiBase |
| Star et al. 2011 [7] | International | Amoxicillin (33%) | Atomoxetine (28%) | Dermatologicals (12%) | Respiratory system (11%) | Alimentary tract and metabolism (10%) | VigiBase |
| Blake et al. 2014 [10] | International | Vaccines | Isotretinoin | Methylphenidate | Etanercept | Paracetamol | Eudra-Vigilance |
| Ferrajolo et al. 2014 [11] | Italy | Amoxicillin/clavulanic acid | Methylphenidate | Ibuprofen | Paracetamol | Clarithromycin | Reports exclude vaccines |
| Carnovale et al. 2014 [12] | Italy | Vaccines | Antibacterials | Antineoplastic agents (9.5%) | Anti-inflammatory (5.0%) | Not reported |
| Aldea et al. 2012 [13] | Spain | Vaccines | Methylphenidate | Respiratory system | Antiepileptics | Antiepileptics | Not reported |
| Hawcutt et al. 2012 [14] | UK | Vaccines | ADHD medication | Antiepileptics | Allergens | Antipsychotics | |
| Aagaard et al. 2010 [15] | Denmark | Vaccines | Antidepressants | Antiepileptics | Antidepressants | |
| Kimland et al. 2005 [16] | Sweden | Vaccines | Vaccines | Clarithromycin | Fluticasone | |
| Schirm et al. 2004 [17] | Netherlands | Anticonvulsants | Analgesics | Antibiotics | Antibiotics | |
| Clarkson et al. 2004 [18] | UK | Vaccines | Topical local anesthetics | Cytokines | Anticonvulsants | Anticonvulsants | |
| Clarkson et al. 2002 [19] | UK | Anticonvulsants | Cytokines | Antibiotics | Anesthetics-intravenous | Anesthetics-intravenous | |
| Morales-Olivas et al. 2000 [20] | Spain | Vaccines | Amoxicillin | Erythromycin | Acetylsalicylic acid | Acetylsalicylic acid | |
| Lee et al. 2014 [21] | USA | Methylphenidate | Montelukast | Ibuprofen | Lisdexamfetamine | Somatropin | Children 1 to <12 years |
| Lee et al. 2014 [21] | USA | Isotretinoin | Infliximab | Drospironone | Methylphenidate | Adalimumab | Children 12 to <18 years |
| Johann-Liang et al. 2009 [22] | USA | ADHD drugs | Anticonvulsants | Antidepressants | Antipsychotics | Chemotherapeutics | |
| Carleton et al. 2007 [23] | Canada | Isotretinoin | Paroxetine | Methylphenidate | Amoxicillin | Valproic acid | |
| Moore et al. 2002 [24] | USA | Palivizumab | Cisapride | Indomethacin | Nitric oxide | Azithromycin | Only drugs associated with serious or fatal outcome; children <2 years |
| Latin America | Arecia et al. 2012 [3] | Cuba | Vaccines | Antibiotics | Analgesics (nonopioid) | Bronchodilators | |
| Arecia et al. 2010 [25] | Cuba | Antibiotics | Vaccines | Analgesics | ACE inhibitors | Bronchodilators | |
| Asia | Li et al. 2014 [26] | China | Vaccines | Cefuroxime | Azithromycin | Cefotiam | Not reported |

ADHD: attention deficit hyperactivity disorders.
pharmacovigilance are needed from low- and middle-income countries in Africa, Asia, and Latin America.

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∗∗ This study included ADR reports from countries in Europe.

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- This is the first study of pediatric ADRs from a national pharmacovigilance database in Africa.
- This is the second study of pediatric ADRs from a national pharmacovigilance database in Africa.