

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

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

## **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.

**Keywords:** adverse drug reactions, paediatric, spontaneous reporting system, pharmacovigilance database

## **INTRODUCTION**

Adverse drug reactions (ADRs) are a major problem for children in all countries [1]. One in ten children in hospital in a high income country (HIC) will experience an ADR [2]. A study in Cuba suggested that at least one 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 (LIC) and lower middle income countries (LMIC). 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.

## **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, adverse drug reaction reporting system, adverse drug reaction reporting, drug surveillance program and adverse event reporting. The databases used were PubMed, Embase and MEDLINE. The PubMed database was searched from when the WHO Collaborating Centre for International Drug Monitoring in Uppsala was established in 1978 to March 2015. The WHO centre receives individual case safety reports of suspected ADRs from national pharmacovigilance centres 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 below in Table 1.

Articles which described ADRs from national, international or regional pharmacovigilance databases were considered. Studies describing specific ADRs and drugs, vaccines, specific treatments and procedures for disease conditions in pharmacovigilance databases were excluded. All ADR studies outside of national, international or regional pharmacovigilance databases were also excluded.

All the included articles were considered by country of study, population, duration of study, number of patients/reports, notifiers, types of drugs and ADRs, death reports,

and whether the data used for the studies were from a regional, national or international ADR database. The articles identified were separated into those reporting on the general population and paediatric population. Only the paediatric studies were analysed.

The ADR reporting rate for studies where this was not reported was calculated as follows:

$$[\textit{Reporting rate} = \textit{annual average number of reports/population} \times 1 \textit{ million}]$$

The population estimates were taken from United Nations Population Division, World Population Prospects: The 2012 Revision [8].

## **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 paediatric studies and 21 for general population studies (Figure 1). Only the 20 paediatric studies were analysed.

### **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.

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 – 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 – 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 HCPs (including nurses) also submitted reports in most countries. The largest proportion of reports from consumers was from the USA.

### **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, diarrhoea 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 system organ class. Only a few studies described ADRs in lowest level terms.

### **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 (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, anatomic therapeutic class were used and in others, specific drugs were described.

### **Deaths reported**

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

## **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 attention deficit hyperactivity disorders (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 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 towards reporting. This is an area open to further research.

The countries which have established programmes of ADR reporting in their healthcare 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 studies in a regional ADR database in Cuba [3, 25] was attributed to a special educational programme on pharmacovigilance for healthcare professionals. The high number of reports received per year in these countries is an indication of success of the reporting scheme.

Even though most of the studies in Europe and North America showed evidence of efficient reporting scheme, not all the HPCs were actively engaged in reporting ADRs. The results showed physicians and doctors submitted more reports than pharmacists and nurses. Other HPCs, especially nurses, could be encouraged by giving them focussed education to detect and report ADRs [30], due to their unique role in observing patients' signs and symptoms. This approach has been successful in Sweden [31] and Latin America [25].



This study has several limitations. Very few studies were conducted in Asia and Latin America, therefore, comparison of reported ADRs and drugs between the continents was not possible. No study was identified from Africa. Since the search was performed, however, we have published two studies describing ADR reports for children in Nigeria and Ghana [32, 33]. There was no uniformity in the reports in terms of ADRs and drugs description. Authors described ADRs and drugs differently in the studies. Some of the studies described ADRs in system organ class and others in lowest level reaction terms. The drugs were also described differently in anatomical therapeutic class and specific drugs/active substances. All these made comparison of the studies difficult.

## **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.

## **Expert Opinion**

ADRs are under-reported world-wide. 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 pharmacovigilance are needed from low and middle income countries in Africa, Asia and Latin America.

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## FIGURES

### Articles from PubMed, Embase and MEDLINE

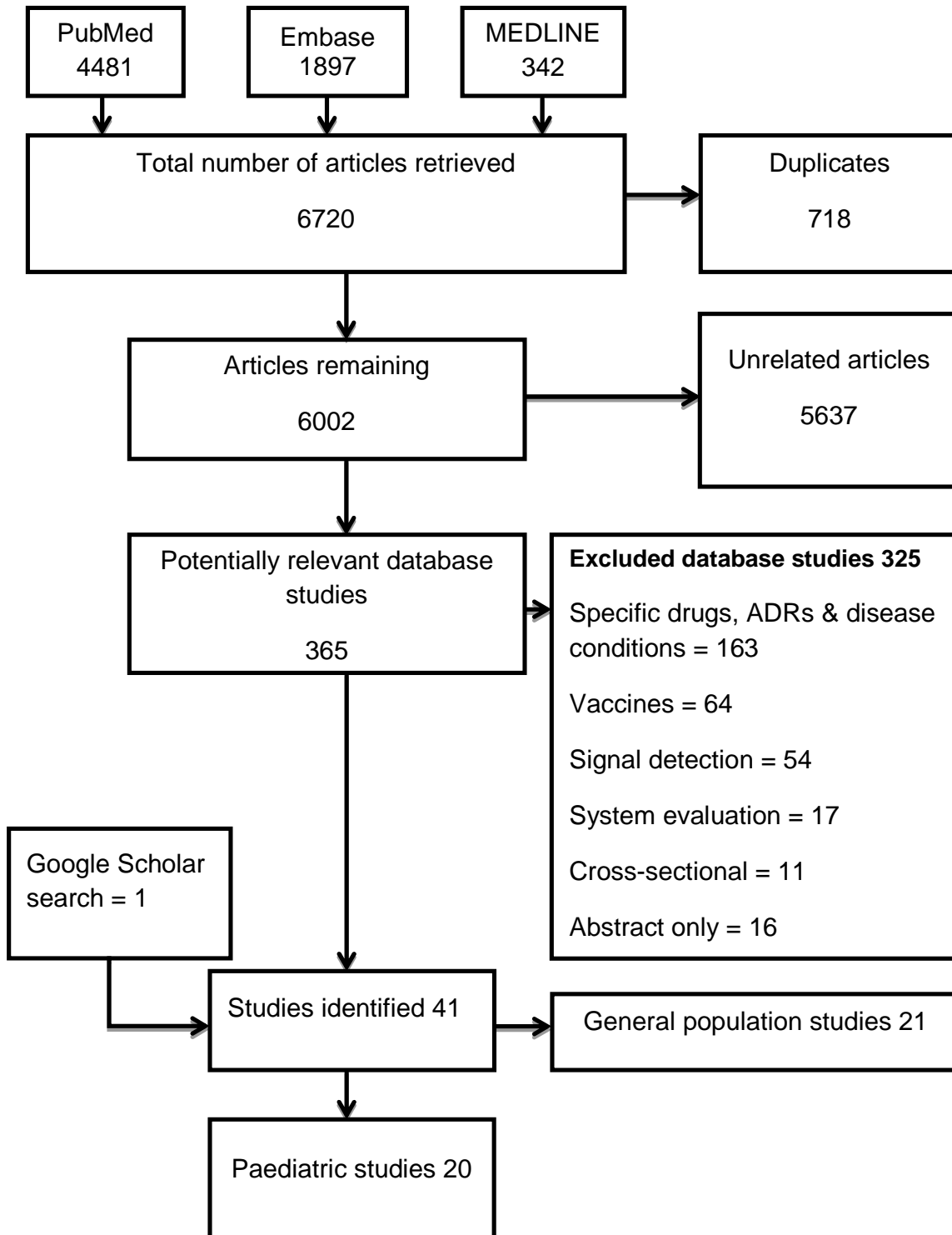


Figure 1: Flow chart of literature search and studies included

## TABLES

**Table 1: Search strategy for articles**

<b>Database</b>	<b>Step</b>	<b>Search Terms</b>
<b>PubMed</b>	1	Adverse drug reaction*
	2	Adverse effect*
	3	Side effect*
	4	1 OR 2 OR 3
	5	Pharmacovigilance
	6	Spontaneous reporting
	7	Adverse drug reaction reporting system
	8	5 OR 6 OR 7
	9	4 AND 8
<hr/>		
<b>Embase/MEDLINE</b>	1	Adverse drug reaction*
	2	Adverse effect*
	3	Adverse event*
	4	Side effect*
	5	1 OR 2 OR 3 OR 4
	6	Pharmacovigilance
	7	Drug surveillance program
	8	Adverse drug reaction reporting
	9	Adverse event reporting
	10	6 OR 7 OR 8 OR 9
	11	5 AND 10



**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
<b>International</b>								
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	268145	-	2.2 billion	12	VigiBase (Vaccines excluded)
<b>Europe</b>								
Blake et al. 2014 [10]	International	< 18	18.5	279359	-	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	31726	-	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	43755	-	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
<b>North America</b>								
Lee et al. 2014 [21]	USA	< 18	5.7	78623	42	75.2 million	183	National study (Vaccines excluded)
Johann-Liang et al. 2009 [22]	USA	< 18	5	36241	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) children < 2 years
<b>Latin America</b>								
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
<b>Asia</b>								
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

**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
<b>Europe</b>						
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
<b>Latin America</b>						
Arencibia et al. 2012 [3]	Cuba	73	15	10	1	Regional
Arencibia et al. 2010 [25]	Cuba	60	16	24	-	Regional
<b>Asia</b>						
Li et al. 2014 [26]	China	52	24	16	3	Regional
<b>North America</b>						
Lee et al. 2014 [21]	USA	31	6	22	31	National

**Table 4: Most frequently reported ADRs**

Author/continent	Country	1 <sup>st</sup> most frequent ADR	2 <sup>nd</sup> most frequent ADR	3 <sup>rd</sup> most frequent ADR	Comments
<b>International</b>					
Aagaard et al. 2014 [9]	International	General disorders (20%)	Nervous system disorders (14%)	Injury, poison & proc compl (7%)	VigiBase data
Star et al. 2011 [7]	International	Skin disorders (35%)	General disorders (20%)	Nervous system disorders (19%)	VigiBase data
<b>Europe</b>					
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%)	Urticaria (3%)	
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%)	
Schirm et al. 2004 [17]	Netherlands	Tooth discolouration (6%)	Rash (5%)	Agitation (3%)	
Clarkson et al. 2004 [18]	UK	Not reported	Not reported	Not reported	
Morales-Olivas et al. 2000 [20]	Spain	Rash (18%)	Urticaria (6%)	Diarrhoea (5.7%)	
<b>North America</b>					
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	
<b>Latin America</b>					
Arencibia et al. 2012 [3]	Cuba	Urticaria/angioedema (29%)	Drowsiness (11%)	Vomiting (9%)	
Arencibia et al. 2010 [25]	Cuba	Drowsiness (14%)	Headache (11%)	Respiratory distress/failure (10%)	
<b>Asia</b>					
Li et al. 2014 [26]	China	Rash (Exanthema) (29%)	Fever (21%)	Application site reaction (9%)	

**Table 5: Most frequently reported drugs**

Author/ continent	Country	1 <sup>st</sup> most frequent drug	2 <sup>nd</sup> most frequent drug	3 <sup>rd</sup> most frequent drug	4 <sup>th</sup> most frequent drug	5 <sup>th</sup> most frequent drug	Comments
<b>International</b>							
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 & metabolism (10%)	VigiBase
<b>Europe</b>							
Blake et al. 2014 [10]	International	Vaccines	Isotretinoin	Methylphenidate	Etanercept	Paracetamol	Eudra-Vigilance
Ferrajolo et al. 2014 [11]	Italy	Amoxicillin/ clavulanic acid	Amoxicillin	Ibuprofen	Paracetamol	Clarithromycin	Reports exclude vaccines
Carnovale et al. 2014 [12]	Italy	Vaccines (37.5%)	Antibacterials (21.6%)	Antineoplastic agents (9.5%)	Psycholeptics (6.7%)	Anti-inflammatory (5.0%)	
Aldea et al. 2012 [13]	Spain	Vaccines	Methylphenidate	Respiratory system		Not reported	
Hawcutt et al. 2012 [14]	UK	Vaccines (74.4%)	ADHD medication (3.7%)	Anti-epileptics (3.1%)	Anti-infectives (2.5%)	Immunosuppressants (2.3%)	
Aagaard et al. 2010 [15]	Denmark	Vaccines (61.1%)	Antidepressants (6.9%)	Antiepileptics (4.0%)	Allergens (3.0%)	Antipsychotics (2.6%)	
Kimland et al. 2005 [16]	Sweden	Vaccines (63.8%)	Antibacterials (10.1%)	Antiasthmatics (4.9%)	Antiepileptics (3.1%)	Not reported	
Schirm et al. 2004 [17]	Netherlands	Amoxicillin (5%)	Salbutamol (3.2%)	Clarithromycin (2.8%)	Methylphenidate (2.7%)	Fluticasone (2.7%)	
Clarkson et al. 2004 [18]	UK	Vaccines (34.7%)	Topical local anaesthetics (17.2%)	Anticonvulsants (11.0%)	Antibiotics (9.1%)	Cytotoxics&immunosuppressants (5.5%)	
Clarkson et al. 2002 [19]	UK	Anticonvulsants (20.0%)	Cytotoxics (10.8%)	Antibiotics (7.9%)	Anaesthetics-intravenous (5.1%)	Anaesthetics-inhaled (4.4%)	Fatal reports only
Morales-Olivas et al. 2000 [20]	Spain	Vaccines (12.9%)	Amoxicillin (8.5%)	Erythromycin (3.7%)	Cotrimoxazole (3.0%)	Acetylsalicylic acid (2.7%)	

**Table 5: Most frequently reported drugs continued**

Author/continent	Country	1 <sup>st</sup> most frequent drug	2 <sup>nd</sup> most frequent drug	3 <sup>rd</sup> most frequent drug	4 <sup>th</sup> most frequent drug	5 <sup>th</sup> most frequent drug	Comments
<b>North America</b>							
Lee et al. 2014 [21]	USA	Methylphenidate (3.5%)	Montelukast (1.9%)	Ibuprofen (1.5%)	Lisdexamfetamine (1.3%)	Somatropin (1.2%)	Children 1 to <12 years
Lee et al. 2014 [21]	USA	Isotretinoin (3.2%)	Infliximab (2.8%)	Drospironone&ethinylestradiol (1.7%)	Methylphenidate (1.6%)	Adalimumab (1.3%)	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 (3.8%)	Paroxetine (2.9%)	Methylphenidate (2.8%)	Amoxicillin (2.7%)	Valproic acid (2.2%)	
Moore et al. 2002 [24]	USA	Palivizumab (27.9%)	Cisapride (4.0%)	Indomethacin (3.8%)	Nitric oxide (3.4%)	Azithromycin (2.1%)	Only drugs associated with serious or fatal outcome; children < 2 years
<b>Latin America</b>							
Arencibia et al. 2012 [3]	Cuba	Vaccines	Antibiotics	Antihistamines	Analgesics (nonopioid)	Bronchodilators	
Arencibia et al. 2010 [25]	Cuba	Antibiotics (32%)	Vaccines (15%)	Analgesics (14%)	ACE inhibitors (6%)	Bronchodilators (6%)	
<b>Asia</b>							
Li et al. 2014 [26]	China	Vaccines (42.2%)	Cefuroxime (9.9%)	Azithromycin (8.8%)	Cefotiam (3.4%)	Not reported	

**Table 6: Death reports**

Author/continent	Country	Number of reports	Number of deaths	Proportion of deaths (%)	Comments on type of data
<b>International</b>					
Aagaard et al. 2014 [9]	International	240	3	1.3	VigiBase (Consumer reports)
<b>Europe</b>					
Ferrajolo et al. 2014 [11]	Italy	8338	28	0.3	
Aldea et al. 2012 [13]	Spain	4279	33	0.8	
Aagaard et al. 2010 [15]	Denmark	2437	28	1.1	
Kimland et al. 2005 [16]	Sweden	5771	8	0.1	
Clarkson et al. 2004 [18]	UK	456	10	2.2	
Clarkson et al. 2002 [19]	UK	43755	331	0.8	Fatal ADR reports only (37-year data)
Morales-Olivas et al. 2000 [20]	Spain	1419	4	0.3	
<b>North America</b>					
Lee et al. 2014 [21]	USA	78623	6290	8.0	
Johann-Liang et al. 2009 [22]	USA	36241	2901	8.0	
Carleton et al. 2007 [23]	Canada	1193	41	3.4	
Moore et al. 2002 [24]	USA	7111	769	13.0	3-year data
<b>Latin America</b>					
Arencibia et al. 2012 [3]	Cuba	533	1	0.2	
Arencibia et al. 2010 [25]	Cuba	124	2	1.6	
<b>Asia</b>					
Li et al. 2014 [26]	China	3848	13	0.3	