Introduction

Adverse drug reactions (ADR) are a major health problem to the individual as well as for society [1]. The World Health Organisation’s definition of an ADR is “a response to a drug which is noxious, and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function” [2]. The frequent occurrence of ADRs in children has been reported in three previous systematic reviews of observational studies covering the period from 1966 to 2010 [3,4,5]. The reviews provided estimates of ADR rates causing hospital admission, in hospitalised children and in outpatient children and demonstrated that ADRs in hospitalised children are a considerable problem. Two of the reviews [4,5] provide data on the clinical presentation of the ADR and the drugs involved. In addition, the more recent review [5] provides information on the methods and persons involved in identifying ADRs.

There are however, a number of limitations to the previous reviews. Each review [3,4,5] applied a search strategy, using a limited number of keywords to just two electronic bibliographic databases - MEDLINE and EMBASE. Importantly, as a consequence, relevant studies may have been excluded. In addition, the reviews excluded studies that included adults as well as children, thus reducing the number of eligible studies, and the more recent reviews excluded studies that evaluated adverse drug events (medication errors as well as ADRs).

These reviews do not provide information about the drugs involved in ADRs or about which methods were used for detecting, or assessing the causality and subsequent of an ADR.

Abstract

Background: Adverse drug reactions in children are an important public health problem. We have undertaken a systematic review of observational studies in children in three settings: causing admission to hospital, occurring during hospital stay and occurring in the community. We were particularly interested in understanding how ADRs might be better detected, assessed and avoided.

Methods and Findings: We searched nineteen electronic databases using a comprehensive search strategy. In total, 102 studies were included. The primary outcome was any clinical event described as an adverse drug reaction to one or more drugs. Additional information relating to the ADR was collected: associated drug classification; clinical presentation; associated risk factors; methods used for assessing causality, severity, and avoidability. Seventy one percent (72/102) of studies assessed causality, and thirty four percent (34/102) performed a severity assessment. Only nineteen studies (19%) assessed avoidability. Incidence rates for ADRs causing hospital admission ranged from 0.4% to 10.3% of all children (pooled estimate of 2.9% (2.6%, 3.1%) and from 0.6% to 16.8% of all children exposed to a drug during hospital stay. Anti-infectives and anti-epileptics were the most frequently reported therapeutic class associated with ADRs in children admitted to hospital (17 studies; 12 studies respectively) and children in hospital (24 studies; 14 studies respectively), while anti-infectives and non-steroidal anti-inflammatory drugs (NSAIDs) were frequently reported as associated with ADRs in outpatient children (13 studies; 6 studies respectively). Fourteen studies reported rates ranging from 7%–98% of ADRs being assessed and avoided.

Conclusions: There is extensive literature which investigates ADRs in children. Although these studies provide estimates of incidence in different settings and some indication of the therapeutic classes most frequently associated with ADRs, further work is needed to address how such ADRs may be prevented.
the avoidability [7] of an ADR in order to try to prevent its future occurrence is crucial to reducing the burden of ADRs.

We therefore undertook this systematic review to provide a more comprehensive assessment of all relevant studies and to understanding how ADRs might be better detected, assessed and avoided.

Methods

Criteria for considering studies for this review

Included studies. Observational studies that estimate the incidence of ADRs including retrospective and prospective cohort studies of children.

Excluded studies. Studies which focus on ADRs in relation to a specific drug (e.g. antibiotics or carbamazepine), clinical condition (e.g. epilepsy, asthma) or specific clinical presentations of ADRs (anaphylaxis); case control studies; those carried out exclusively on a neonatal intensive care unit; studies reporting medication errors, therapeutic failures, non-compliance, accidental and intentional poisoning and drug abuse.

Participants. Children as defined by the original study authors.

Studies included three defined populations: 1) children admitted to hospital, 2) children in hospital and 3) children within the community.

Interventions. Exposure to any systemic or topical medicinal product including herbal and aromatherapy, as defined by researchers.

Types of outcome measure. Any clinical event described as an adverse drug reaction or non-avoidable adverse drug event to an individual or group of drugs.

Search methods for identification of studies

A range of electronic bibliographic databases were searched (Table 1) using a search strategy of text words and indexing terms (Table 2). In addition, we examined references in relevant studies and those cited by previous systematic reviews. Contact with experts was made to identify other potentially relevant published and unpublished studies. We did not apply language restrictions to the search.

Selection of studies

Screening on title, abstract and full publication stage. Duplicate citations were removed. A study eligibility screening proforma based on pre-specified inclusion criteria was used. Two reviewers (RMDS, EG) independently screened each title and categorised as include, exclude or unsure. The two independent categorisations for all titles were compared and the title categorised again following discussion if two reviewers disagreed. Where there was agreement to exclude, the citation was excluded at this stage. All other citations were reviewed at abstract level. This process was repeated and where there was disagreement, discussion took place between reviewers and citations were re-categorised. Those with agreement to include or as unsure were reviewed at full publication level. The process was repeated at full publication stage. Studies considered as unsure or included at full publication stage were reviewed by a third reviewer (JK). Reasons for exclusion were documented at the abstract and full paper stage of the screening process.

Checking for correct exclusion at each stage. At title stage, two reviewers (RMDS, EG) independently viewed the abstracts for a proportion (2%) of studies excluded. Independent categorisation were compared (as above). This process was repeated at abstract stage where a third reviewer (JK) reviewed 10% of full papers for studies excluded based on abstract. This was repeated at full publication stage where the same reviewer (JK) reviewed 20% of excluded full papers. If any studies were excluded incorrectly at any stage, additional checking was performed.

Data extraction

We extracted the following data from each study:

1) Study characteristics: country; year completed; duration; number of sites; design (prospective or retrospective); clinical setting; number of children.

2) Identification of ADR: definition of ADR, including definition of drug exposure; incidence definition and calculation (numerator and denominator, either at patient or episode level); assessment of causal relationship to drug; person who assessed and categorised ADRs; any method (e.g. case record review) or reporting system used (e.g. Yellow Card).

3) Information relating to the ADR: clinical presentation; associated drug(s)/drug classification; associated risk factors (including age, gender, polypharmacy); ADR considered avoidable.

Assessment of methodological quality of included studies

As we were unable to find a validated assessment tool for critically appraising observational studies of adverse drug reactions, we developed a quality assessment form specifically for the review. The following aspects were deemed important when assessing study quality: study design; methods for identifying ADRs; methods used to establish the causal relationship between drug and effect; tools for assessing avoidability of the ADR; and tools for assessing severity of the ADR. Criteria were graded as yes, no, unclear, or not reported. Two reviewers (RMDS, EG) independently assessed methodological quality of each study (Table 3).

Statistical analysis and data synthesis

For each of the three defined populations; children admitted to hospital, children in hospital and children within the community, a forest plot was produced to present the ADR incidence rate and 95% confidence interval for each relevant study. Studies were sub grouped according to whether the incidence rate was reported at the patient and/or episode level and whether or not all patients had been exposed to a drug. Further, for rates reported at the patient level, a distinction was made between studies that had included one admission per patient and those that had included multiple admissions per patient. All results provided per study were included. Pooled estimates were calculated if the variability in incidence rates was not considered too large.

Univariate meta-regression was used to determine if study level characteristics (setting, gender, age, oncology and number of drugs used) are associated with ADR incidence. Incidence rates for ADRs causing admission and occurring in hospital, calculated at the patient level for a single episode were included. Multivariate meta-regression was not undertaken due to the paucity of covariate data. Risk factor analyses reported by any study were collated.

Results

The search was originally undertaken in November 2009 and retrieved 20,906 potentially relevant citations. An update search was subsequently performed in October 2010 and retrieved an
Included studies

A total of 102 studies (117 citations), were included in the review. Eighty (80/102) studies described the clinical event as an ADR. In 10 of these studies, ADR was a category within ‘drug related’ problems/admissions; three studies described ADRs as drug induced disease/illness. Sixteen described an ADE where the non-preventable ADE was the same as our definition and two studies used the term iatrogenic disease to describe an ADR. Some studies included multiple settings; 42 studies investigated ADRs as the cause of admission to hospital, 51 studies investigated ADRs in the hospital setting, and 36 studies investigated ADRs in the community setting. Studies included in our review were conducted in 31 different countries, mostly Europe (40/102) and America (32/102). The earliest study assessed the year 1964, the latest assessed years 2008–2009 for causing admission, study size ranged from 24 children to 39,625 admissions. For studies carried out in hospital; the earliest study assessed the year 1964, the latest 2009, study size ranged from 81 children to 64,403 children, and the earliest study assessed the years 1970–1973, the latest 2007, study size ranged from 73 children to 47,107 children for community studies. Characteristics for each individual study are provided in Table 4.

Assessment of methodological quality of included studies

All studies, including those that evaluated ADEs, explicitly stated that they had used either the WHO ADR definition [8] or a comparable one and that they excluded drug errors. Methodological features of each individual study are provided in Table 4.

Study design

The majority of studies were carried out prospectively (n = 85; 83%), which included 13 in those causing admission, 26 studies with the ADR occurring in hospital, 24 in the community, 16 in hospital and causing admission and 6 in mixed hospital and community settings. Fourteen studies were carried out retrospectively, which included six causing hospital admission, two in hospital studies, and four in the community, one causing admission and in the hospital setting and one the study that considered ADRs that resulted in any medical care contact. Two studies (one in hospital, and one in hospital and causing admission), used both study designs. For the remaining study we were unable to determine the study design (Table 4).

Persons involved in identifying ADRs

Sixty-four studies reported that a clinician; either a medical doctor, nurse or pharmacist, was involved in the identification of ADRs. Thirty studies reported also involving either the child or parent. Eight studies did not provide information about who identified the ADRs.

Methods for identifying ADRs

Several methods were used to detect ADRs. Multiple ADR detection methods were employed in 38/102 studies; these consisted of a combination of case record review, drug chart review, laboratory data, computerised ADR reporting system,
attendance at ward rounds, and interviewing patients/parents or clinicians. In thirty-one studies case record review alone was undertaken. The remaining eleven studies used: parental interviews/questionnaires (5 studies), clinical assessments (3 studies), clinician questionnaires (1 study), ward round (1 study) and a nationwide computer database (1 study). The remaining study report did not refer to the methods used.

Studies estimating the proportion of paediatric hospital admissions related to ADRs

**Description of studies.** There were 42 studies, where ADRs have been investigated as the cause of admission to hospital. The period under study varied widely and ranged from 1 week to 11 years. The majority of studies were described as being performed in a general paediatric unit or ward (n = 22) [9–29,34]. Four studies included general medicine [30–33] one study in a hospital emergency department [35]. Two studies covered general medicine and a hospital emergency department, [36,37], and one study an integrated primary care information database [38]. Two studies were performed in the paediatric intensive care setting [39], one in combination with general paediatrics also [40]. Seven studies covered a combination of clinical settings [41–47]. The remaining three studies were performed in dermatology and venereology [48], Infectious diseases [49] and an isolation ward [50].

**ADR incidence.** We do not have ADR incidence rates for 12/42 of these studies as the child only data was not available (n = 4), data were not split by clinical setting (n = 5), data provided for ADRs in hospital but not causing admission (n = 2) and data were provided for the total number of ADRs but not the ADR.

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**Table 2. MEDLINE search strategy.**

| 1st Concept - general terms used to describe the participants - infants and children. |
| 1. exp Child/ |
| 2. exp Adolescent/ |
| 3. [young adj (person| or people or adult| or individual| or women or woman or men or man)].ti,ab. |
| 4. (child| or adolescent| or kid or kids or youth| or youngster| or minor or minors or teen| or juvenile| or student| or pupil| or boy| or girl).ti,ab. |
| 5. exp Students/ |
| 6. Puberty/ |
| 7. Pediatrics/ |
| 8. (infant| or newborn| or new born| or baby| or babies or child| or schoolchild| or kid or kids or toddler| or adole| or teen| or boy| or girl| or minor| or juvenile| or youth| or kindergar| or nursery| or pre| or prepuber| or prepuber| or prepubescent| or prepubescent| or pre pubescent| or pubescent| or pediatric| or paediatric| or schoolage).ti,ab. |

| 2nd Concept including terms relating to adverse drug reactions |
| 9. side effect| or drug induced or drug related or drug safety).ti,ab. |
| 10. toxicity| or Harm).ti,ab. |
| 11. adverse adj3 (effect or effects or reaction or reactions or event or events or outcome or outcomes).ti,ab. |
| 12. exp adverse drug reaction reporting systems/ or exp drug toxicity/ or exp abnormalities, drug induced/ or exp drug hypersensitivity/ |

| 3rd Concept – terms relating to the occurrence of ADRs |
| 13. incidence/ or prevalence/ |
| 14. (incidence| or prevalence| or occurrence or admission| or admitted or visit| or hospitalisation or hospitalised or hospitalization or hospitalized).ti,ab. |

| 4th Concept - terms that encompass the intervention |
| 15. (drug| or pharmaceutical| or medicine).ti,ab. |
| 16. Pharmacological Preparations/ |
| 17. herb| or medicinal| or plant or plants or herb or herbs or aromatherapy| or aroma therapy).ti,ab. |
| 18. Medicine, Chinese Traditional/ or Plant Preparations/ or Plants, Medicinal/ or Plant Extracts/ or Drugs, Chinese Herbal/ |
| 19. Aromatherapy/ |

| 5th Concept - study design |
| 20. (observational| or nonrandomized or cross sectional or cross-sectional or case control or case-control).ti,ab. |
| 21. (prospective| or cohort).ti,ab. |
| 22. (retrospective| or case series).ti,ab. |
| 23. (population-based| or review| or summary).ti,ab. |
| 24. Cohort Studies/ |
| 25. Health Care Surveys/ |
| 26. Retrospective Studies/ |
| 27. Prospective Studies/ |
| 28. Cohort Studies/ |
| 29. observational stu| or review|).ti,ab. |
| 30. (prospective| or review|).ti,ab. |
| 31. (prospective| or study|).ti,ab. |
| 32. (retrospective| or study|).ti,ab. |
| 33. (retrospective| or review|).ti,ab. |
| 34. population-based stu|).ti,ab. |
| 35. cohort stu|).ti,ab. |
| 36. incidence stu|).ti,ab. |
| 37. Sn.fs. |
| 38. Ep.fs. |
| 39. monitor|).ti,ab. |
| 40. surveillance).ti,ab. |

The terms within each concept were ORed, and then all 5 concepts were combined using the AND Boolean operator. This search strategy was translated as appropriate for the other databases.
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frequency at the patient or episode level (n = 1). Figure 1 presents data from all studies that provide incidence rates for ADRs causing admission to hospital (n = 30). These rates range from 0.4% to 10.3% of children (single admission). One study was an extreme outlier [20] and if this was excluded we found a reduction in the upper limit of this range to 4%, and a pooled incidence estimate of 2.9% (2.6%, 3.1%).

Studies estimating the proportion of children experiencing an ADR during their admission

**Description of studies.** We have included 51 studies, where ADRs have been investigated in the hospital setting. The period under study varied widely and ranged from 1 day to ten years. The majority of studies where described as being performed in a general paediatric unit or ward (n = 24) [14,19,20,22–26,28,34,37,51–54,56–63,85] two of which included intensive care also [64], [40]. Six studies were performed solely in the intensive care setting [39,65–69], one of which included general medicine [70]. Three studies included children on an isolation ward [71–73]. One study was performed using an integrated primary care information database [38] and one in an isolation ward [50]. The remaining thirteen studies covered a combination of clinical settings [41,43–47,49,74–79].

**ADR incidence.** We do not have ADR incidence rates for 18/54 of these studies as the child only data was not available (n = 3), the data were not split by clinical setting (n = 7), data were provided for the total number of ADRs but not the ADR frequency at the patient or episode level (n = 5), data provided for ADRs and ADEs combined (n = 2), and data provided for ADRs causing admission but not in hospital (n = 1). Figure 2 presents data from all studies that provide incidence rates for ADRs in hospital (n = 36). These estimates range from 0.6% to 16.8% of patients (at a single episode and with prior drug exposure). A pooled estimate has not been calculated since the rates are considered too varied.

Studies estimating the incidence of ADRS in outpatient children

**Description of studies.** We have included 36 studies, where ADRs have been investigated in the community setting. The period under study varied widely and ranged from 1 week to 11 years. The majority of studies where described as being performed in a hospital outpatient or accident emergency department (n = 21) [25,25,47,55,78,80–84,86–97]. Nine studies were performed in general practice [98–106]. The remaining six studies were performed in an infant care and educational establishment [107], local community setting [108,109], general practice and accident and emergency department [37], outpatient population seeking medical care [110], and after discharge from hospital [26].

**ADR incidence.** We do not have ADR incidence rates for 19/36 of these studies as the child only data were not available (n = 10), the data were not split by clinical setting (n = 3), data not available for the total number of children/visits (n = 4), data were provided for the total number of ADRs but not the ADR frequency at the patient or visit level (n = 1) and data were provided for errors only (n = 1). Figure 3 presents data from studies that provide incidence rates for ADRs in the community (n = 15). Two studies were not included in this figure due to their method of ADR ascertainment.

All Settings

**Drugs and clinical presentation associated with ADR.** We do not have information on the drugs involved in ADRs for 50/102 studies, as the child only data were not available (37 studies), ADRs were a subset of events looked at and ADR specific data were not reported (10 studies), and drug data were not available in the publication (3 studies). For studies that provided data (52/101) (Table 5); anti-infectives were the drug class most commonly reported across the three settings. Proportions ranged from 3.5%–66.6% for causing admission studies (17 studies); 8.6%–100% for in hospital studies (24 studies); and 17%–78% for community studies (13 studies). The most common associated clinical presentations reported were nausea, vomiting, diarrhoea and skin rash. Anti-epileptics were the second most common reported drug class in both the causing admission and in hospital studies; proportions ranging from 0.8%–30% (12 studies); and 3.9%–46.6% (14 studies) respectively. Reported clinical presentations were ataxia, skin rash, increased fitting, and drowsiness. Non-steroidal anti-inflammatory drugs (NSAIDs) were...
Table 4. Study characteristics.

| Study                  | Country        | Study duration/design | Clinical setting                  | Population                                | Causality assessment                      | Avoidability assessment                  |
|------------------------|----------------|-----------------------|-----------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|
| Al-Olah 2008           | Saudi Arabia   | 28 days Prospective   | Causing admission Emergency department | Children and adults Not reported in publication/unable to obtain from author | Naranjo                                   | Definite preventable and definite non-preventable defined as 3 evaluators in agreement; possible preventable and possible non-preventable 2 in agreement |
| Classen 1991           | USA            | 18 months Prospective | Acute care referral hospital      | Children and adults 0–20 years            | Naranjo Score Algorithm                   | Not reported in publication/unable to obtain from author |
| Duczmal 2006           | Poland         | Not reported in publication/unable to obtain from author Retrospective | Paediatric department | Children 0–15 years                       | Naranjo                                   | Not reported in publication/unable to obtain from author |
| Easton 1998            | Australia      | 56 days Prospective   | Medical ward                      | Children 19 weeks – 18 years, 19 weeks – 20 years | Naranjo Score Algorithm                   | Schumock and Thornton 1992               |
| Easton-Carter 2004     | Australia      | 22 weeks Prospective  | Specialist paediatric hospital and general regional teaching hospital | Children Not reported – 17 years         | Dartnell et al 1996                       | Schumock and Thornton 1992               |
| Gallagher 2010         | UK             | 2 weeks Prospective   | Large tertiary - paediatric hospital | Children ≤18 years                        | Naranjo                                   | Hallas et al 1990                        |
| Gallagher 2011         | UK             | 12 month Prospective  | Large tertiary - paediatric hospital | Children ≤18 years                        | Naranjo Liverpool Causality Tool          | Hallas et al 1990                        |
| Ganeva 2007            | Bulgaria       | 5 years Prospective   | Dermatology and venerology        | Children and adults 6–18 years            | Naranjo Score Algorithm                   | Not reported in publication/unable to obtain from author |
| Hewitt 1995            | Australia      | 4 months Retrospective | General teaching hospital         | Children and adults Age not reported      | Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author |
| Ives 1987              | US             | 1 year Retrospective  | Family medicine inpatient service at hospital | Children and adults <20 years             | Naranjo Score Algorithm                   | Not reported in publication/unable to obtain from author |
| Kunac 2009             | New Zealand    | 12 weeks Prospective  | Paediatric                         | Children Newborn-16 years                 | Naranjo Score Algorithm                   | Schumock and Thornton 1992               |
| Lamabadusurya 2003     | Sri Lanka      | 11 months Prospective | Medical ward                       | Children Not reported in publication/unable to obtain from author | Naranjo Score Algorithm                   | Not reported in publication/unable to obtain from author |
| Major 1998             | Lebanon        | 6 months Prospective  | Medical, paediatric               | Children and adults Up to 19 years         | Naranjo Score Algorithm                   | Not reported in publication/unable to obtain from author |
| McDonnell 2002         | US             | 11 months Retrospective | University affiliated teaching hospital | Children and adults Not reported – 15 years | Naranjo Score Algorithm                   | Adapted from Schumock & Thornton         |
| Mitchell 1988          | US             | 11 years Prospective  | Teaching and community hospitals  | Children 0–15 years                       | Definite - clear implicated drug caused the reaction; Possible – other factors might have caused the reaction. | Not reported in publication/unable to obtain from author |
| Pouyanne 2000          | France         | 14 days Prospective   | Medical, Public hospital           | Children and adults Not reported – 15 years | Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author |
| Santos 2000            | Philippines    | 3 months Prospective  | Paediatric unit                    | Children 0–18 years                       | Naranjo Score Algorithm                   | Not reported in publication/unable to obtain from author |
| Schneeweiss 2002       | Germany        | 2 yrs and 5 months Prospective | Internal medicine or emergency departments of all hospitals | Children and adults Age not provided   | Begaud et al 1985                        | Not reported in publication/unable to obtain from author |
| Van der Hooft 2006     | Netherlands    | 1 year Retrospective  | Academic and general hospitals     | Children and adults Not reported – <18 years | Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author |
Table 4. Cont.

### Causing admission studies

| Study                  | Country       | Study duration/ design | Clinical setting                  | Population              | Causality assessment                                                                 | Avoidability assessment                                |
|------------------------|---------------|------------------------|-----------------------------------|-------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------|
| Yosselson-Superstine   | Israel        | 7 months Prospective   | General paediatric ward           | Children 0–16 years     | Seidl et al 1965; Seidl et al 1966; McKenzie 1973; McKenzie 1976; Whyte 1977         | Not reported in publication/unable to obtain from author |
| Dharnidharka           | India         | 18 months Prospective  | Paediatric unit                   | Children 0–12 years     | Stephens et al 1998                                                                   | Not reported in publication/unable to obtain from author |
| Dos Santos 2009        | Brazil        | 2 years Prospective    | General paediatric ward           | Children 1 month–14.4 years | Naranjo                                                                             | Not reported in publication/unable to obtain from author |
| dos Santos 2006        | Brazil        | 5 months Prospective   | General paediatric ward           | Children 1 month–14.4 years | WHO                                                                                 | Not reported in publication/unable to obtain from author |
| Easton-Carter 2003b    | Australia     | 39 weeks Prospective & prospective | General paediatric ward          | Children 0–17 years     | Naranjo Score Algorithm                                                              | Schumock and Thornton 1992                             |
| Farrokhi 2006          | Iran          | 5 months Prospective   | Paediatric surgery                | Children 0.5 months–11 years | Not reported in publication/unable to obtain from author                             | Not reported in publication/unable to obtain from author |
| Gonzalez-Martín 1998   | Chile         | 1 year Prospective     | Paediatric wards                  | Children 5 days–15 years | Naranjo Score Algorithm                                                              | Naranjo and Busto 1989                                |
| Imbs 1999              | France        | 1 day Prospective      | Departments of medicine, surgery and geriatrics | Children and adults 0–19 years | Two members of the pharmacovigilance team validated each ADR.                      | Not reported in publication/unable to obtain from author |
| Jha 2007               | Nepal         | 5 months Prospective   | General paediatric ward           | Children and adults 0–18 years | Naranjo Score Algorithm                                                              | Not reported in publication/unable to obtain from author |
| Kaushal 2001           | US            | 36 days Prospective    | General paediatric ward           | Children and adults neonates – teenagers | Naranjo Score Algorithm                                                              | Not reported in publication/unable to obtain from author |
| Leach 1998             | UK            | 14 months Prospective  | Regional ICU, a general medical ward, cardiac ICU and cardiac medical ward | Children Not reported in publication/unable to obtain from author | Naranjo, Karch and Lasagna, and Kramer 1979                                         | Not reported in publication/unable to obtain from author |
| Maistrello 1999        | Italy         | 6 months Prospective   | Emergency ward, Infectology ward, general paediatric ward, Pneumology ward | Children 0–17 years | Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author |
| Mitchell 1979          | US            | 4 years Prospective    | General medical, oncology, NICU   | Children 0–17 years     | Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author |

### In hospital studies

| Study                  | Country       | Study duration/ design | Clinical setting                  | Population              | Causality assessment                                                                 | Avoidability assessment                                |
|------------------------|---------------|------------------------|-----------------------------------|-------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------|
| Agarwal et al 2010     | USA           | 4 mths Retrospective   | Paediatric intensive care         | Children 0–13 years     | Not reported in publication/unable to obtain from author                             | ADEs assessed, non preventable = ADR                    |
| Barstow 1988           | US            | 4 month prospective    | Paediatric units                  | Children and adults Age not provided | Not reported in publication/unable to obtain from author                             | Not reported in publication/unable to obtain from author |
| Benkirane 2009         | Morocco       | 3 month prospective Intensive care unit | Children and adults Age not provided | Not reported in publication/unable to obtain from author | ADEs assessed, non preventable = ADR.                                                 |
| Buckley 2007           | US            | 12 days Prospective    | Paediatric intensive care         | Children Not reported --<18 years | Not reported in publication/unable to obtain from author                             | ADEs assessed using Bates et al, non preventable ADE = ADR |
| Choonara 1984          | UK            | 6 months Prospective   | General paediatric ward           | Children Not reported in publication/unable to obtain from author | Seidl et al 1966                                                                    | 6 avoidable: 3 dose prescribed too high, 1 treatment not necessary, 2 application of pharmacological principles would have prevented reactions |
| Dharidharka 1993       | India         | 18 months Prospective  | Paediatric unit                   | Children 0–12 years     | Stephens et al 1998                                                                  | Not reported in publication/unable to obtain from author |
| Dos Santos 2009        | Brazil        | 2 years Prospective    | General paediatric ward           | Children 1 month–14.4 years | Naranjo                                                                             | Not reported in publication/unable to obtain from author |
| dos Santos 2006        | Brazil        | 5 months Prospective   | General paediatric ward           | Children 1 month–14.4 years | WHO                                                                                 | Not reported in publication/unable to obtain from author |
| Easton-Carter 2003b    | Australia     | 39 weeks Prospective & prospective | General paediatric ward          | Children 0–17 years     | Naranjo Score Algorithm                                                              | Schumock and Thornton 1992                             |
| Farrukhi 2006          | Iran          | 5 months Prospective   | Paediatric surgery                | Children 0.5 months–11 years | Not reported in publication/unable to obtain from author                             | Not reported in publication/unable to obtain from author |
| Gonzalez-Martín 1998   | Chile         | 1 year Prospective     | Paediatric wards                  | Children 5 days–15 years | Naranjo Score Algorithm                                                              | Naranjo and Busto 1989                                |
| Imbs 1999              | France        | 1 day Prospective      | Departments of medicine, surgery and geriatrics | Children and adults 0–19 years | Two members of the pharmacovigilance team validated each ADR.                      | Not reported in publication/unable to obtain from author |
| Jha 2007               | Nepal         | 5 months Prospective   | General paediatric ward           | Children and adults 0–18 years | Naranjo Score Algorithm                                                              | Not reported in publication/unable to obtain from author |
| Kaushal 2001           | US            | 36 days Prospective    | General paediatric ward           | Children and adults Neonates – teenagers | Naranjo Score Algorithm                                                              | Not reported in publication/unable to obtain from author |
| Leach 1998             | UK            | 14 months Prospective  | Regional ICU, a general medical ward, cardiac ICU and cardiac medical ward | Children Not reported in publication/unable to obtain from author | Naranjo, Karch and Lasagna, and Kramer 1979                                         | Not reported in publication/unable to obtain from author |
| Maistrello 1999        | Italy         | 6 months Prospective   | Emergency ward, Infectology ward, general paediatric ward, Pneumology ward | Children 0–17 years | Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author |
| Mitchell 1979          | US            | 4 years Prospective    | General medical, oncology, NICU   | Children 0–17 years     | Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author |
### Table 4. Cont.

#### In hospital studies

| Study                      | Country | Duration | Setting                          | Children | Naranjo Score Algorithm | Methodology                          | Schumock and Thornton 1992 |
|---------------------------|---------|----------|----------------------------------|----------|-------------------------|--------------------------------------|------------------------------|
| Neubert 2004              | Germany | 8 months | Prospective                      | Children 5 days–17 years | Naranjo Score Algorithm | Assessed but no detail provided, non preventable ADE = ADR |
| Neubert 2006              | Germany | 6 months | Prospective                      | Children and adults 0–18 years | Naranjo Score Algorithm | Assessed but no detail provided, non preventable ADE = ADR |
| Shockrollah 2009          | Iran    | 3 months | Retrospective                    | Children 2 days–12 years | Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author |
| Takata 2008a              | USA     | 3 months | Prospective                      | Children <18 years | Not reported in publication/unable to obtain from author | Assessed but no detail provided, non preventable ADE = ADR |
| Takata 2008b              | USA     | 6 months | Prospective                      | Children <18 years | Naranjo Score Algorithm | Assessed but no detail provided, non preventable ADE = ADR |
| Telechea 2010             | Uruguay | 2 months | Prospective                      | Children 1 month – 14 years | Karch and Lasagna | Not reported in publication/unable to obtain from author |
| Turner 1999               | UK      | 13 weeks | Prospective                      | Children 1 day–18 years | Choonara & Harris 1984 | Not reported in publication/unable to obtain from author |
| Uppal 2000                | India   | 3 years  | Prospective                      | Children and adults Not reported in publication/unable to obtain from author | Karch and Lasagna | Not reported in publication/unable to obtain from author |
| Vazquez de la Villa 1989  | Spain   | 12 months| Prospective                      | Children 1–8 years | Naranjo Score Algorithm | Not reported in publication/unable to obtain from author |
| Wang 2007                 | US      | 3 months | Prospective                      | Children Age not provided | Not reported in publication/unable to obtain from author | ADEs assessed, non preventable = ADR |
| Weiss 2002                | Germany | 8 months | Prospective                      | Children 1 month–18 years | adapted Naranjo (Evans et al 1994) | Avoidable or tolerated – toxicity, drug interactions, secondary effects. |

#### Community studies

| Study                      | Country | Duration | Setting                          | Children | Naranjo Score Algorithm | Methodology                          | Schumock and Thornton 1992 |
|---------------------------|---------|----------|----------------------------------|----------|-------------------------|--------------------------------------|------------------------------|
| Calderon-Ospina 2008      | Colombia| 12 days  | Prospective                      | Children and adults 0–20 years | WHO | Schumock and Thornton 1992 |
| Campbell 1978             | USA     | 48 months| Prospective                      | Children and adults ≤20 years | Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author |
| Cirko-Begovic 1989        | Croatia | 3 months | Prospective                      | Children 0-7 years | Hutchinson 1979 | Not reported in publication/unable to obtain from author |
| Dennehy 1996              | USA     | 1 month  | Retrospective                    | Children and adults ≤25 years | Strand et al 1990 | Considered preventable if avoided through appropriate prescribing, outpatient monitoring or patient compliance. |
| Doval 1981                | India   | Not reported in publication/unable to obtain from author | Outpatient department | Children and adults 1 year–20 years | Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author |
| Easton-Carter 2003a       | Australia| 18 weeks | Prospective                      | Children ≤17 years | Dartnell et al 1996 | Schumock and Thornton 1992 |
| Horen 2002                | France  | Not reported in publication/unable to obtain from author | Office-based practice | Children 0–15 years | Begaud et al 1985 | Not reported in publication/unable to obtain from author |
| Juntti-Patinen 2006       | Finland | 6 months | Prospective                      | Children 0–15 years | WHO | Not reported in publication/unable to obtain from author |
| Kaushal 2007              | US      | 2 months | Prospective                      | Children <21 years | Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author |
| Knopf 2010                | Germany | 3 years  | Prospective                      | Children ≤17 years | WHO | Not reported in publication/unable to obtain from author |
### Community studies

| Study            | Country | Study Duration | Setting                          | Patient Age | Outcome Description                                                                 |
|------------------|---------|----------------|----------------------------------|-------------|--------------------------------------------------------------------------------------|
| Kramer 1985      | Canada  | 1 year         | Prospective                      | Children 2 days–18.9 years | Kramer 1979 Predictive - realistic nondrug alternative available; Possibly preventable - safer alternative drug available/lower dosage might have been modified; Unpreventable - would not have changed the choice/dose of drug. |
| Kushwaha 1994    | India   | 2 years        | Prospective                      | Children 0–14 years | Not reported in publication/unable to obtain from author                              |
| Lemer 2009       | USA     | 10mths         | Prospective                      | Children ≤12 years | ADEs assessed, non preventable = ADR                                                        |
| Lewinski 2010    | Germany | 3 mths         | Prospective                      | Children and adults ≤16 years | Strand et al 1990 Not reported in publication/unable to obtain from author           |
| Martys 1979      | UK      | 2 years        | Prospective                      | Children and adults 2 months–19 years | Not reported in publication/unable to obtain from author                                |
| Menmiti-Ippolito 2000 | Italy | 1 year         | Prospective                      | Children 0–14 years | Not reported in publication/unable to obtain from author                                |
| Miller 2006      | Australia | 10 months    | Prospective                      | Children and adults ≤14 years | Thomas & Brennan 2000                                                                 |
| Mulroy 1973      | UK      | 1 year         | Prospective                      | Children and adults ≤20 years | Not reported in publication/unable to obtain from author                                |
| Munoz 1998       | Spain   | 25 months      | Prospective                      | Children 4 weeks–13 years | Karch and Lasagna Not reported in publication/unable to obtain from author           |
| Otero Lopez 1999 | Spain   | 6 months       | Prospective                      | Children <15 years | Schumock and Thornton 1992                                                             |
| Phan 2010        | USA     | 5 mths         | Retrospective                    | Children ≤18 years | Naranjo Not reported in publication/unable to obtain from author                      |
| Planchamp 2009    | France  | 6 months       | Retrospective                    | Children 0–18 years | Begaud et al 1985 Olivier et al 2005                                                  |
| Prince 1992      | US      | 4 months       | Retrospective                    | Children and adults Age not provided | Michel and Knodel 1986 Not reported in publication/unable to obtain from author    |
| Rebelo Gomes 2008 | Portugal | 4 months     | Retrospective                    | Children Age not provided | Not reported in publication/unable to obtain from author Not reported in publication/unable to obtain from author |
| Sanz 1987        | Spain   | 6 months       | Prospective                      | Children <14 years | Karch and Lasagna, Vensel, Dangoumau, Kramer, Naranjo and Blanc                       |
| Sharma 2007      | India   | 4 months       | Prospective                      | Children and adults 0–20 years | WHO Not reported in publication/unable to obtain from author                         |
| Smith 1997       | US      | 1 month        | Retrospective                    | Children and adults ≤18 years | Not reported in publication/unable to obtain from author                               |
| Stoukides 1993   | US      | 6 months       | Retrospective                    | Children and adults ≤20 years | Not reported in publication/unable to obtain from author Not reported in publication/unable to obtain from author |
| Valladares 1992  | Spain   | 4 years        | Prospective                      | Children and adults 0–14 years | Karch and Lasagna Not reported in publication/unable to obtain from author           |
| Woods 1987       | UK      | 26 weeks       | Prospective                      | Children Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author Not reported in publication/unable to obtain from author |
### Table 4. Cont.

#### Community studies

| Study                  | Country | Duration   | Setting                        | Age | Linkage | Diagnosis | Outcome                  | Author                  |
|------------------------|---------|------------|-------------------------------|-----|---------|-----------|---------------------------|-------------------------|
| Zahroui 2010           | Morocco | 7 months   | Prospective                   | Children ≤16 years | NOT REPORTED | Referral centre | NOT REPORTED | Schumock and Thornton 1992 |
| Baniasadi 2008         | Iran    | 12 months  | Prospective                   | Children 0-18 years | NOT REPORTED | Multidisciplinary hospital | WHO                     | Begaud et al 1985       |
| Bordet 2001            | France  | 18 months  | Prospective                   | Children 0-20 years | NOT REPORTED | General paediatric ward | NOT REPORTED | NOT REPORTED | Unable to obtain from author |
| Fattahi 2005           | Iran    | 5 months   | Prospective                   | Children 0-14 years | WHO        | Paediatric infectious diseases | NOT REPORTED | NOT REPORTED | Unable to obtain from author |
| Fincham 1989           | USA     | 3 months   | Prospective                   | Children Age not provided | NOT REPORTED | Hospital and private practice | NOT REPORTED | NOT REPORTED | Unable to obtain from author |
| Gill 1995              | UK      | 3 months   | Prospective                   | Children 4 days-16 years | Kramer 1979 | Paediatric intensive care | WHO                     | NOT REPORTED | Unable to obtain from author |
| Haffner 2005           | Germany | 91 days; 80 days; overlap of 52 days | Prospective | ICU, General paediatric ward, Department of Paediatrics | Children Age not provided | WHO | NOT REPORTED | NOT REPORTED | Unable to obtain from author |
| Impicciatore 2002      | Italy   | 9 months   | Prospective                   | Children 3 months-14 years | WHO - confirmed by author | Paediatric unit | NOT REPORTED | NOT REPORTED | Unable to obtain from author |
| Le 2006                | US      | 10 years   | Retrospective                 | Children 0-15 years | Definite; Probable; Possible; Conditional | Children's Hospital | NOT REPORTED | NOT REPORTED | Unable to obtain from author |
| Martinez-Mir 1996      | Spain   | 90 days; and 99 days | Prospective | Paediatric hospital; Paediatric isolation ward, Lactants B ward | Children 1 month–24 months | Spanish Drug Surveillance Scheme (Meyboom 1992) | NOT REPORTED | NOT REPORTED | Unable to obtain from author |
| McKenzie 1973          | US      | 8 months   | Prospective                   | Children 0 – no upper limit provided | Definite - directly attributable to drug | University affiliated teaching hospital, paediatric medicine services | Not reported in publication/unable to obtain from author |
| McKenzie 1976          | US      | 3 years    | Prospective                   | Children 0 – no upper limit provided | Definite - directly attributable to drug | University affiliated teaching hospital | Not reported in publication/unable to obtain from author |
| Oshikoya 2007          | Nigeria | 3 years    | Both                          | Children 4 months–12 years | Jones 1982 | General paediatric ward | NOT REPORTED | Done but no reference provided |
| Ramesh 2003            | India   | 7 months   | Prospective                   | Children and adults 0-18 years | WHO | Memorial hospital | NOT REPORTED | NOT REPORTED | Unable to obtain from author |
| Seidl 1966             | US      | 3 months   | Prospective                   | Children and adults 0-20 years | Documented- confirmatory re-challenge test or a lab result indicating the unwanted effect. Probable - improvement or cessation of symptoms upon withdrawal of drug | General medical service | NOT REPORTED | NOT REPORTED | Unable to obtain from author |
| Smidt1972              | New Zealand | 6 months | Prospective                   | Children and adults Not reported in publication/unable to obtain from author | Not reported in publication/unable to obtain from author | General hospital | NOT REPORTED | NOT REPORTED | Unable to obtain from author |
| Speranza 2008          | Uruguay | 1 week     | Prospective                   | Children 0-12 years | Karch and Lasagna | Paediatric hospital | NOT REPORTED | NOT REPORTED | Unable to obtain from author |
| Van der Hooft 2008     | Netherlands | 1 year | Retrospective | Integrated Primary Care Information Database | Children and adults Not reported-16 years | WHO | NOT REPORTED | Not reported in publication/unable to obtain from author |
| Whyte 1977             | UK      | 10 months  | Prospective                   | Children 0-12+ (maximum not stated) | Not reported in publication/unable to obtain from author | Paediatric unit | NOT REPORTED | Not reported in publication/unable to obtain from author |
frequently reported as being associated with ADRs in studies in children in both the causing admission and outpatient studies, proportions ranging from 4.1%–25% (9 studies) and 1%–10% (6 studies) respectively. Reported clinical presentations were cutaneous reactions, haematuria, hypertranspiration, drowsiness, abdominal pain, aggressiveness and vomiting.

In addition, corticosteroids were commonly reported across the three settings. Proportions ranging from 5.5%–41.0% for causing admission studies (7 studies); 1.7%–23.4% for in hospital studies (10 studies); and 0.05%–5% for community studies (3 studies). The most common associated clinical presentations reported were immunosuppression, post-operative bleeding, gastric irritation, and diarrhoea.

The distribution of drugs implicated in ADRs reflect the prescribing practices for the individual settings. For example; vaccines were commonly reported in causing admission studies (7 studies) and community studies (5 studies). Proportions ranged from 1.7%–20.0% and 9.2%–25% respectively, with rash and fever being the most common associated clinical presentations. Cytotoxics were reported in both causing admission (8 studies) and in hospital studies (7 studies), proportions ranged from 14.2%–50%, and 1.7%–66.6% respectively. The remaining studies reported a variety of drugs implicated in ADRs, for some more than one drug was the cause of a single ADR (Table 5).

Meta-regression

Univariate meta-regression results (Table 6) suggest that the incidence rate for ADRs occurring in hospital is higher than for ADRs causing admission (OR = 2.73 (0.93, 8.03)). In addition, the results suggest that the incidence rate is higher for studies with a relatively high mean/median number of drugs per patient (OR = 1.49 (1.14, 1.94)), high percentage of females (OR = 1.13 (0.91, 1.40)), high percentage of oncology patients (OR = 1.15 (0.89, 1.50)) and low mean age of patients (OR = 0.71 (0.39, 1.27)). However, only the variable representing the mean/median number of drugs per patient achieves statistical significance.

Risk factors

Risk factor analyses reported by all studies were collated. Consistent with the meta-regression results, evidence is provided, from 10/19 studies that consider gender as a risk factor, that boys are less likely to have an ADR, and, from 16/17 studies, that risk increases with the number of drugs taken. In addition, 3/3 studies suggest that the risk of ADRs is greater with off-label use. Only two studies considered oncology as a risk factor. The results for the age analyses do not follow a clear pattern and are difficult to interpret due to the variety of age categorisations used.

Tools for assessing causality

Nearly three quarters of the studies (72/102) mentioned a causality assessment, of which the Naranjo algorithm was the most frequently used tool (30/72). Of the 72 studies, seven used a self-assessment method rather than a published causality tool. Despite the majority of studies mentioning a causality assessment, only half of these studies (36/72) reported causality data that were complete for all identified ADRs, specific to the paediatric population and did not include errors as part of the assessment (Table 4).

Tools for assessing severity

Thirty-four (34/102) studies performed an ADR severity assessment. Rates ranged from 0%–66.7% of reported ADRs considered to be severe. By setting, the proportion of ADRs occurring in hospital assessed as severe ranged from 0% to 66.7%, compared with 0% to 45.5% of ADRs causing admission, and 0% to 32.6% of ADRs occurring in the community. Twenty studies provided a reference to indicate the severity tools used, however tools differed widely. Examples of ADRs assessed as severe were those that caused death or were directly life-threatening, caused hospital admission, prolonged hospitalisation or caused transfer to higher level of clinical care.

Assessment of avoidability

Nineteen (19/101) studies performed an avoidability assessment, however, data were only available for 14/19 studies as child only data were not available in 4/19 and ADR specific data were not provided in 1/19. For these 14 studies 7%–98% of ADRs were designated either definitely/possibly avoidable. Three studies provided the rationale for sixty-two avoidable ADRs: inappropriate selection or indication for use of drug (n = 14), inadequate patient education (n = 14), prescribing not rationale (n = 11), lack of appropriate prophylaxis for known ADR (n = 9), lack of appropriate monitoring of drugs (n = 5), previous known ADR to medication (n = 3), dose prescribed was too high (n = 5), inappropriate duration of treatment (n = 1), drug was not prescribed per treatment protocol (n = 1), inappropriate duration of drug and monitoring of treatment (n = 1). Ten studies used a recognised avoidability assessment; of which half used Schumock and Thornton [111] (Table 4).

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Table 4. Cont.

Combined settings (in hospital & in community)

| Study | Country | Setting | Duration | Setting | Children and adults | Naranjo Score | Author |
|-------|---------|---------|----------|---------|---------------------|---------------|--------|
| Doomra 2001 | India | Prospective | 15 months | Various | Children and adults 0–15 years | Naranjo Score Algorithm | Not reported in publication/unable to obtain from author |

Combined settings (causing admission, in hospital & community)

| Study | Country | Setting | Duration | Setting | Children and adults | Naranjo Score | Author |
|-------|---------|---------|----------|---------|---------------------|---------------|--------|
| Al-Tajir 2005 | United Arab Emirates | Prospective | 12 months | General paediatric ward | Children and adults <15 years | Naranjo Score Algorithm | Schumock and Thornton 1992 |
| Buajordet 2002 | Norway | Prospective | 5 months | General paediatric ward | Children 0–16 years | Naranjo Score Algorithm | Not reported in publication/unable to obtain from author |
| Jonville-Bera 2002 | France | Prospective | 1 week | Paediatric wards, A&E, private paediatricians | Children Age not provided | Naranjo Score Algorithm | Begaud et al 1985 |
| Jose and Padma 2006 | India | Prospective | 12 months | Various departments (not stated) | Children and adults 0–15 years | Naranjo Score Algorithm | Lau et al 2003 |
### Table 1: Incidence of Adverse Drug Reactions (ADRs) in Pediatric Patients Across Various Studies

| Study                        | Setting | Events | Total | Prop (in %) | 95% CI     |
|------------------------------|---------|--------|-------|-------------|------------|
| **All patients (single admission)** |         |        |       |             |            |
| ADRIC 2010                   |         | 142    | 6021  | 2.08        | [1.76, 2.45] |
| Jeruelle-Bera 2002           |         | 4      | 260   | 1.54        | [0.42, 1.80] |
| Mitchell 1986                |         | 283    | 73721 | 3.86        | [3.52, 4.33] |
| Palazzini 2000               |         | 10     | 625   | 1.60        | [0.92, 2.34] |
| Szanto 2002                  |         | 14     | 808   | 1.75        | [0.96, 2.93] |
| Yosses & Superstine 1982     |         | 29     | 906   | 3.08        | [2.66, 4.44] |
| Impicciatore 2002            |         | 12     | 116   | 10.54       | [4.60, 17.37] |
| Oshikoya (Ref) 2007          |         | 13     | 3139  | 0.41        | [0.22, 0.71] |
| Oshikoya (Proc) 2007         |         | 4      | 662   | 0.65        | [0.16, 1.49] |
| Speranza 2005                |         | 3      | 173   | 1.73        | [0.36, 4.50] |
| Fatani 2005                  |         | 3      | 408   | 2.22        | [1.02, 4.19] |
| **All patients (some multiple admissions)** |         |        |       |             |            |
| Bujaardt 2002                |         | 35     | 665   | 5.26        | [3.68, 7.34] |
| Gellagher 2010               |         | 10     | 462   | 3.48        | [1.99, 5.55] |
| Whyte 1977                   |         | 12     | 844   | 1.42        | [0.74, 2.47] |
| Bantissadi 1999              |         | 2      | 748   | 0.14        | [0.00, 0.75] |
| Bantu 2006                   |         | 2      | 135   | 2.22        | [0.46, 3.68] |
| Martinez-Mir 1986            |         | 2      | 492   | 4.28        | [2.67, 6.49] |
| **Only patients with prior drug exposure (single admission)** |         |        |       |             |            |
| ADRIC 2010                   |         | 142    | 4655  | 3.05        | [2.57, 3.58] |
| Jeruelle-Bera 2002           |         | 4      | 119   | 3.38        | [0.92, 5.30] |
| Major 1998                   |         | 24     | 457   | 5.25        | [3.38, 7.11] |
| Santos 2000                  |         | 14     | 624   | 2.24        | [1.23, 3.74] |
| Ions 1987                    |         | 8      | 24    | 0.00        | [0.00, 0.14] |
| **Only patients with prior drug exposure (some multiple admissions)** |         |        |       |             |            |
| Martinez-Mir 1986            |         | 2      | 21    | 8.20        | [5.16, 12.27] |
| Geneva 2007                  |         | 4      | 7     | 8.22        | [3.06, 17.04] |
| **All admissions**           |         | 240    | 8345  | 2.20        | [2.53, 3.29] |
| Al-Tair 1986                 |         | 1      | 2591  | 0.00        | [0.00, 0.18] |
| Bujaardt 2002                |         | 49     | 919   | 5.33        | [3.97, 6.99] |
| Gellagher 2010               |         | 19     | 473   | 3.61        | [2.27, 5.55] |
| Hussain 1995                 |         | 13     | 703   | 1.85        | [0.98, 3.14] |
| Lamarche-Bussières 2003      |         | 63     | 39625 | 0.16        | [0.12, 0.20] |
| McDonnell 2002               |         | 8      | 2048  | 0.42        | [0.11, 0.65] |
| McKenzie 1976               |         | 72     | 3598  | 2.02        | [1.56, 2.58] |
| van der Hofstede 2006        |         | 971    | 109947| 0.06       | [0.05, 0.08] |
| van der Hofstede 2008        |         | 1      | 301   | 0.33        | [0.01, 1.04] |
| Whyte 1977                   |         | 12     | 932   | 1.28        | [0.67, 2.24] |
| Easton 1984                  |         | 2      | 1682  | 0.59        | [0.29, 1.09] |
| Easton 2004                  |         | 2      | 2633  | 0.99        | [0.66, 1.42] |
| Martinez-Mir 1986            |         | 2      | 512   | 4.10        | [2.58, 6.23] |
| Gill 1975                    |         | 10     | 969   | 1.10        | [0.52, 2.01] |

#### Setting Key

1. All wards including Oncology
2. Excluding Oncology
3. Infectious diseases department
4. Dermatology department
5. ICU

Figure 1. What proportion of all paediatric hospital admissions are ADR related?
doi:10.1371/journal.pone.0024061.g001
Figure 2. What proportion of children in hospital experience an ADR during their admission?
doi:10.1371/journal.pone.0024061.g002

| Study/ Setting Events Total | Prop in % | 95% CI |
|-----------------------------|-----------|--------|
| Only patients with prior drug exposure (single episode) | | |
| Garcia-Lara 1999 | 1 | 219 | 12.70 | [9.44, 18.97] |
| Jervis-Brolla 2002 | 1 | 227 | 3.84 | [0.89, 6.88] |
| Mitchell 1976 | 1 | 199 | 10.78 | [5.01, 16.00] |
| Clasek 1991 | 2 | 17 | 2078 | 0.82 | [0.48, 1.31] |
| Oksenholt 2002 | 2 | 338 | 12.44 | [7.23, 17.04] |
| O'Keeffe 2005 | 2 | 16 | 24 | 10.87 | [0.00, 5.25] |
| O'Keeffe 2007 (reg) | 2 | 16 | 24 | 0.57 | [0.24, 0.90] |
| Benesimone 2008 | 3 | 155 | 2.23 | [0.68, 7.73] |
| Faulkner 2005 | 5 | 40 | 10.51 | [7.63, 14.06] |
| Reuben 2006 | 6 | 46 | 12.40 | [9.22, 16.18] |
| Only patients with prior drug exposure (some may have had multiple episodes) | | |
| Budnert 2003 | 1 | 165 | 16.13 | [15.09, 21.52] |
| Dharmadhikari 1983 (HIS) | 1 | 6 | 340 | 1.76 | [1.65, 3.00] |
| Dharmadhikari 1983 (HIS) | 1 | 6 | 340 | 0.26 | [0.01, 0.53] |
| Uspall 2000 | 1 | 35 | 1615 | 0.22 | [0.15, 0.30] |
| Whyb 1977 | 1 | 39 | 596 | 6.55 | [4.70, 8.35] |
| Ronassassad 2008 | 2 | 27 | 845 | 3.94 | [2.48, 5.56] |
| Xun 2009 | 2 | 15 | 135 | 11.11 | [0.35, 17.06] |
| Martinez-Mir 1985 | 2 | 59 | 498 | 14.43 | [11.17, 18.71] |
| Viegas & de la Villa 1989 | 2 | 26 | 577 | 4.36 | [3.86, 6.53] |
| Stocker & Merchant 2000 | 3 | 5 | 230 | 2.17 | [0.71, 5.00] |
| Farrell 2006 | 2 | 37 | 270 | 0.77 | [0.37, 1.04] |
| Reuben 2004 | 6 | 31 | 136 | 16.97 | [13.82, 20.70] |
| Weiss 2002 | 8 | 33 | 181 | 16.23 | [12.89, 20.64] |
| All patients (single episode) | | |
| Oksenholt 2002 | 1 | 6 | 260 | 2.31 | [1.89, 4.09] |
| Jha 2007 | 2 | 33 | 272 | 12.12 | [8.05, 16.61] |
| Sparranzo 2008 | 2 | 20 | 173 | 11.56 | [7.72, 17.25] |
| Faulkner 2005 | 5 | 40 | 494 | 9.08 | [7.17, 15.23] |
| All patients (some may have had multiple episodes) | | |
| Budnert 2003 | 1 | 165 | 15.79 | [13.10, 18.19] |
| Dharmadhikari 1983 (HIS) | 1 | 6 | 347 | 1.73 | [1.64, 3.75] |
| Whyb 1977 | 1 | 39 | 392 | 4.18 | [2.99, 5.58] |
| Gool 1994 | 1 | 7 | 82 | 11.20 | [4.68, 21.00] |
| Dojvagola 2008 | 2 | 27 | 740 | 3.95 | [1.42, 5.38] |
| Chomnara 1984 | 1 | 15 | 268 | 5.00 | [3.17, 7.06] |
| Martinez-Mir 1985 | 2 | 59 | 490 | 12.04 | [9.29, 15.25] |
| Teichler 2006 | 3 | 34 | 213 | 16.57 | [13.23, 20.63] |
| Farrell 2005 | 4 | 34 | 194 | 3.19 | [2.66, 4.00] |
| Reuben 2004 | 6 | 31 | 181 | 17.42 | [12.15, 23.80] |
| Only episodes with prior drug exposure | | |
| Oksenholt 2002 | 1 | 382 | 372 | 8.11 | [7.25, 9.03] |
| Low 1998 | 1 | 51 | 499 | 10.22 | [7.70, 12.72] |
| Turner 1997 | 2 | 119 | 396 | 12.39 | [10.35, 14.49] |
| Gool 1995 | 3 | 63 | 89 | 7.01 | [5.43, 8.59] |
| Stocker & Merchant 2000 | 3 | 5 | 232 | 1.98 | [0.65, 4.57] |
| All episodes | | |
| At-Talib 2005 | 1 | 2 | 2351 | 0.09 | [0.01, 0.31] |
| Hoffner 2005 | 1 | 7 | 708 | 10.16 | [7.97, 12.57] |
| Low 2008 | 1 | 1061 | 64643 | 1.66 | [1.56, 1.75] |
| Esteban-Carter 2003b | 2 | 41 | 1742 | 0.22 | [0.16, 0.27] |
| Turner 1989 | 2 | 119 | 1045 | 11.09 | [9.25, 13.15] |
| Farrell 2005 | 4 | 3 | 192 | 2.34 | [1.61, 3.68] |
| Pehrson 2003 | 5 | 6 | 2151 | 0.46 | [0.24, 0.78] |

Setting Key

1. All wards including Oncology
2. Excluding Oncology
3. ICU
4. Surgery
5. Infectious diseases department
6. Isolation ward
7. Paediatric Emergency department
Discussion

This is the largest systematic review of ADRs in children to date and shows clearly that ADRs are an important clinical problem for children and have been the subject of a large number of studies.

Unlike previous systematic reviews [3,4,5], our review searched for studies using a comprehensive search strategy of a large number of databases, including those specific to toxicology and pharmacology. Nineteen databases were searched of which eight retrieved eligible studies. When compared with the previous reviews this resulted in an additional 73 studies being included in our review, of which, in 24, we were able to extract data. We included studies where ADEs had been evaluated, and that included both adults and children. In addition, we contacted authors of studies to obtain unpublished information. As a result, we were able to obtain unreported ADR incidence data for an additional 24/102 studies. This allowed us to make a more informed judgement regarding ADR incidence estimates.

In agreement with previous studies, including those specific to adults [112], this review found that ADR incidence rates were generally higher in hospitalised children than ADR rates causing hospital admission or in an outpatient setting. One of the main difficulties when comparing ADR incidence rates, particularly from observational studies, is that the studies differ in a number of ways, such as clinical setting, population characteristics and study duration. This may explain the large variation in the incidence rates reported. However, since the numerators and denominators used to calculate ADR incidence were not consistent across studies it was not possible to apply statistical methods to comprehensively explore the heterogeneity. Due to the large amount of heterogeneity, a pooled estimate of the incidence rate has been provided for ADRs causing admission only.

Concerning risk factors associated with ADRs, we found evidence, from both univariate meta-regression and the collation of risk factor analyses from individual studies, that the use of multiple drugs is an important predictor of ADRs. This may be due to the additive risk of an ADR when receiving several drugs or to drug-drug interactions.

We report where possible the drugs associated with ADRs and the clinical presentation, although information regarding drugs involved was poorly reported. The types of drugs associated with ADRs differed substantially between studies due to differences between patient populations there were a number of similarities, and many of the drugs analysed in this review are commonly used in children. The results of this review will facilitate a greater understanding of prescribing practices, thus ultimately reduce drug harm. This may help in the development of interventions to improve drug prescribing and monitoring.

We examined the methods used for detecting, and assessing the causality, severity and avoidability of an ADR. The assessment of
### Table 5. Drug class and clinical presentation of ADRs.

| Drug class          | Study                      | Population of study | Total number of ADRs reported in study | Number of ADRs due to drug class (%) | Clinical presentation                                      |
|---------------------|----------------------------|---------------------|----------------------------------------|--------------------------------------|-----------------------------------------------------------|
| **Anti-infectives** |                            |                     |                                        |                                      |                                                           |
|                     | Easton (1998)              | 1682 admissions     | 10                                     | 1 (10%)                              | Colitis, ileus                                            |
|                     | Impicciatore (2002)        | 116 children        | 12                                     | 4 (33.3%)                            | Urticaria, periorbital oedema, neutropenia                |
|                     | Lamababusuriya (2003)     | 39625 admissions    | 63                                     | 38 (60.3%)                           | Erythema multiforme, stevens-johnson syndrome, rash, raised intracranial pressure |
|                     | Oshikoya (2007)            | 3821 children       | 17                                     | 7 (41.1%)                            | Provided for deaths only ×1                              |
|                     | Easton Carter (2004)       | 2933 admissions     | 29                                     | Not reported in publication          | Not reported in publication                             |
|                     | Mitchell (1988)            | 7271 children       | 288                                    | 10 (3.5%)                            | Diarrhoea, fever, erythema multiforme death ×2           |
|                     | Major (1998)               | 457 children        | 26                                     | 6 (23%)                              | Not reported in publication                             |
|                     | Santos (2000)              | 624 children        | 14                                     | 6 (42.8%)                            | Not reported in publication                             |
|                     | Gallagher (2010)           | 462 children        | 18                                     | 3 (16.6%)                            | Diarrhoea                                                |
|                     | Duczmal (2006)             | 4996 admissions     | 58                                     | Not reported in publication          | Not reported in publication                             |
|                     | Ganeva (2007)              | 73 children         | 6                                      | 4 (66.6%)                            | Not reported in publication                             |
|                     | Fattahi (2005)             | 404 children        | 9                                      | 4 (44.4%)                            | Not reported in publication                             |
|                     | Martinez-Mir (1996)        | 490 children        | 21                                     | 10 (47.6%)                           | Not reported in publication                             |
|                     | Yosselson-Superstine (1982)| 906 children        | 29                                     | Not reported in publication          | Not reported in publication                             |
|                     | McKenzie (1976)            | 3556 admissions     | 72                                     | Not reported in publication          | Provided for deaths only ×2                              |
|                     | Gallagher (2011)           | 6821 children       | 249                                    | 16 (6.4%)                            | Diarrhoea, Rash, Vomiting, Lip swelling, Deranged LFTs, Thrush |
| **Anti-epileptics** | Easton (1998)              | 1682 admissions     | 10                                     | 3 (30%)                              | Increased fitting, Rash, aphasia/motor regression         |
|                     | Impicciatore (2002)        | 116 children        | 12                                     | 2 (16.6%)                            | coma                                                      |
|                     | Lamababusuriya (2003)     | 39625 admissions    | 63                                     | 4 (6.3%)                             | Ataxia and cerebellar signs, liver failure, stevens-johnson syndrome |
|                     | Oshikoya (2007)            | 3821 children       | 17                                     | 1 (5.8%)                             | Not reported in publication                             |
|                     | Mitchell (1988)            | 7271 children       | 288                                    | 23 (7.9%)                            | Lethargy, ataxia, rash, erythema                          |
| **Anti-epileptics** | Le (2006)                  | 64 403 admissions   | 35                                     | Not reported in publication          | Not reported in publication                             |
|                     | Santos (2000)              | 624 children        | 14                                     | 1 (7.1%)                             | Not reported in publication                             |
|                     | Yosselson-Superstine (1982)| 906 children        | 29                                     | Not reported in publication          | Not reported in publication                             |
|                     | McKenzie (1976)            | 3556 admissions     | 72                                     | Not reported in publication          | Not reported in publication                             |
|                     | Fattahi (2005)             | 404 children        | 9                                      | 1 (11.1%)                            | Not reported in publication                             |
|                     | Jonville-Bera (2002)       | 260 children        | 4                                      | 1 (25%)                              | Convulsion                                               |
|                     | Gallagher (2011)           | 6821 children       | 249                                    | 2 (0.8%)                             | Constipation, respiratory depression                     |
| **NSAIDS**          | Duczmal (2006)             | 4996 admissions     | 58                                     | Not reported in publication          | Not reported in publication                             |
|                     | Impicciatore (2002)        | 116 children        | 12                                     | 1 (8.3%)                             | Coma                                                     |
|                     | Lamababusuriya (2003)     | 39625 admissions    | 63                                     | 3 (4.7%)                             | Rectal bleeding, Aspirin – Reye syndrome                 |
Table 5. Cont.

Causing admission studies

| Drug class | Study | Population of study | Total number of ADRs reported in study | Number of ADRs due to drug class (%) | Clinical presentation |
|------------|-------|---------------------|---------------------------------------|--------------------------------------|-----------------------|
|            | Major (1998) | 457 children | 26 | 2 (7.6%) | Not reported in publication |
|            | Gill (1995)  | 909 admissions | 10 | 1 (10%) | Not reported in publication |
|            | Gallagher (2011) | 6821 children | 249 | 31 (12.4%) | Post-op bleeding, haematemesis, constipation, abdominal pain |
|            | Gallagher (2010) | 462 children | 18 | 1 (5.5%) | Haematemesis |
|            | Mitchell (1988) | 7271 children | 288 | 12 (4.1%) | Gastritis |
|            | Jonville-Bera (2002) | 260 children | 4 | 1 (25%) | Melaena |
| Cytotoxics | (n = 8) | | | | |
|            | Mitchell (1988) | 7271 children | 288 | Not reported in publication | Deaths ×2 |
|            | Major (1998) | 457 children | 26 | 10 (38.4%) | Not reported in publication |
|            | Santos (2000) | 624 children | 14 | 2 (14.2%) | Not reported in publication |
|            | Yosselson-Superstine (1982) | 906 children | 29 | Not reported in publication | Death ×1 |
|            | McKenzie (1976) | 3556 admissions | 72 | Not reported in publication | Provided for deaths only ×3 |
|            | Fatah (2005) | 404 children | 9 | 2 (22.2%) | Not reported in publication |
|            | Gallagher (2010) | 6821 children | 249 | 110 (44.2%) | Thrombocytopenia, Anaemia, Vomiting, Mucositis, Deranged LFTs, Immunosuppression, Diarrhoea, Nausea, Constipation, Headache, Abdominal pain, Back pain, Haematuria, Leukencephalopathy, Deranged renal function |
|            | Gallagher (2010) | 462 children | 18 | 9 (50%) | Pyrexia, neutropenia, lethargy, decreased responsiveness, vomiting |
| Corticosteroids | (n = 7) | | | | |
|            | Easton (1998) | 1682 admissions | 10 | 1 (10%) | Unstable diabetes |
|            | Santos (2000) | 624 children | 14 | 1 (7.1%) | Upper GI bleed |
|            | Yosselson-Superstine (1982) | 906 children | 29 | Not reported in publication | Not reported in publication |
|            | McKenzie (1976) | 3556 admissions | 72 | Not reported in publication | Not reported in publication |
|            | Ganeva (2007) | 73 children | 6 | 2 (33.3%) | Not reported in publication |
|            | Gallagher (2010) | 6821 children | 249 | 102 (41.0%) | Immunosuppression, Post-op bleeding, Hyperglycaemia, Hypertension, Gastritis, Increased appetite, Impaired healing, adrenal suppression |
|            | Gallagher (2010) | 462 children | 18 | 1 (5.5%) | Vomiting |
| Vaccines | (n = 7) | | | | |
|            | Easton (1998) | 1682 admissions | 10 | 1 (10%) | Hypotonic-hyporesponsive episode |
|            | Lamababusuriya (2003) | 39625 admissions | 63 | 9 (14.2%) | Rash, encephalopathy, fits, head lag |
|            | Easton Carter (2004) | 2933 admissions | 29 | Not reported in publication | Not reported in publication |
|            | Mitchell (1988) | 7271 children | 288 | 5 (1.7%) | Not reported in publication |
|            | Santos (2000) | 624 children | 14 | 1 (7.1%) | Not reported in publication |
|            | Gill (1995) | 909 admissions | 10 | 2 (20%) | Seizures, fever |
|            | Gallagher (2010) | 6821 children | 142 | | Fever, Rash, Irritability, Seizure, Vomiting, Pallor, Apnoea, Limb swelling, Lethargy, Thrombocytopenia Diarrhoea, Abdominal pain, Respiratory distress, Kawasaki disease |
### Table 5. Cont.

#### In hospital studies

**Anti-infectives**

| Study                  | Number of Children/Episodes | Adverse Reactions                                                                                           | Not Reported in Publication |
|------------------------|----------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------|
| Al-Tajir (2005)        | 2351 episodes 2            | Not reported in publication                                                                                    | Not reported in publication |
| Baniasadi (2008)       | 693 children 27            | Not reported in publication                                                                                    | Not reported in publication |
| Choonara (1984)        | 268 children 15            | Vomiting, oral monilia, diarrhoea                                                                              | Not reported in publication |
| Dharmidharka (1993)    | 703 children 7             | Skin rash                                                                                                      | Not reported in publication |
| Dos Santos (2008)      | 265 children 47            | Not reported in publication                                                                                    | Not reported in publication |
| Dos Santos (2009)      | 3726 episodes 302          | Not reported in publication                                                                                    | Not reported in publication |
| Easton Carter (2003b)  | 17432 episodes 41          | Not reported in publication                                                                                    | Not reported in publication |
| Farrokh (2006)         | 81 children 3              | Not reported in publication                                                                                    | Not reported in publication |
| Fattahi (2005)         | 380 children 40            | Not reported in publication                                                                                    | Not reported in publication |
| Gill (1995)            | 899 episodes 76            | Vomiting, rash, diarrhoea, arthropathy, neutropenia, nausea, fits                                            | Not reported in publication |
| Gonzalez-Martin (1998) | 219 children 46            | Not reported in publication                                                                                    | Not reported in publication |
| Jha (2007)             | 943 children 13            | Maculapular rashes, vomiting, diarrhoea, drug fever                                                           | Not reported in publication |
| Jonville-Bera (2002)   | 227 children 6             | Diarrhoea, rash                                                                                                | Not reported in publication |
| Impicciatore (2002)    | 1619 children 29           | Urticaria, increased transaminase levels, vomiting, diarrhoea                                                 | Not reported in publication |
| Le et al (2006)        | 64 403 admissions 1060     | Not reported in publication                                                                                    | Not reported in publication |
| Leach (1998)           | 499 episodes 58            | Vomiting, rash, diarrhoea, arthropathy, neutropenia, nausea, fits                                            | Not reported in publication |
| Mitchell (1979)        | 1669 children 280          | Not reported in publication                                                                                    | Not reported in publication |
| Maistrello (1999)      | 1103 children 59           | Gasto-intestinal disorders,                                                                                   | Not reported in publication |
| Martinez-Mir (1996)    | 490 children 68            | Not reported in publication                                                                                    | Not reported in publication |
| Neubert (2004)         | 156 children 31            | Not reported in publication                                                                                    | Not reported in publication |
| Oshikoya (2007)        | 3821 children 27           | Red man syndrome, pustular rash, stevens-johnson syndrome, erythema, jaundice, anaphylaxis, urticaria, fever  | Not reported in publication |
| Shockrollah (2009)     | 230 children 5             | Not reported in publication                                                                                    | Not reported in publication |
| Turner (1999)          | 936 episodes 157           | Not reported in publication                                                                                    | Not reported in publication |
| Vazquez de la villa (1999) | 597 children 26         | Diarrhoea, vomiting, rash                                                                                   | Not reported in publication |

**Anti-epileptics**

| Study                  | Number of Children/Episodes | Adverse Reactions                                                                                           | Not Reported in Publication |
|------------------------|----------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------|
| Choonara (1984)        | 268 children 15            | Drowsiness, hyperactivity, ataxia                                                                            | Not reported in publication |
| Dharmidharka (1993)    | 703 children 7             | Skin rash                                                                                                      | Not reported in publication |
| Dos Santos (2009)      | 3726 episodes 302          | Not reported in publication                                                                                    | Not reported in publication |
| Easton Carter (2003b)  | 17432 episodes 41          | Not reported in publication                                                                                    | Not reported in publication |
| Gill (1995)            | 899 episodes 76            | Not reported in publication                                                                                    | Not reported in publication |
| Gonzalez-Martin (1998) | 219 children 46            | Not reported in publication                                                                                    | Not reported in publication |
| Le et al (2006)        | 64 403 admissions 1060     | Not reported in publication                                                                                    | Not reported in publication |
| Leach (1998)           | 499 episodes 58            | Apnoea                                                                                                         | Not reported in publication |
| Mitchell (1979)        | 1669 children 280          | Not reported in publication                                                                                    | Not reported in publication |
| Martinez-Mir (1996)    | 490 children 68            | Not reported in publication                                                                                    | Not reported in publication |
| Neubert (2004)         | 156 children 31            | Not reported in publication                                                                                    | Not reported in publication |
| Oshikoya (2007)        | 3821 children 27           | Erythema                                                                                                       | Not reported in publication |
| Table 5. Cont. |  |
| --- | --- |
| **In hospital studies** |  |
| Telechea (2010) | 123 children | 46 | 15 (32.6%) | Not reported in publication |
| Vazquez de la villa (1999) | 597 children | 26 | 4 (15.3%) | Sedation, paradoxil reaction |
| **Corticosteroids (n = 10)** |  |
| Dos Santos (2006) | 265 children | 47 | 11 (23.4%) | Not reported in publication |
| Gill (1995) | 899 episodes | 76 | 6 (7.8%) | Not reported in publication |
| Gonzalez-Martin (1998) | 219 children | 46 | 3 (6.5%) | Not reported in publication |
| Impicciatore (2002) | 1619 children | 29 | 1 (3.4%) | Rash |
| Leach (1998) | 499 episodes | 58 | 1 (1.7%) | Gastric irritation |
| Mitchell (1979) | 1669 children | 280 | Not reported in publication | Not reported in publication |
| Neubert (2004) | 156 children | 31 | Not reported in publication | Not reported in publication |
| Telechea (2010) | 123 children | 46 | 4 (8.6%) | Not reported in publication |
| Turner (1999) | 936 episodes | 157 | 10 (6.3%) | Not reported in publication |
| Vazquez de la villa (1999) | 597 children | 26 | 1 (3.8%) | Cushing syndrome |
| **Bronchodilators (n = 9)** |  |
| Choonara (1984) | 268 children | 15 | 3 (20%) | Tachycardia |
| Easton Carter (2003b) | 17432 episodes | 41 | Not reported in publication | Not reported in publication |
| Gill (1995) | 899 episodes | 76 | 8 (10.5%) | Not reported in publication |
| Gonzalez-Martin (1998) | 219 children | 46 | 8 (17.3%) | Not reported in publication |
| Impicciatore (2002) | 1619 children | 29 | 5 (17.2%) | Tremor, tachycardia |
| Neubert (2004) | 156 children | 31 | Not reported in publication | Not reported in publication |
| Telechea (2010) | 123 children | 46 | 8 (17.3%) | Not reported in publication |
| Turner (1999) | 936 episodes | 157 | 8 (5.0%) | Not reported in publication |
| Vazquez de la villa (1999) | 597 children | 26 | 11 (42.3%) | Tachycardia, nervousness, vomiting |
| **Cytotoxics (n = 7)** |  |
| Dos Santos (2009) | 3726 episodes | 302 | 10 (3.3%) | Not reported in publication |
| Gonzalez-Martin (1998) | 219 children | 46 | 7 (15.2%) | Not reported in publication |
| Jonville-Bera (2002) | 227 children | 6 | 4 (66.6%) | Vomiting |
| **Cytotoxics** |  |
| Le et al (2006) | 64 403 admissions | 1060 | Not reported in publication | Not reported in publication |
| Leach (1998) | 499 episodes | 58 | 1 (1.7%) | Thrombocytopenia |
| Mitchell (1979) | 1669 children | 280 | Not reported in publication | Not reported in publication |
| Telechea (2010) | 123 children | 46 | 1 (2.1%) | Not reported in publication |
| **Diuretics (n = 6)** |  |
| Easton Carter (2003b) | 17432 episodes | 41 | Not reported in publication | Not reported in publication |
| Leach (1998) | 499 episodes | 58 | 1 (1.7%) | Over diureses |
| Mitchell (1979) | 1669 children | 280 | Not reported in publication | Not reported in publication |
| Neubert (2004) | 156 children | 31 | Not reported in publication | Not reported in publication |
| Telechea (2010) | 123 children | 46 | 9 (19.5%) | Not reported in publication |
| Turner (1999) | 936 episodes | 157 | 31 (19.7%) | Not reported in publication |
| **Community** |  |
| **Anti-infectives (n = 13)** |  |
| Cirko-Begovic (1989) | 2459 children | 63 | 49 (78%) | Not reported in publication |
| Community                                      | Number of consultations | Number of children | Reported ADRs                                      | Not reported in publication                                                                 |
|-----------------------------------------------|-------------------------|--------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------|
| **Table 5. Cont.**                            |                         |                    |                                                  |                                                                                             |
| Easton-Carter (2003a)                         | 8601                    | 118                | Not reported in publication                      | Not reported in publication                                                                 |
| Horen (2002)                                  | 1419                    | 20                 | 9 (45%)                                          | Not reported in publication                                                                 |
| Junitti-Patinen (2006)                        | Not reported for children| 4                 | Not reported for children only                   | Not reported for children only                                                               |
| Kaushal (2007)                                | 1689                    | 226                | 158 (70%)                                        | Nausea, vomiting and diarrhoea.                                                               |
| Kramer (1985)                                 | 4244                    | 200                | Not reported in publication                      | Diarrhoea, other gastrointestinal complaints and skin rashes                                 |
| Menniti-Ippolito (2000)                       | 7890                    | 119                | 79 (66%)                                         | Cutaneous, gastrointestinal, eosinophilia, neurological, angioedema, fever                    |
| Planchamp (2009)                              | 12995                   | 43                 | Not reported in publication                      | Not reported in publication                                                                 |
| Sanz (1987)                                  | 1327                    | 10                 | 4 (40%)                                          | Cutaneous reaction and diarrhoea                                                             |
| Munoz (1998)                                  | 47107                   | 447                | 49.5%                                            | Included skin reactions                                                                     |
| Jonville-Bera (2002)                         | A&E: 428 children        | Private paediatricians: 1192 | A&E: 2 (50%)                                    | Private paediatricians: 6 (75%)                                                             |
| Anti-infectives                               |                         |                    |                                                  |                                                                                             |
| Woods (1987)                                 | 1590                    | 235                | 40 (17%)                                         | Diarrhoea, drowsiness, rash, headache, hyperactivity, anorexia, abdominal pain, vomiting, sleep disturbance |
| Zahraoui (2010)                               | Not reported            | 24                 | Not reported in publication                      | Not reported in publication                                                                 |
| **NSAIDs (n = 6)**                            |                         |                    |                                                  |                                                                                             |
| Kaushal (2007)                                | 1689                    | 226                | 2 (1%)                                           | Not reported in publication                                                                 |
| Menniti-Ippolito (2000)                       | 7890                    | 119                | 3 (3%)                                           | Cutaneous, haematuria, hypertranspiration                                                    |
| Munoz (1998)                                 | 47107                   | 447                | Not reported                                     | Not reported in publication                                                                 |
| Planchamp (2009)                              | 12995                   | 43                 | Not reported in publication                      | Not reported in publication                                                                 |
| Sanz (1987)                                  | 1327                    | 10                 | 1 (10%)                                          | Not reported in publication                                                                 |
| Woods (1987)                                 | 1590                    | 235                | 9 (4%)                                           | Drowsiness, abdominal pain, aggressiveness, vomiting                                         |
| **Analgesics (n = 5)**                        |                         |                    |                                                  |                                                                                             |
| Kaushal (2007)                                | 1689                    | 226                | 1 (0.4%)                                         | Not reported in publication                                                                 |
| Munoz (1998)                                 | 47107                   | 447                | Not reported in publication                      | Not reported in publication                                                                 |
| Planchamp (2009)                              | 12995                   | 43                 | Not reported in publication                      | Not reported in publication                                                                 |
| Sanz (1987)                                  | 1327                    | 10                 | 1 (10%)                                          | Not reported in publication                                                                 |
| Woods (1987)                                 | 1590                    | 235                | 11 (5%)                                          | Drowsiness, irritability, aggressiveness                                                     |
| Zahraoui (2010)                               | Not reported            | 24                 | Not reported in publication                      | Not reported in publication                                                                 |
| **Vaccines (n = 5)**                          |                         |                    |                                                  |                                                                                             |
| Horen (2002)                                  | 1419                    | 20                 | 5 (25%)                                          | Not reported in publication                                                                 |
| Jonville-Bera (2002)                         | A&E: 428 children        | Private:1192 children | A&E: 1 (25%)                                    | Private: 2 (25%)                                                                            |
| Menniti-Ippolito (2000)                       | 7890                    | 119                | 14 (12%)                                         | Not reported in publication                                                                 |
| Munoz (1998)                                 | 47107                   | 447                | ? 9.2%                                           | Not reported in publication                                                                 |
| Planchamp (2009)                              | 12995                   | 43                 | Not reported in publication                      | Not reported in publication                                                                 |
| **Antihistamine (n = 4)**                    |                         |                    |                                                  |                                                                                             |
| Cirko-Begovic (1989)                         | 2459                    | 63                 | 2 (3%)                                           | Not reported in publication                                                                 |
| Kaushal (2007)                                | 1689                    | 226                | 2 (1%)                                           | Not reported in publication                                                                 |
| Menniti-Ippolito (2000)                       | 7890                    | 119                | 2 (2%)                                           | Not reported in publication                                                                 |
| Community | Woods (1987) | 1590 children | 235 | 46 (20%) | Drowsiness, aggressiveness, dry mouth, headache, irritability, diarrhoea |
|-----------|--------------|---------------|-----|---------|-----------------------------------------------------------------------|
| Bronchodilators (n = 3) | | | | | |
| Kaushal (2007) | 1689 children | 226 | 16 (7%) | Not reported in publication |
| Kramer (1985) | 4244 courses of therapy | 200 | Not reported in publication | Various manifestations of central nervous stimulation |
| Woods (1987) | 1590 children | 235 ADRs | 6 (3%) | Hyperactivity, shakiness, dizziness, irritability, sleep disturbance. |
| Steroid (n = 3) | | | | | |
| Horen (2002) | 1419 consultations | 20 | 1 (0.05%) | Not reported in publication |
| Kaushal (2007) | 1689 children | 226 | 12 (5%) | Not reported in publication |
| Woods (1987) | 1590 children | 235 | 5 (2%) | Abdominal pain, diarrhoea |
| Combined settings (causing admission & in hospital) | | | | | |
| Anti-infectives (n = 2) | | | | | |
| Haffner (2006) | 703 admissions | 101 | Not reported in publication | Not reported in publication |
| Speranza (2008) | 173 children | 24 | 10 (41.6%) | Not reported in publication |
| Bronchodilators (n = 1) | | | | | |
| Haffner (2006) | 703 admissions | 101 | Not reported in publication | Not reported in publication |
| Anti-epileptics (n = 2) | | | | | |
| Haffner (2006) | 703 admissions | 101 | Not reported in publication | Not reported in publication |
| Speranza (2008) | 173 children | 24 | 4 (16.6%) | Not reported in publication |
| Cardiovascular (n = 1) | | | | | |
| Haffner (2006) | 703 admissions | 101 | Not reported in publication | Not reported in publication |
| Analgesics (n = 1) | | | | | |
| Speranza (2008) | 173 children | 24 | 2 (8.3%) | Not reported in publication |
| Anti-ulcer (n = 1) | | | | | |
| Speranza (2008) | 173 children | 24 | 2 (8.3%) | Not reported in publication |
| Psychotropic (n = 1) | | | | | |
| Speranza (2008) | 173 children | 24 | 2 (8.3%) | Not reported in publication |
| Combined settings (in hospital & community) | | | | | |
| Anti-infectives (n = 1) | | | | | |
| Kushwaha (1994) | 20310 admissions | 267 | Not reported in publication | Erythematous maculopapular rash, thrombophlebitis, erythema multiforme, fixed drug reaction, urticaria, jaundice, aplastic anaemia, thrombocytopenia purpura |
| Vaccines (n = 1) | | | | | |
| Kushwaha (1994) | 20310 admissions | 267 | Not reported in publication | Nodular cyst in gluteal region, injection abscess |
| NSAID (n = 1) | | | | | |
| Kushwaha (1994) | 20310 admissions | 267 | Not reported in publication | Erythematous maculopapular rash |
causality in individual cases of ADRs is required to establish whether there is an association between the untoward clinical event and the suspected drug [6]. The detection of ADRs depends on the validity and reliability of the tests employed and if sensitive methods are performed, in theory, all ADRs should be detected. We found a third (31/102) of studies did not report which causality assessment they used, with an additional six not using a recognised algorithm. As a consequence there may be either an underestimation or overestimation of ADRs in these studies. Over a third of studies (34/102) assessed ADRs for the severity of the reactions; just eight of which did not report any severe ADRs. Severe ADRs were described as those that caused either death or were directly life-threatening, caused hospital admission, prolonged hospitalisation or caused transfer to higher level of clinical care [113]. The ability to classify ADRs by severity provides a mechanism for clinicians to identify problem areas and implement interventions to inform paediatric pharmacovigilance practice.

The absence of avoidability data was most noticeable in this review; with only fourteen studies (14/102; 14%) providing avoidability data. Therefore it is not possible to consider this important aspect of drug safety in order to prevent future ADRs [7]. Further studies are clearly required to determine which ADRs are potentially avoidable. These studies could provide the necessary data in order to enable clinicians to administer medications in the safest and appropriate way.

The reporting quality of some of the included studies was poor, which may have affected the results. Not all provided a clear definition of the term ‘adverse drug reaction’; often insufficient information was in the publication in order to determine whether ADRs included medication or prescribing errors. ADR incidence data were not always clearly described in the publications. In many studies (n = 48/102) reporting was unclear regarding whether the incidence rate was reported at the patient and/or episode level and whether or not all children had been exposed to a drug.

It is disappointing given the large number of studies we identified which addressed this problem that most did not include these important methodological aspects. We recommend researchers should consider the approach which we have taken to assess the quality of these studies, although we recognise that further work is needed to develop a quality assessment tool which meets rigorous standards of development. We recommend that future studies provide information on the avoidability of ADRs; this may help in the development of interventions to improve drug prescribing and

| Table 5. Cont. |
| --- |
| **Combined settings (in hospital & community)** |
| **Analgesic**  
(n = 1) |
| Kushwaha (1994)  
20310 admissions  
267  
Not reported in publication  
Erythematous maculopapular rash, urticaria |
| **Steroid**  
(n = 1) |
| Kushwaha (1994)  
20310 admissions  
267  
Not reported in publication  
Injection abscess |

| **Combined settings (causing admission, in hospital & community)** |
| --- |
| **Steroid**  
(n = 1) |
| McKenzie (1973)  
658 children  
175  
Not reported in publication  
Psychotic reaction, cushingoid syndrome, cataracts, hypertension |
| **Anti-infectives**  
(n = 1) |
| McKenzie (1973)  
658 children  
175  
Not reported in publication  
Rash, diarrhoea, facial flush, monilia, pain in injection site |
| **Cytotoxics**  
(n = 1) |
| McKenzie (1973)  
658 children  
175  
Not reported in publication  
Alopecia, peripheral neutitis, mouth ulcer, injection site inflammation, leukopenia, secondary infection |

Note 1 patient in the Zahraoui (2010) study died (gastrointestinal bleeding and severe thrombocytopenia after prolonged anti-convulsant treatment. Mitchell (1988) – 5 deaths (fever, vomiting, arrhythmia and cardiopulmonary arrest attributed to theophylline and erythromycin; cardiac arrest and hypernatremia attributed to halothane and nitrous oxide pneumonia attributed to chemotherapy-induced immunosuppression; cardiotoxicity attributed to doxorubicin; candida sepsis and meningitis attributed to chemotherapy-induced immunosuppression). Yosselson-Superstine (1982) – 1 death (no detail provided). doi:10.1371/journal.pone.0024061.0005

| Table 6. Univariate meta-regression results for causing admission and in hospital incidence rates. |
| --- |
| **Covariate** | **OR (95% CI)** | **P** |
| Setting: Admission | | |
| Hospital | 2.73 (0.93,8.03) | 0.07 |
| % Female patients | 1.13 (0.91,1.40) | 0.23 |
| Mean age (years) | 0.71 (0.39,1.27) | 0.21 |
| Mean/median number of drugs | 1.49 (1.14,1.94) | 0.01 |
| % Oncology patients | 1.15 (0.89,1.50) | 0.25 |

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monitoring. There are several outcomes that warrant further investigation or require more detailed information to be collected. Important risk factor data and the number of medications each child received needs to be reported fully in order to explore possible sources of heterogeneity between studies. Future studies need to use clear, unambiguous terminology to describe how ADR incidence rates are calculated. This would improve understanding of the clinical relevance of individual study findings and allow comparisons between studies for the purposes of systematic review, enabling more robust conclusions and recommendations.

This review confirms previous studies which have shown ADRs to be a significant problem in children and has highlighted therapeutic classes of drugs most commonly associated with them. We strongly recommend further work to address prescribing practices in different settings and avoidability of ADRs is needed to indicate how such ADRs may be prevented.

Supporting Information

Figure S1 Flow diagram.

TIF

Checklist S1 PRISMA Checklist.

DOC

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Author Contributions

Conceived and designed the experiments: PRW RLS RMS SG JJK EG. Performed the experiments: PRW RLS RMS JJK LC SG. Analyzed the data: PRW RLS RMS EG JJK LC SG. Contributed reagents/materials/analysis tools: PRW RLS RMS EG SG JJK LC. Wrote the paper: PRW RLS RMS EG JJK LC SG.

References

1. Wester K, Jonsson AK, Spigset O, Druud H, Hagg S (2008) Incidence of fatal adverse drug reactions: a population based study. Br J Clin Pharmacol 65: 573–579.
2. (WHO) WHO (2002) Safety of Medicines - a guide to detecting and reporting adverse drug reactions. WHO, Geneva.
3. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, et al. (2001) Incidence of adverse drug reactions in paediatric in/out-patients: A systematic review and meta-analysis of prospective studies. British Journal of Clinical Pharmacology 52: 77–83.
4. Clavenna A, Bonati M (2009) Adverse drug reactions in childhood: a review of prospective studies and safety alerts. Arch Dis Child 94: 724–729.
5. Aagaard L, Christensen A, Hansen EH (2010) Information about adverse drug reactions reported in children: a qualitative review of empirical studies. Br J Clin Pharmacol 70: 481–491.
6. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, et al. (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30: 239–245.
7. Schumock GT, Thornton JP (1992) Focusing on the preventability of adverse drug reactions. Hospital Pharmacy 27: 530.
8. WHO (1997) International drug monitoring: the role of national centres. Tech Rep Ser 496.
9. Duzczal E, Berborowicz A (2006) Adverse drug reactions as a cause of hospital admission. Przegląd Pediatryczny 36: 14–18.
10. Easton KL, Chapman CB, Brien JE (2004) Frequency and characteristics of hospital admissions associated with drug-related problems in paediatrics. British Journal of Clinical Pharmacology 57: 611–615.
11. Hewitt J (1995) Drug-related unplanned readmissions to hospital. Australian Journal of Hospital Pharmacy 25: 400–407.
12. Ives TJ, Benzij EJ, Gowyber RE (1987) Drug-related admissions to a family medicine inpatient service. Archives of Internal Medicine 147: 1117–1120.
13. McDonnell PJ, Jacobs MR (2002) Hospital admissions resulting from preventable adverse drug reactions.[see comment]. Annals of Pharmacotherapy 36: 1331–1339.
14. McKenize MW, Marchall GL, Netzelf ML, Cluff LE (1976) Adverse drug reactions leading to hospitalization in children. J Pediatr 89: 467–490.
15. Mitchell AA, Lacouture PG, Sherehan JE, Kaufmann RE, Shapiro S (1980) Adverse drug reactions in children leading to hospital admission. Pediatrics 62: 24–29.
16. Santos RP, Benjamin G, Paje-Villar E (2000) Drug-related hospitalization among pediatric patients in a tertiary hospital Santo Tomas. Journal of Medicine 49: 141–152.
17. van der Hooft CS, Sturkenboom MCM, van Grootheest K, Kinnga HJ, Stricker BHC (2006) Adverse drug reaction-related hospitalisations: a nationwide study in The Netherlands. Drug Safety 29: 161–168.
18. Youseme-Supreme X, Weiss T (1982) Drug-related hospitalization in pediatric patients. J Clin Hosp Pharm 7: 195–203.
19. Bordet R, Gautier S, Le Louet H, Dupuis B, Caron J (2001) Analysis of the direct cost of adverse drug reactions in hospitalised patients. European Journal of Clinical Pharmacology 56: 933–941.
20. Impicciatore P, Moin A, Chiarelli F, Pandolfini C, Bonati M (2002) Adverse drug reactions to off-label drugs on a paediatric ward: An Italian prospective pilot study. Paediatric and Perinatal Drug Therapy 5: 19–24.
21. Kumar DL, Kennedy J, Austin N, Reith D (2009) Incidence, preventability, and impact of Adverse Drug Events (ADEs) and potential ADEs in hospitalized children in New Zealand: a prospective observational cohort study. Paediatric Drugs 11: 153–160.
22. Le J, Nguyen T, Law AV, Hoddinig J (2005) Retrospective analysis of adverse drug reactions in pediatrics over a 10-year period. Pharmacotherapy 25: 1432.
23. Osakbaya KA, Nwakaoma OF, Ghilfunctional HA, Ojo RO (2007) Adverse drug reactions in Nigerian children. Paediatric and Perinatal Drug Therapy 8: 81–88.
24. Whyte J, Greenan E (1977) Drug usage and adverse drug reactions in paediatric patients. Acta Paediatrica Scandinavica 66: 767–775.
25. Al-Tajir G, Kelly WN (2005) Epidemiology, comparative methods of detection, and preventability of adverse drug events. Annals of Pharmacotherapy 39: 1169–1174.
26. Bujaforder I, Wessenberg F, Boers O, Langlet A (2002) Adverse drug event in children during hospitalization and after discharge in a Norwegian University Hospital. Acta Paediatrica, International Journal of Paediatrics 91: 88–94.
27. Gallagher (2011) Adverse drug reactions causing admission to a paediatric hospital: a pilot study. J Clin Pharm Ther 36: 194–199.
28. Sporanza N, Lucas L, Teleschea H, Santaruo A, Giachetto G, et al. (2008) Adverse Drug Reactions in Hospitalized Children A Public Health Problem. Drug Safety 31(10): 805–906. doi: 10.2165/0002018-200831100-00007.
29. Gallagher (2011) Adverse Drug Reactions Causing Admission to a Paediatric Hospital Unpublished.
30. Eston KL, Parsons BJ, Starr M, Brien JE (1998) The incidence of drug-related problems as a cause of hospital admissions in children. Medical Journal of Australia 169: 336–343.
31. Lanabasabasaci SP, Sathiadas G (2003) Adverse drug reactions in children requiring hospital admission. Ceylon Medical Journal 48: 86–87.
32. Major S, Badr S, Bahalwan I, Hassan G, Khoglaishanian T, et al. (1998) Drug-related hospitalization at a tertiary teaching center in Lebanon: Incidence, associations, and relation to self-prescribing behavior. Clinical Pharmacology & Therapeutics 64: 450–461.
33. Poyanne P, Haramburu F, Imbs JL, Bagaud B (2000) Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. French Pharmacovigilance Centres. BMJ 320: 1036.
34. McKenize MW, Stewart RB, Weiss CF, Cluff LE (1973) Pharmacist-based study of the epidemiology of adverse drug reactions in pediatric medicine patients. American Journal of Hospital Pharmacy 30: 898–903.
35. At-Olah YH, Al Thabi KM (2008) Admissions through the emergency department due to drug-related problems. Annals of Saudi Medicine 28: 429–429.
36. Schnerewiss S, Hasford J, Gottler M, Hoffmann A, Rielhing A-K, et al. (2002) Admissions caused by adverse drug reactions to medical and emergency departments in hospitals: a longitudinal population-based study. European Journal of Clinical Pharmacology 58: 285–291.
37. Jouville-Bera AP, Giraudreau B, Blanc P, Beau-Salinia F, Astoret-Laca E (2002) Frequency of adverse drug reactions in children: A prospective study. British Journal of Clinical Pharmacology 53: 207–210.
38. van der Hooft CS, Dieleman JP, Niemel G, Azarnoudi A, Hjverhamme KMC, et al. (2008) Adverse drug reaction-related hospitalizations: A population-based cohort study. Pharmacoeconomics and Drug Safety 17: 365–371.
39. Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, et al. (1995) Adverse drug reactions in a paediatric intensive care unit. Acta Paediatrica, International Journal of Paediatrics 84: 438–441.

40. Haffner S, von Laue N, Wirth S, Thurnhammer PA (2005) Detecting adverse drug reactions on paediatric wards - Improved surveillance versus computerised screening of laboratory values. Drug Safety 28: 453–464.

41. Baniasadi S, Fahimi F, Shaviri G (2008) Developing an adverse drug reaction reporting system at a teaching hospital. Base & Clinical Pharmacology & Toxicology 102: 409–411.

42. Claassen DC, Pestonik SL, Evans RS, Burke JP (1991) Computerized surveillance of adverse drug events in hospital patients. Journal of the American Medical Association 266: 2047–2051.

43. Fischbach (1989) Pilot Study of Adr Reporting by Physicians - Phase II. ASHP Annual Meeting: 41.

44. Ramesh S, Pandit J, Tothill RN, Heath CE, Smith NA, et al. (2001) Adverse drug reactions in a South Indian hospital - Their severity and cost involved. Pharmacoeconomics and Drug Safety 12: 687–692.

45. Seidl TG, Thornton GE, Smith JW, Cliff LE (1966) Studies on the epidemiology of adverse drug reactions III. Reactions in patients on a general medical service. The Johns Hopkins Hospital bulletin 119: 299–315.

46. Smith NA, McQueen EG (1972) Adverse reactions to drugs: a comprehensive hospital inpatient survey. New Zealand Medical Journal 76: 397–401.

47. Jose J, Rao PGM (2006) Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. Pharmacological Research 55: 231–236.

48. Ganeva M, Gianchetti V, Lazareva R, Tetzrofina Y, Heistikova E (2007) A prospective study of adverse drug reactions in a dermatology department. Methods & Findings in Experimental & Clinical Pharmacology 29: 107–112.

49. Fattahi F, Pourpak Z, Moin M, Kazeremnejad A, Khoterei GT, et al. (2005) Adverse drug reactions in hospitalized children in a department of infectious diseases. Journal of Clinical Pharmacology 45: 1311–1318.

50. Martinez-Mir I, Garcia LM, Palop V, Ferrer JM, Estan L, et al. (1996) A prospective study of adverse drug reactions as a cause of admission to a paediatric hospital. British Journal of Clinical Pharmacology 42: 319–324.

51. Barstow L, Vorce-West T, Buncher CR (1988) Comparative Study of Three Voluntary Adr Reporting Systems. Ashp Midyear Clinical Meeting 23: P-290.

52. Choanor A, Harris P (1984) Adverse drug reactions in medical inpatients. Archives of Disease in Childhood 59: 578–580.

53. Dhamimadarka VR, Kandoth PN, Anand RK (1993) Adverse drug reactions in pediatrics with a study of in-hospital intensive surveillance. Indian Pediatrics 30: 745–751.

54. dos Santos DB, Coelho HLL (2006) Adverse drug reactions in hospitalized children in Fortaleza, Brazil. Pharmacoeconomics & Drug Safety 15: 635–640.

55. Easton-Carter KL, Chapman CB, Brien JE (2003) Emergency department attendances associated with drug-related problems in paediatrics. Journal of Paediatrics and Child Health 39: 124–129.

56. Gonzalez-Martín G, Caroca CM, Paris E (1998) Adverse drug reactions (ADRs) in hospitalized pediatric patients. A prospective study. International Journal of Clinical Pharmacology and Therapeutics 36: 330–335.

57. Baz N, Bajcarova O, Nasuyal T (2007) Prevalence of adverse drug reactions in hospital patients with commonly prescribed drugs in different hospitals of Khamtani valley.[see comment]. Kathmandu University Medical Journal 5: 504–510.

58. Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, et al. (2001) Adverse drug reactions and adverse drug events in hospitals participating in the California Pediatric Drug Safety Project. Pediatrics 108: 651–658.

59. Mitchell AA, Goldman P, Shapiro S, Stone D (1979) Drug utilization and adverse drug events in pediatric inpatients. Journal of Clinical Pharmacology and Therapeutics 36: 530–533.

60. Mitchell AA, Goldman P, Shapiro S, Stone D (1979) Drug utilization and adverse drug events in pediatric inpatients. Journal of Clinical Pharmacology and Therapeutics 36: 530–533.

61. Neubert A, Bornmann H, Weiss J, Egger T, Criegee-Rieck M, et al. (2004) The prevalence of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. Drug Safety 27: 1059–1067.

62. Neubert A, Bornmann H, Weiss J, Criegee-Rieck M, Ackermann A, et al. (2006) Are computerised monitoring systems of value to improve pharmacovigilance in paediatric patients? European Journal of Clinical Pharmacology 62: 929–935.

63. Weiss J, Krebs S, Hoffmann C, Werner U, Neubert A, et al. (2002) Survey of adverse drug reactions on a paediatric ward: A strategy for early and detailed detection. Pediatrics 110: 254–257.

64. Farrokh S, Nahta H, Pourpak Z, Moin M, MajdiNasab P, et al. (2006) Adverse drug reactions in a department of pediatric surgery. Journal of Tropical Pediatrics 52: 72–73.

65. Imbs JL, Pouyanne P, Haramburu F, Welsch M, Decker N, et al. (1999) [Iatrogenic medication: estimate of its prevalence in French public hospitals. Regional Centers of Pharmacovigilance]. Therapie 54: 21–27.

66. Mitchell AA, Goldman P, Shapiro S, Stone D (1979) Drug utilization and adverse drug reactions in hospitalized children. American Journal of Diseases in Children 110: 196–204.

67. Turner S, Nunn AJ, Fielding K, Choanor A (1999) Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatrica 88: 965–968.

68. Donnurna R, Gupta SK (2001) Intensive adverse drug reaction monitoring in various specialty clinics of a tertiary care hospital in North India. International Journal of Medical Toxicology and Legal Medicine 4: 1–14.

69. Maistrello I, Di Pietro P, Renna S, Boscaini M, Nobili A (1999) A surveillance-oriented medical record as a source of data for both drug quality and care of surveillance. Pharmacoeconomics and Drug Safety 8: 131–139.

70. Calderon-Osmina G, Orozco-Diaz J (2008) [Adverse drug reactions as the reason for visiting an emergency department]. Revista de Salud Publica 10: 315–321.

71. Cirko-Begovic A, Vrhovac B, Bakran I (1989) Intensive monitoring of adverse drug reactions in infants and preschool children. European Journal of Clinical Pharmacology 36: 63–65.

72. Demehy CE, Kishi DT, Louie C (1996) Drug-related illness in emergency department patients. Am J Health Syst Pharm 53: 1422–1426.

73. Doval DN, Gualati C, Bhargava A (1981) A survey of adverse effects of drugs in an outpatient population. Indian Journal of Public Health 25: 133–138.

74. Phan H, Leder M, Fuldlye M, Moeller M, Nahata M (2010) Off-label and unlicensed medication use and associated adverse drug events in a pediatric emergency department. Pediatric Emergency Care 26: 424–430.

75. Easton-Carter KL, Chapman CB, Brien JE (2003) Adverse drug reactions in paediatrics: Are we getting the full picture? Journal of Pharmacy Practice and Research 33: 106–110.

76. Junti-Patinen I, Kuutinen T, Pere P, Neuvonen PJ (2006) Drug-related visits to a district hospital emergency room. Basic and Clinical Pharmacology and Toxicology 90: 212–217.

77. Planchamp F, Nguyen KA, Vial T, Nasiri S, Javouhey E, et al. (2009) Active drug monitoring of adverse drug reactions in pediatric emergency department. Archives de Pediatric 16: 106–111.

78. Prince BS, Goetz CM, Rihon TL, Oksly M (1992) Drug-related emergency department visits and hospital admissions. Am J Hosp Pharm 49: 1096–1070.

79. Rebollo Gomes E, Fonseca J, Araujo L, Demoly P (2008) Drug allergy claims in children: From self-reporting to confirmed diagnosis. Clinical and Experimental Allergy 38: 191–198.

80. Sharma H, Agui M, Inam F, Alam MS, Kapur P, et al. (2007) A pharmacovigilance study in the Department of Medicine of a University Teaching Hospital. Pharmacovigilance Practice and Research 5: 46–49.

81. Stokides CA, D'Agostino PR, Kaufman MB (1993) Adverse drug reaction surveillance in an emergency room. Am J Hosp Pharm 50: 712–714.

82. Valladare J, Ferrer JM, Palop V, Rubio E, Morales Olivas EJ (1992) [Adverse reactions to medications in patients in an ambulance service]. Revista de Atencion Primaria 11: 92–98.

83. Otero Lopez MJ, Bajo Bajo A, Medreroa Fernandez JA, Domínguez-Gil Hurle A (1999) Preventable adverse drug events in a hospital Emergency Department. Revista Clinica Espanola 199: 736–805.
95. Smith KM, McAdams JW, Frenia ML, Todd MW (1997) Drug related problems in emergency department patients. American Journal of Health-System Pharmacy 54: 295–298.
96. Kushwaha KP, Verma RB, Singh YD, Rathi AK (1994) Surveillance of drug induced diseases in children. Indian Journal of Pediatrics 61: 357–365.
97. Zahraoui M (2010) Study for developing intensive pharmacovigilance system at paediatric emergency department. Fundamental and Clinical Pharmacology 24.
98. Horen B, Montastruc J-L, Lapeyre-Mestre M (2002) Adverse drug reactions and off-label drug use in paediatric outpatients. British Journal of Clinical Pharmacology 54: 665–670.
99. Kaushal R, Goldmann DA, Krohane CA, Christine M, Honour M, et al. (2007) Adverse drug events in pediatric outpatients. Ambulatory Pediatrics 7: 393–399.
100. Kramer MS, Hutchinson TA, Flegel KM, Naimark L, Contardi R, et al. (1985) Adverse drug reactions in general pediatric outpatients. Journal of Pediatrics 106: 305–310.
101. Martyr CR (1979) Adverse reactions to drugs in general practice. British Medical Journal 2: 1194–1197.
102. Menniti-Ippolito F, Rascetti R, Da Cas R, Giaquinto C, Cantarutti L, et al. (2000) Active monitoring of adverse drug reactions in children. Lancet 355: 1613–1614.
103. Lerner C, Bates DW, Yoon C, Krohane C, Fitzmaurice G, et al. (2009) The role of advice in medication administration errors in the pediatric ambulatory setting. Journal of patient safety 5: 168–175.
104. Miller GC, Britt HC, Valenti L (2006) Adverse drug events in general practice patients in Australia. Medical Journal of Australia 184: 321–324.
105. Mulroy R (1973) Iatrogenic disease in general practice: its incidence and effects. British Medical Journal 2: 407–410.
106. Saiz E, Boida J (1987) Adverse drug reactions in pediatric outpatients. Int J Clin Pharmacol Res 7: 169–172.
107. Woods CG, Rylance ME, Cullen RE, Rylance GW (1987) Adverse reactions to drugs in children. Br Med J 294: 869–870.
108. Lewinski D, Wind S, Belgardt C, Plate V, Behles C, et al. (2010) Prevalence and safety-relevance of drug-related problems in German community pharmacies. Pharmacoepidemiology & Drug Safety 19: 141–149.
109. Knopf H, Du Y (2010) Perceived adverse drug reactions among noninstitutionalized children and adolescents in Germany. British Journal of Clinical Pharmacology 70: 409–417.
110. Campbell WH, Johnson RE, Senft RA (1978) Adverse drug reactions in a disadvantaged population. J Community Health 3: 205–215.
111. Schumock GT, Thornton JP (1992) Focusing on the preventability of adverse drug reactions. Hosp Pharm 27: 538.
112. Lazarou J, Pomeranz BH, Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 279: 1200–1205.
113. Hartwig SC, Siegel J, Schneider PJ (1992) Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 49: 2229–2232.