Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies

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Aims To explore the usefulness of data derived from observational studies on adverse drug reactions (ADRs) in defining and preventing the risk of pharmacological interventions in children in different health care settings.

Methods A systematic review of studies on ADRs in hospitalized children, in outpatient children, and on ADRs causing paediatric hospital admissions was performed. Studies were identified through a search of the MEDLINE and EMBASE databases. The inclusion criteria required that the population was not selected for particular conditions or drug exposure and prospective monitoring was used for identifying ADRs. Data were analysed by a random-effects model.

Results Seventeen prospective studies were included. In hospitalized children, the overall incidence of ADRs was 9.53% (95% confidence interval [CI], 6.81,12.26); severe reactions accounted for 12.29% (95%CI, 8.43,16.17) of the total. The overall rate of paediatric hospital admissions due to ADRs was 2.09% (95%CI, 1.02,3.77); 39.3% (95%CI, 30.7,47.9) of the ADRs causing hospital admissions were life threatening reactions. For outpatient children the overall incidence of ADRs was 1.46% (95%CI, 0.7,3.03).

Conclusions The results show that ADRs in children are a significant public health issue. The completeness and accuracy of prescription reporting as well as clinical information from studies was a rarity, making it difficult for health practitioners to implement evidence based preventive strategies. Further, methodologically sound drug surveillance studies are necessary for an effective promotion of a safer use of drugs in children.

Keywords: adverse drug reactions, child, meta-analysis, prospective studies, systematic review

Introduction

The safety of drug prescribing has become a highly visible topic in adult medicine, due in part to research suggesting that there are important ADRs caused by commonly used medications [1]. Much less attention has been focused on neonates, infants, children and adolescents [2, 3].

Paediatric patients constitute a vulnerable group with regard to rational drug prescribing since many new drugs are released onto the market without the benefit of even limited experience in this age group [4]. This deficiency causes paediatricians to often prescribe children drugs in an 'off-label' manner, thereby increasing the risk of drug toxicity [5].

Adequate controlled clinical trials in children are lacking, mainly because of issues of cost and responsibility, and to regulations that frequently act as major obstacles [6]. Moreover, until recently, the few clinical trials that had been performed involving children focused on the efficacy of drugs and rarely monitored their safety [7].

Meta-analysis is already a well-established methodological approach for evaluating the effectiveness of therapies. However, in contrast to the published experience of using meta-analysis to evaluate drug efficacy, the use of this

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method to also quantify the risk of therapies remains limited to date [8]. A recently published meta-analysis on the incidence of ADRs in hospitalized US patients shows that ADRs represent an important public health issue, making these reactions between the fourth and sixth leading cause of death in the USA, even when the drugs are used in proper doses and for approved indications [9].

Although paediatric pharmacotherapy has recently come to the fore both in Europe and USA [10], so far no meta-analytical review has been performed to assess the risk of drugs in the paediatric population. Recently published drug surveillance studies allow an estimation of the overall incidence of ADRs in different child health care settings. In this study we systematically review prospective studies on ADRs in children and provide a summary quantitative estimate of their occurrence.

Methods

Identification of relevant literature

The English and foreign-language medical literature was searched using the Medline (from January 1966 to May 2000) and Embase (from January 1988 to May 2000) databases. The search strategy employed the following keywords: ('adverse drug reaction reporting system' or 'drug therapy/adverse effects' or 'pharmaceutical preparations/adverse effects') and ('child' or 'child-preschool') and 'prospective studies'. The references of the retrieved studies and of published reviews on ADRs in children found via a manual search of various journals were examined in order to identify additional appropriate studies.

The following criteria were used for considering studies in the review: the patients studied were not selected for particular conditions or specific drug exposures, prospective monitoring was used to identify ADRs, and sufficient information was reported to calculate their incidence.

Data abstraction

Of the studies resulting from the screened electronic bibliographic search and the hand search, those that met previously defined inclusion criteria were selected and included in the analysis. Two researchers reviewed each study independently and, using a standard form, extracted data on methodology, outcome, and quality criteria. For each study the proportion of children who developed ADRs was extracted. The classification of ADRs in terms of likelihood and severity was also taken into account; in particular ADRs were considered severe when fatal or potentially life threatening. Other data considered in the analysis included the year of publication, the country in which the study was performed, and the duration of the data collection period.

Data synthesis

We analysed the incidence of ADRs obtained from different studies to determine the meta-analytic weighted average and the 95%CIs. We used a random-effects model to perform the analysis in order to take into account the heterogeneity of the various studies [11]. Briefly, the measured incidence of each study is considered to be a random variable with a total variance given by the sum of a within-study term (estimated from data as P_i $(1\text{-}P_i)/n_i$) and an unknown between-study term (accounting for heterogeneity between studies). The overall incidence (i.e. the pooled risk parameter) was estimated as a weighted average, iteratively calculating the weights and the heterogeneity variance they depend upon [12]. Separated pooled incidences were obtained for ADRs that occurred in hospitalized children, in children admitted to the hospital due to ADRs, and in general paediatric outpatients.

The random effects model was also used to explain the heterogeneity between studies. A meta-analytical regression was performed using the mean number of drugs per child as the covariate and the ADR incidence as the outcome variable. This covariate was chosen as it was the only available information reported in most studies in the hospital setting.

Results

The initial electronic search strategy identified 37 citations. Twenty-one studies were identified for assessment, of which four were excluded because they did not fulfil the above mentioned criteria. One study was excluded because the population was selected for a particular condition (paediatric haematology-oncology patients) [13], two because they reported ADR occurrence in relation to courses of drug therapy [14, 15], one because it did not report the size of population exposed to drug treatment, making the calculation of ADR incidence not feasible [16]. The remaining 17 papers were included in the meta-analysis [17-33].

Prospective paediatric drug surveillance studies were performed in seven different countries, mainly in the USA, UK and Spain (four each). A majority of the reports concerned the ADR incidence in hospitalized children (9/17) [17–25], five dealt with ADRs in children leading to hospital admission [26–30], and three papers reported the incidence of ADRs in outpatient children [31-33].

ADRs in hospitalized children

The reported ADR incidence ranged from 4.37% to 16.78% among the studies. As shown in Table 1, the

Table 1 Overall estimate of the incidence of ADRs in paediatric in/out-patients.

Setting/Source, y	*Incidence of ADRs*	*95% CI*
ADRs in hospitalized children		
McKenzie *et al.* [17]	10.64	8.28,12.99
Whyte *et al.* [18]	6.0	4.43,7.65
Mitchell *et al.* [19]	16.78	14.98-18.57
Choonara *et al.* [20]	5.60	2.84-8.35
Vasquez De La Villa *et al.* [21]	4.35	2.72,5.99
Gill *et al.* [22]	7.01	5.34,8.68
Gonzales-Martin *et al.* [23]	13.70	9.14,18.25
Turner *et al.* [24]	11.08	9.18,12.98
Martinez-Mir *et al.* [25]	11.52	8.76,14.29
Meta-analytic weighted average	9.53	6.81,12.26
ADRs leading to paediatric hospital admission		
McKenzie *et al.* [26]	2.02	1.56,2.48
Yosselson-Superstine *et al.* [27]	3.20	2.05,4.35
Mitchell *et al.* [28]	2.00	1.66,2.34
Martinez-Mir *et al.* [29]	4.10	2.38,5.82
Easton *et al.* [30]	0.59	0.22,0.96
Meta-analytic weighted average	2.09	1.02,3.77
ADRs in outpatient children		
Sanz *et al.* [31]	0.75	0.29,1.22
Cirko-Begovic *et al.* [32]	2.74	2.08,3.41
Menniti-Ippolito *et al.* [33]	1.51	1.24,1.78
Meta-analytic weighted average	1.46	0.70,3.03

meta-analytic estimated average, adjusted and weighted by sample size, was 9.53% (95%CI 6.81,12.26). Table 2 summarizes, according to year of publication, the major findings from the selected studies on the incidence of ADRs that occurred in children while in the hospital. All the studies were conducted in teaching hospitals located in large urban areas.

Seven studies provided an expert verification of the reactions in terms of likelihood. The severity of the reactions was reported in six studies. The rate of severe ADRs ranged from 7 to 20% among the studies, the weighted proportion was 12.29% (95%CI: 8.43,16.17). Eight studies reported the average number of drugs received by the children: this ranged from 1.5 to 7.6 drugs per child. The meta-analytical regression, which evaluates the relationship between child drug exposure and ADR incidence, yielded a between-study variability reduction of 0.52 and a regression coefficient of 0.017 (1.7 adverse reactions per additional drug used). This finding shows that about 50% of the variability in the reported ADR incidences may be explained by the different prescription rates in the various studies.

Concerning specific issues dealing with the safety of medicines in children, two studies examined the contribution to ADR occurrence of drugs used in an 'off-label' or unlicensed manner [20, 24]. The first study reported that 30% of the drugs causing ADRs were used outside their product license with regard to dose, indication or age of the patient [20]. In the most recent study, ADRs were associated with 6% of the unlicensed or off-label prescriptions and only 3.9% of the licensed drug prescriptions (RR = 1.55, 95%:1.19–2.03). Moreover 74% of the drugs causing ADRs classified as 'severe' were used in an unlicensed or off-label manner, even though only 35% of the total prescriptions were unlicensed or off-label.

ADRs leading to paediatric hospital admissions

The reported incidence of paediatric hospital admissions related to ADRs ranged from 0.59 to 4.1% among the studies; the meta-analytic weighted average was 2.09% (95%CI:1.02,3.77). (Table 1)

Table 3 shows a summary of published studies on ADRs in children leading to hospitalization. Five studies provided an expert verification of the ADRs in terms of likelihood. In three studies ADRs were classified in terms of severity. The proportion of severe reactions ranged from 38 to 45% among the studies; the weighted average was 39.3% (95%IC 30.7,47.9).

ADRs in outpatient children

The reported incidence ranged from 0.7 to 2.7%, and, as shown in Table 1, the meta-analytic weighted average was 1.46% (95%CI:0.70,3.03). The major findings of the two studies examining the incidence of ADRs in an outpatient setting are summarized in Table 4. Only one study reported ADR incidence according to age groups [33], the results show a higher risk of ADRs in children aged 1 year or less compared with other age groups (3.4% *vs* 1.4%). The study results also show a linear trend in the ADR incidence in relation to child's age (from younger to older: chi-square for linear trend 40.2; $P < 0.001$)

Discussion

The data resulting from this study, collected from a geographically variegated sample of observational drug surveillance studies, offer insight for health professionals into the potential impact of ADRs in the paediatric population in different health care settings. The study's results may also have implications for the design, management and reporting of paediatric drug surveillance studies.

The two previously published meta-analyses on the incidence of ADRs in the general population, which included 6 out of the 17 studies considered in this review, found that 5.1% of hospital admissions are drug related and 10.9% of patients develop ADRs during their stay in the hospital [9, 34]. Our findings show that the corresponding rates for paediatric patients are, respectively, 2.1% and

Table 2 Summary of prospective studies on ADRs in hospitalized children.

Setting/year [ref.]	*Population studied*	*Prescription level (mean)*	*ADRs occurrence*
Paediatric teaching hospital			70 children (10.6%) experienced ADRs
Gainesville (USA)	658 children	4.2 drugs per child	ADRs probability/severity not reported
1973 [17]	Age not reported		
Paediatric teaching hospital			51 children (6.0%) experienced ADRs
Glasgow (UK)	844 children	2.3 drugs per child	119 ADRs were reported:
1977 [18]	Age not reported		106 (89%) definite/probable
			24 (20%) severe
Paediatric teaching hospital			
Boston (USA)	1669 children	7.6 drugs per child	280 children (16.8%) experienced ADRs
1979 [19]	Mean age: 6.8 years		ADR probability/severity not reported
Paediatric teaching hospital			15 children (5.6%) experienced ADRs
Liverpool (UK)	268 children	1.5 drugs per child	17 ADRs were reported
1984 [20]	Age not reported		17 (100%) definite/probable
			Severity not reported
Teaching hospital			26 children (4.4%) experienced ADRs
Granada (Spain)	597 children	3.8 drugs per child	28 ADRs were reported:
1989 [21]	Mean age: 3.8 years		19 (68%) definite/probable
	Age range:1–8 years		3 (11%) severe
Paediatric teaching hospital			63 children (7%) experienced ADRs
Liverpool (UK)	899 children		76 ADRs were reported:
1995 [22]	Age range: 0–16 years	Not reported	40 (53%) definite/probable
			8 (11%) severe
Teaching hospital			30 children (13.7%) experienced ADRs
Santiago (Chile)	219 children	4.3 drugs per child	46 ADRs were reported:
1998 [23]	Mean age: 3.8years		30 (65%) definite/probable
	Age range: 0–15 years		8 (17%) severe
Paediatric teaching hospital			116 children (11.1%) experienced ADRs
Liverpool (UK)	3 months	4.3 drugs per child	157 ADRs were reported:
1999 [24]			89 (57%) definite/probable
	1047 children		17 (11%) severe
	Mean age: 1 year		
Paediatric teaching hospital	512 children		59 children (11.5%) experienced ADRs
Valencia (Spain)	Median age:8.5 months	2.6 drugs per child	68 ADRs were reported:
1999 [25]	Age range:1–24 months		53 (78%) definite/probable
			5 (7%) severe

9.5%. Moreover, 12% of the ADRs which occurred in hospitalized children, and about 39% of the ADRs causing hospitalization, were fatal or life-threatening reactions. These results suggest that, also in the paediatric population, ADRs are a significant public health issue.

Concerning risk factors associated with ADR incidence in children we found polypharmacy as a potential predictor of adverse events. The data analysed in the present study suggest an association between number of drugs received by children and the risk of ADRs. The results are consistent with recently published investigations conducted in adult patients that also show polypharmacy to be an important factor that predisposes patients to ADRs [35, 36].

The factors that predispose children to ADRs are similar to those in adults, but can be enhanced by age related differences in physiological function, differences in pattern of disease, and smaller size [37]. The results of this review show that important issues concerning the risk assessment of drug therapies in children are hidden realities in the biomedical literature. Few studies have analysed peculiar paediatric safety issues such as ADR occurrence according to developmental stages, and the risk related to off-label drug uses.

Recent studies conducted in the general population confirm that age is a significant correlate for ADR incidence [38]. Concerning paediatric patients, only one of the studies included in this meta-analysis reported ADR incidence for different age groups. It was therefore not possible to consider this important covariate in the meta-analytical regression because of the lack of information in most of the retrieved studies.

Table 3 Summary of prospective studies on ADRs leading to hospitalization in children.

Setting/year [ref.]	*Population studied*	*ADRs occurrence*
Paediatric teaching hospital	3556 paediatric admissions	72 admissions for ADRs (2%):
Gainesville (USA)	Age not reported	69 (96%) definite/probable
1976 (26		28 (39%) severe
Teaching hospital	906 paediatric admissions	29 admissions for ADRs (3.2%):
Jerusalem (Israel)	Age range: 0–16 years	19 (66%) definite/probable
1982 [27]		12 (45%) severe
Teaching and community hospitals	6546 paediatric admissions	131 admissions for ADRs (2%):
Boston (USA)	Age range: 0–15 years	67 (51%) definite/probable
1988 [28]		Severity not reported
Paediatric teaching hospital	512 paediatric admissions	21 admissions for ADRs (4.1%):
Valencia (Spain)	Age range: 4 months-2 years	16 (76%) definite/probable
1996 [29]	Mean age: 9 months	8 (38%) severe
Paediatric teaching hospital	1682 paediatric admissions	10 admissions for ADRs
Melbourne (Australia)	Age range: 4 months – 18 years	3 (30%) definite/probable
1998 [30]	Mean age: 9 years	Severity not reported

Table 4 Summary of prospective studies on ADRs in outpatient children.

Setting/year (ref.)	*Population studied*	*Occurrence of ADRs*
25 outpatient practices	1327 children	10 children (0.75%) experienced ADRs
Tenerife (Spain)	Age range: 0-14 years	8 (80%) definite/probable
1987 [31])	1 (10%) severe	
Paediatric outpatient unit	2296 children	63 children (2.7%) experienced ADRs
Zagreb (Croatia)	Age range: 0-7 years	56 (89%) definite/probable
1989 [32]		Severity not reported
29 outpatient practices	7890 children	119 children experienced ADRs
Padova (Italy)	Age range: 0-14 years	ADR probability/severity not reported
2000 [33]		

Another important long-term issue, which has received little attention in the biomedical literature, is the risk of ADRs related to the unlicensed and off-label use of drugs in children. A recent multicentre study, which involved different paediatric wards across Europe, has shown that many children receive drugs without labelling for paediatric use [7]. Whereas licensed drugs are monitored by spontaneous reporting, epidemiological surveys or surveillance systems, there is currently no similar process for monitoring and collecting information on ADRs due to unlicensed and off-label drug use.

Further studies are clearly required to determine the risk of an ADR in relation to such uses both in the hospital and in primary care. These studies could provide the necessary data to enable child health care providers to administer such medications in the safest and most effective manner, since the lack of paediatric labelling does not prevent a practitioner from prescribing an approved drug for unapproved uses [39].

The use of drugs and pathological conditions inside and outside the hospital differ considerably, and most paediatric drugs are used in a community setting. Only three studies have been published that allow one to estimate the occurrence of ADRs in outpatients. Other studies, not included in the meta-analysis, suggest that ADRs both in outpatient children [14] and in the community [15] are a significant problem, occurring in 11.1% and 9.8% of courses of therapy, respectively.

The paucity of information available is a major obstacle to the promotion of rational drug use, as primary health care is the core of health systems in many developed and developing countries and is the 'natural laboratory' in which the efficacy and safety of therapies need to be evaluated [40].

The findings of this study must be interpreted in light of its limitations. This systematic review of the literature included only studies recruiting nonselected paediatric populations in which ADRs were prospectively monitored. However, even among the most homogeneous and methodologically sound papers, there is substantial variability in the reported incidences. This heterogeneity is only partly explained by the different number of drugs

administered to children in each study. Other predictors, perhaps more informative, such as patient age, diagnosis and drug prescription patterns could not be considered in the analysis as they were not adequately and homogeneously reported. The differences in the reported incidence between studies may also be related to the variability in the methods for determining ADR occurrence, as the collection and assessment of ADRs involves considerable subjectivity depending on the clinical judgement of various medical personnel in different clinical settings. Further aspects that make it difficult to confidently extrapolate these results to an international level are the exclusive academic context in which most of the studies were performed and the restricted number of nations that contributed. The findings of the present meta-analysis are mostly derived from studies on paediatric patients admitted to wards in large teaching hospitals and therefore should not necessarily be generalized to all children or even to all hospitalized children. The nature of the population under study clearly affects patterns of drug utilization, which in turn affect the nature and frequency of adverse drug reactions. Finally, for compelling reasons related to feasibility of the review, we did not consider evidence derived from grey literature (i.e. studies that are unpublished, have limited distribution, and/or are not included in bibliographical retrieval systems). This omission may have affected the accuracy of the reported meta-analytic incidence estimates [41], but not the relevance of findings and the implications for practice.

Meta-analysis of observational studies presents particular challenges because of inherent biases and differences in study design. However, it may provide a tool for helping health practitioners to understand and quantify sources of variability in results across studies. This is especially true for the evaluation of drug safety in paediatrics mainly because of the small number of clinical trials actually conducted in children. Following the example of the CONSORT statement [42], issued for harmonizing the reporting of randomised clinical trials in biomedical journals, at least as much care should also be devoted to observational studies [43].

This systematic review of the existing literature on ADRs in children shows that the overall reporting of the main determinants for the risk of drug therapies appears to be a rarity more than a routine approach. In the future, in paediatric drug surveillance studies, prescription as well clinical data should be reported in a reasonably standard manner. This would allow the statistical technique of meta-analysis to provide child health professionals with useful information for an effective prevention of ADRs in children. Paediatricians, clinical pharmacologists and other figures involved in the care of children must all be involved in any such effort, keeping in mind that information, communication, and education concerning the appropriate use of drugs in children are vital.

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References

1 Lawson DH. Pharmacovigilance in the 1990s. *Br J Clin Pharmacol* 1997; **44**: 109–110.

2 Impicciatore P, Pandolfini C, Bosetti C, Bonati M. Adverse drug reactions in children: a systematic review of published case reports. *Pediatr Perinat Drug Ther* 1998; **2**: 27–36.

3 Bonati M, Marchetti F, Zullini MT, Pistotti V, Tognoni G. Adverse drug reactions in neonatal intensive care units. *Adverse Drug Reactions Poisoning Rev* 1990; **9**: 103–118.

4 Impicciatore P, Choonara I. Status of new medicines approved by the European Medicines Evaluation Agency regarding paediatric use. *Br J Clin Pharmacol* 1999; **48**: 15–18.

5 Conroy S, Choonara I, Impicciatore P, *et al*. Unlicensed and off-label durg use in paediatric wards in different European countries. *Br Med J* 2000; **320**: 79–82.

6 Bonati M, Impicciatore P, Pandolfini C. The registry of clinical trials in children must be set up. *Br Med J* 2000; **320**: 1339–1340.

7 Conroy S, McIntyre J, Choonara I, Stephenson T. Drug trials in children: problems and the way forward. *Br J Clin Pharmacol* 2000; **49**: 93–97.

8 Temple R. Meta-analysis and epidemiologic studies in drug development and post marketing surveillance. *JAMA* 1999; **281**: 841–844.

9 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. *JAMA* 1998; **279**: 1200–1205.

10 Bonati M, Choonara I, Hoppu K, Pons G, Seyberth H. Closing the gap in drug therapy. *Lancet* 1999; **355**: 1625.

11 Greenland S. Meta-analysis. In *Modern Epidemiology* eds Rothman KJ, Greenland S. Philadelphia; Lippincott Raven Publishers, 1998: pp 643–675.

12 Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. *Stat Med* 1995; **14**: 395–411.

13 Collins GE, Clay MM, Falletta JM. A prospective study of the epidemiology of adverse drug reactions in pediatric hematology and oncology patients. *Am J Hosp Pharm* 1974; **31**: 968–975.

14 Kramer MS, Hutchinson TA, Flegel KM, Naimark L, Contardi R, Leduc DG. Adverse drug reactions in general pediatric outpatients. *J Pediatr* 1976; **89**: 487–490.

15 Woods CG, Rylance ME, Cullen RE, Rylance GW. Adverse reactions to drugs in children. *Br Med J* 1987; **294**: 869–870.

16 Dharnidharka VR, Kandoth P, Anand RK. Adverse drug reactions in pediatrics with a study of in-hospital intensive surveillance. *Indian Pediatr* 1993; **30**: 745–751.

17 McKenzie MW, Stewart RB, Weiss CF, Cluff LE. A pharmacist based study of the epidemiology of adverse drug reactions in pediatric medicine patients. *Am J Hosp Pharm* 1973; **30**: 898–903.

18 Whyte J, Greenan E. Drug usage and adverse drug reactions in paediatric patients. *Acta Paediatr Scand* 1977; **66**: 767–775.

19 Mitchell AA, Goldman P, Shapiro S, Slone D. Drug utilisation and reported adverse reactions in hospitalised children. *Am J Epidemiol* 1979; **110**: 196–204.

20 Choonara IA, Harris F. Adverse reactions in medical inpatients. *Arch Dis Child* 1984; **59**: 578–580.

21 Vazques de la Villa A, Luna del Castillo JD, Galdo-Munoz G, Puche-Canas E. Reacciones adversas causadas por medicamentos en Pediatria. *An Esp Pediatr* 1989; **31**: 49–53.

22 Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, Choonara I. Adverse drug reactions in a paediatric intensive care unit. *Acta Paediatrica* 1995; **84**: 438–441.

23 Gonzales-Martin G, Caroca CM, Paris E. Adverse drug reactions (ADRs) in hospitalized pediatric patients. A prospective study. *Int J Clin Pharm Ther* 1998; **36**: 530–533.

24 Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatrica* 1999; **88**: 965–968.

25 Martinez-Mir I, Garcia-Lopez M, Palop V, Ferrer JM, Rubio E, Morales-Olivas FJ. A prospective study of adverse drug reactions in hospitalized children. *Br J Clin Pharmacol* 1999; **47**: 681–688.

26 McKenzie MW, Marchall GL, Netzloff ML, Cluff LE. Adverse drug reactions leading to hospitalization in children. *J Pediatr* 1976; **89**: 487–490.

27 Yosselson-Supertimes G, Weiss T. Drug related hospitalization in pediatric patients. *J Clin Hosp Pharm* 1982; **713**: 195.

28 Mitchell AA, Lacoutre PG, Sheehan JE, Kauffman RE, Shapiro S. Adverse drug reactions in children leading to hospital admission. *Pediatrics* 1988; **82**: 24–29.

29 Martinez-Mir I, Garcia-Lopez M, Palop V, *et al*. A prospective study of adverse drug reactions as a cause of admission to a paediatric hospital. *Br J Clin Pharmacol* 1996; **42**: 319–324.

30 Easton KL, Parsons BJ, Starr M, Brien J. The incidence of drug-related problems as a cause of hospital admissions in children. *Med J Austr* 1998; **169**: 356–359.

31 Sanz E, Boada J. Adverse drug reactions in pediatric outpatients. *Int J Clin Pharm Res* 1987; **7**: 169–172.

32 Cirko-Begovic A, Vrhovac B, Bakran I. Intensive monitoring of adverse drug reactions in infants and preschool children. *Eur J Clin Pharmacol* 1989; **36**: 63–65.

33 Menniti-Ippolito F, Raschetti R, Da Cas R, Giaquinto C, Cantarutti L. Active monitoring of adverse drug reactions in children. *Lancet* 2000; **355**: 1613–1614.

34 Einarson T. Drug related hospital admissions. *Ann Pharmacother* 1993; **27**: 832–840.

35 Fattinger K, Roos M, Vergeres P, *et al*. Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. *Br J Clin Pharmacol* 2000; **49**: 158–167.

36 Bates DW, Miller EB, Cullen DJ, *et al*. Patient risk factors for adverse drug events in hospitalized patients. *Arch Intern Med* 1999; **159**: 2553–2560.

37 Choonara I, Gill A, Nunn A. Drug toxicity and surveillance in children. *Br J Clin Pharmacol* 1996; **42**: 407–410.

38 Pouyanne P, Haramburu F, Imbs JL, Begaud B. Admission to hospital caused by adverse drug reactions: cross sectional incidence study. *Br Med J* 2000; **320**: 1036.

39 Collier J. Paediatric prescribing: using unlicensed drugs and medicines outside their licensed indications. *Br J Clin Pharmacol* 1999; **48**: 5–8.

40 Bonati M. Epidemiological evaluation of drug use in children. *J Clin Pharmacol* 1994; **34**: 300–305.

41 McAuley L, Pham B, Tugwell P, Moher D. Does the inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses? *Lancet* 2000; **356**: 1228–1231.

42 Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. *Br Med J* 1996; **313**: 570–571.

43 Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology. A proposal for reporting. *JAMA* 2000; **283**: 2008–2012.