Eur J Clin Pharmacol (2012) 68:801–810
DOI 10.1007/s00228-011-1183-4

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Risk factors associated with adverse drug reactions in hospitalised children: international multicentre study

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Received: 29 July 2011 / Accepted: 22 November 2011 / Published online: 14 December 2011

Abstract
Background Understanding the epidemiology and risk factors of adverse drug reactions (ADRs) is important in order to develop appropriate prevention strategies. This study aimed to identify risk factors associated with ADRs in hospitalised children and recommend strategies to minimise ADRs.
Methods A prospective multicentre cohort study was conducted on paediatric general medical wards in five European and non-European hospitals. ADRs were identified by intensive chart review. Multivariable logistic regression was used to investigate risk factors associated with ADRs. For the risk factor analysis, prescribed drugs were divided into high-risk and low-risk drug groups. Analgesics, antiepileptics, antibacterials and antimycotics for systemic use, corticosteroids for systemic use and immunosuppressant agents were considered as high-risk groups whereas the remaining drug classes were defined as low-risk drug groups.
Results A total of 1,253 paediatric patients were identified [Australia (n=145), Germany (n=372), Hong Kong (n=138), Malaysia (n=291), UK (n=307)]. A total of 328 ADRs were observed in 16.7% of patients (186/1,115). Use of five or more low-risk drugs per patient or three or more high-risk drugs was a strong predictor for ADRs (OR 4.7, 95% CI 2.4–9.3; OR 6.5, 95% CI 2.7–16.0 respectively; p<0.001). Older children were more likely to experience ADRs; gender was not significantly associated.
Conclusion To reduce the risk of ADRs in children, clinicians and pharmacists should aim to minimise polypharmacy and be aware of higher ADR risks associated with some drug groups.

Keywords Risk factors · ADRs · Paediatric · Children · Inpatient · Multicentre study

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Introduction

Children are thought to be at a higher risk of adverse drug events including medication errors and adverse drug reactions (ADRs) than adults due to their physiology and immature mechanism of drug metabolism [1, 2]. Previous studies have reported different factors that predispose patients to ADRs [3–6]. In some of these studies female gender was considered an important risk factor for ADRs [3, 4, 6]. However, compared to adults fewer data are available regarding risk factors for ADRs in children [7–9]. A previous meta-analysis reported that the number of drugs

administered to children was a potential predictor for ADRs [9]. Other predictors, such as patient age, diagnosis and drug prescription patterns, were not considered as they were not adequately reported in the primary studies included in the meta-analysis. A recent review conducted by Aagaard et al. (2010) provides comprehensive information on ADRs in children from prospective and retrospective studies, however, the authors did not report on risk factors [10].

It has been recognised that the nature of the population under study affects patterns of drug utilisation, which in turn affects the nature and frequency of ADRs [11]. Previous studies that explored common risk factors associated with the occurrence of ADRs were often limited to one hospital, to a certain type of ward or to hospitals representing a local population. Different study designs, settings, patient populations, the definition of ADR used, and the statistical methods applied affect the generalisability. Consequently, these results are difficult to extrapolate at an international level.

This study, ADVISE (Adverse Drug Reaction in Children – International Surveillance and Evaluation), was designed to investigate the incidence and characteristics of ADRs in paediatric hospitalised patients in five European and non-European countries and included statistical evaluation of potential risk factors. We have previously reported descriptive results on the incidence of ADRs [12]. In this study we conducted an in-depth statistical analysis of potential risk factors associated with ADRs in hospitalised children in five countries.

Methods

Study design

The study methodology has been reported previously [12] and the following is a brief summary.

A prospective multicentre cohort study was conducted in paediatric general medical wards in five hospitals in five countries including Australia, Germany, China [Hong Kong (HK)], Malaysia and the United Kingdom (UK). Data were collected over a 3-month period in each country between 1 October 2008 to 31 December 2009 using a web-based data entry tool (www.paediatric-adr.com). All children admitted during the study period were initially included. Children with a hospital stay of less than 24 h were subsequently excluded. ADRs were defined according to the World Health Organisation (WHO) as '*any 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*' [13]. ADRs were identified by intensive chart review and evaluated by the research team, which consisted of at least one clinical pharmacist and one paediatrician/paediatric pharmacologist.

For standardisation across the participating study sites, established international terminologies were used for documentation and analysis: Anatomical Therapeutic Chemical (ATC) classification [14] was used for the classification of drugs, International Classification of Diseases version 10 (ICD 10) [15] for diagnoses, and WHO Adverse Reaction Terminology (WHO-ART) [16] to standardise ADRs.

Preventability, severity and seriousness of identified ADRs were assessed using standardised criteria and are presented in detail elsewhere [12, 17–19].

Prescribed drugs

High-risk drugs definition

Based on drug groups being described as most frequently involved in the occurrence of ADRs in the literature [5, 20–23] and the opinions of two paediatric clinical pharmacologists involved in the project (W.R., N.C.) we defined five drug groups (ATC therapeutic level) as high risk: these were analgesics (N02), antiepileptics (N03), antibacterials and antimycotics for systemic use (J01, J02), corticosteroids for systemic use (H02), and immunosuppressant agents (L04). For the risk factor analysis, all other prescribed drugs were grouped as low-risk drugs.

Associated diagnosis

To identify the potential impact of diagnosis on the occurrence of ADRs the main diagnosis for each patient was recorded based on ICD 10 [15]. The higher levels of ICD 10 'blocks' were used in the analyses. The inclusion of a diagnosis in the univariable and multivariable analyses was based on the statistical significance of the association between each 'block' of disease and the occurrence of ADRs.

ADR incidence

The overall incidence of ADRs in the cohort and in each country cohort was defined as the number of patients with at least one ADR during their hospitalisation divided by the total number of patients receiving medications multiplied by 100.

For ADR incidence and risk factor calculations, only patients with at least one drug prescription during admission were included. Also, only the first admission was considered for investigating the association between ADR incidence and the potential risk factors.

Patients who only had an ADR before admission or were admitted due to an ADR and did not experience another ADR during hospitalisation were excluded from the analysis of risk factors.

Risk factors

Risk factors investigated were age, gender, number of drugs (low-risk drugs, high-risk drugs), diagnoses, length of stay.

Statistical analysis

Descriptive statistical methods

For the descriptive analysis of patient characteristics and differences between groups and countries, chi-squared, Kruskal-Wallis rank and Wilcoxon rank-sum (Mann-Whitney) tests were used as appropriate.

Statistical modelling

Potential risk factors associated with ADRs were identified using univariable and multivariable logistic regression models at patient level, using ADR occurrence as the outcome. Univariable odds ratios (OR) and 95% confidence intervals (CI) were calculated for each independent variable. Those factors which showed a significant association with the occurrence of ADRs in the univariable analysis were included in the multivariable regression analysis. Consequently, the final model included age (in groups: 0 to≤2, >2 to≤11, >11 to ≤18 years), gender, number of low-risk drugs per patient (in groups: 1–4, 5–10, >10 drugs), number of high-risk drugs per patient (in groups: 1, 2–3, >3 drugs), diagnosed with 'diseases of the blood or blood-forming organs and certain disorders involving the immune mechanism' (D50–D89), 'diseases of the nervous system' (G00–G99), 'certain conditions originated in the perinatal period' (P00–P96), 'endocrine, nutritional and metabolic diseases' (E00–E90), 'certain infectious and parasitic diseases' (A00–B99). The final model was adjusted by country.

Gender and younger age (0 to ≤2 years and >2 to ≤11 years) were included in the full model despite their non-significance in the univariable analysis because previous studies had identified sex and gender as risk factors for ADR incidence [3, 24].

In all statistical tests p values <0.05 were considered statistically significant. Data analysis was performed using Stata 11 (StataCorp, College Station, TX, USA). Data are presented as percentages, median, inter-quartile range [IQR (Q1–Q3)], and ORs with 95% CI unless otherwise specified.

Results

Patient characteristics

A total of 1,253 paediatric patients fulfilled the inclusion criteria and were included in the cohort [Australia (n=145), Germany (n=372), Malaysia (n=291), HK (n=138), and UK (n=307)]. Of 1,253 children, 693 (55.3%) were male. The median age of the study population was 2 years (IQR 0–7). A total of 82.7% of children were admitted as an emergency admission. The total length of hospital stay in the whole cohort was 8,198 days with median 4 days (IQR 3–7). Of the 1,253 hospitalised children, 1,115 (89.0%) received 5,013 prescribed drugs during their hospitalisation (median 3 drugs per patient, IQR 2–5). Of the 1,115 children, 980 (87.9%) received at least one of the high-risk drugs (median 2, IQR 1–3). Demographic characteristics of children included from each country are shown in Table 1. There was a significant difference between countries in regards to patient age, length of hospital stay, number of drugs prescribed per patient and number of high risk drugs prescribed per patient (p<0.001).

The number of drugs prescribed per patient in the UK was found to be significantly higher than in the other countries (p<0.001). There was no significant difference in gender between countries (p=0.899). Table 2 shows the drug groups most frequently prescribed to the cohort.

Respiratory system diseases were most common in all countries, followed by infectious and parasitic diseases in Australia, Germany, UK and Malaysia. In the HK cohort only a few patients were reported with infectious diseases. Diseases of the nervous system were common in Germany, Malaysia and the UK. Endocrine, nutritional and metabolic diseases were most frequent in Germany followed by Australia, but none were reported in Malaysia and the UK (Table 3).

ADR characteristics

A total of 328 ADRs were identified. Overall ADR incidence during hospitalisation was found to be 16.7% (95% CI 14.5–19.0). Table 4 gives details of the incidence, preventability and seriousness of ADRs in the total study cohort and in each country. Table 5 shows identified ADRs in the study cohort classified according to WHO-ART classification.

Potential risk factors associated with ADRs

Descriptive statistics

Overall, children with ADRs were hospitalised longer compared to those without ADRs (median 6 days, IQR 4–11 vs. 4 days, IQR 3–6; p<0.001). Overall, age and gender were found not to be associated with the incidence of ADRs. However, on a country level, in Australia, Germany, Malaysia and the UK, patients having an ADR were significantly older compared to those not having an ADR (p<0.05). The total number of drugs prescribed per patient for children with

Table 1 Patient demographic characteristics

Patient characteristics	Country					Total
	Australia	Germany	UK	Hong Kong	Malaysia	
Number of patients	145	372	307	138	291	1,253
Patients by age groups						
0 to ≤2 years	81 (55.9)	132 (35.5)	173 (56.4)	60 (43.5)	218 (74.9)	664 (53.0)
>2 to ≤11 years	52 (35.9)	154 (41.4)	100 (32.6)	42 (30.4)	70 (24.1)	417 (33.3)
>11 to ≤18 years	13 (9.0)	86 (23.1)	34 (11.1)	36 (26.1)	3 (1.0)	172 (13.7)
Age (years)	2 (0–7)	4.5 (1–10.5)	2 (0–6)	4 (0–12)	1 (0–3)	2 (0–7)
Gender						
Female	64 (44.1)	162 (43.5)	138 (45.0)	67 (48.6)	129 (44.3)	560 (44.7)
Male	81 (55.9)	210 (56.5)	169 (55.0)	71 (51.4)	162 (55.7)	693 (55.3)
Length of stay (days)	4 (3–7)	4 (3–6)	4 (3–6)	6 (4–8)	5 (4–8)	4 (3–7)
Number of patients who received medications	139 (95.9)	289 (77.7)	297 (96.7)	111 (80.4)	279 (95.9)	1,115 (89.0)
Total number of drugs prescribed	731	1,158	1,907	341	876	5,013
Number of drugs prescribed per patient[a]	4 (3–7)	3 (2–5)	5 (3–8)	2 (2–4)	3 (2–4)	3 (2–5)
Number of patients prescribed high-risk drugs	123 (88.5)	234 (81.0)	284 (95.6)	72 (64.9)	267 (95.7)	980 (87.9)
Total number of high-risk drugs prescribed	371	576	827	130	634	2,538
Number of high-risk drugs prescribed per patient[a]	3 (1–4)	2 (1–3)	2 (1–4)	1 (0–2)	2 (1–3)	2 (1–3)
Type of admission						
Emergency	142 (97.9)	328 (88.2)	215 (70.0)	61 (44.2)	290 (99.7)	1,036 (82.7)
Scheduled	3 (2.1)	42 (11.3)	16 (5.2)	27 (19.6)	1 (0.3)	89 (7.1)
Transferred	–	2 (0.54)	76 (24.8)	50 (36.2)	–	128 (10.2)

Values are *n* (%) or median (inter-quartile range)

[a] Considering only patients prescribed drugs

ADRs was significantly higher compared to children without ADRs (median 6 drugs, IQR 4–10 vs. 3 drugs, IQR 2–5; $p<0.001$). On a country level this was significant for all countries except HK where most of the patients with ADRs had fewer

Table 2 Drug groups most frequently prescribed to patients in study cohort

Therapeutic level	ATC code	No. of prescriptions (% of total[a])	No. of patients exposed (% of total[b])
Antibacterials for systemic use	J01	1,288 (25.7)	724 (64.9)
Analgesics	N02	860 (17.2)	676 (60.6)
Drugs for obstructive airway diseases	R03	444 (8.9)	263 (23.6)
Anti-inflammatory and antirheumatic products	M01	256 (5.1)	248 (22.2)
Corticosteroids for systemic use	H02	221 (4.1)	191 (17.13)
Anti-epileptics	N03	122 (2.4)	69 (6.2)
Blood substitutes and perfusion solutions	B05	132 (2.6)	112 (10)
Drugs for acid-related disorders	A02	161 (3.2)	141 (12.6)
Psycholeptics	N05	114 (2.3)	91 (8.2)
Laxatives	A06	119 (2.4)	86 (7.7)
Vitamins	A11	83 (1.7)	64 (5.7)
Mineral supplements	A12	78 (1.6)	67 (6)
Anti-anemic preparations	B03	75 (1.5)	62 (5.6)
Antihistamines for systemic use	R06	72 (1.4)	66 (5.9)
Diuretics	C03	61 (1.2)	46 (4.1)
Others	–	927 (18.5)	445 (39.9)

[a]Total number of prescriptions = 5,013

[b]Total number of patients prescribed drugs = 1,115. Patients may have received drugs from more than one group

Table 3 Main diagnoses and ADRs in study cohort and in country cohort

Diagnosis (ICD 10 code)	No. of patients (%)	No. of patients on drugs (%)	No. of patients with diagnoses (no. of patients with ADR)					No. of patients with ADRs (%)[a]
			Australia	Germany	UK	Hong Kong	Malaysia	
Diseases of the respiratory system (J00–J99)	415 (33.1)	408 (36.6)	45 (3)	88 (6)	81 (28)	23 (4)	178 (21)	62 (15.2)
Certain infectious and parasitic diseases (A00–B99)	147 (11.7)	120 (10.8)	11 (0)	85 (1)	29 (4)	4 (0)	18 (3)	8 (6.7)
Diseases of the nervous system (G00–G99)	94 (7.5)	85 (7.6)	6 (0)	26 (1)	19 (9)	8 (1)	35 (14)	25 (29.4)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	92 (7.3)	74 (6.6)	9 (0)	20 (0)	28 (8)	20 (0)	15 (2)	10 (13.5)
Diseases of the genitourinary system (N00–N99)	77 (6.1)	75 (6.7)	13 (1)	24 (3)	13 (4)	16 (1)	11 (0)	9 (12.0)
Injury, poisoning and certain other consequences of external causes (S00–T98)	74 (5.9)	44 (4.0)	2 (0)	40 (2)	20 (5)	12 (0)	–	7 (15.9)
Diseases of the digestive system (K00–K93)	56 (4.5)	45 (4.0)	7 (0)	22 (3)	16 (4)	4 (0)	7 (0)	7 (15.6)
Endocrine, nutritional and metabolic diseases (E00–E90)	50 (4.0)	39 (3.5)	19 (1)	22 (0)	–	9 (0)	–	1 (2.6)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50–D89)	38 (3.0)	38 (3.4)	5 (1)	5 (2)	22 (13)	3 (0)	3 (0)	16 (42.1)
Certain conditions originating in the perinatal period (P00–P96)	35 (2.8)	30 (2.7)	3 (0)	2 (0)	16 (7)	9 (1)	5 (1)	9 (30.0)
Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	25 (2.0)	24 (2.2)	6 (1)	4 (2)	12 (2)	2 (0)	1 (0)	5 (20.8)
Other diseases	150 (12.0)	133 (11.9)	19 (3)	34 (3)	51 (16)	28 (0)	18 (5)	27 (20.3)
Total	1,253 (100)	1,115 (100)	145 (10)	372 (23)	307 (100)	138 (7)	291 (46)	186 (16.7)

[a] Percentage of patients with ADRs based on number of patients receiving drugs

than five drugs prescribed. Moreover, the number of high-risk drugs prescribed per patient was found to be significantly higher in children with ADRs than in children without ADRs (median 3 drugs, IQR 2–5 vs. 2 drugs, IQR 1–3; $p<0.001$). This was the case in the overall study cohort and all country cohorts except Australia and HK.

Statistical modelling

The univariable analysis showed that 9 of 15 variables were significantly associated with the occurrence of ADRs. In the multivariable modelling only seven variables remained statistically significant.

Table 4 Incidence, preventability and seriousness of ADRs stratified by country

Country	Incidence of patients with ADRs[a]	Number of ADRs (%)	Number of preventable ADRs (%)[b]	Number of serious ADRs (%)[b]
Australia	10/139 (7.2%) [3.5–12.8]	18 (5.5)	7 (38.9)	2 (11.1)
Germany	23/289 (8.0%) [5.1–11.7]	37 (11.3)	5 (13.5)	12 (32.4)
Hong Kong	7/111 (6.3%) [2.6–12.6]	8 (2.4)	2 (25.0)	1 (12.5)
Malaysia	46/279 (16.5%) [12.3–21.4]	60 (18.3)	1 (1.7)	26 (43.3)
UK	100/297 (33.7%) [28.3–39.4]	205 (62.5)	39 (19.0)	21 (10.2)
Overall	186/1,115 (16.7%) [14.5–19.0]	328 (100)	54 (16.5)	62 (18.9)

[a] Values are number of patients with ADRs/total number of patients prescribed drugs (%) [95% CI]

[b] Percentage of serious and preventable ADRs related to total number of ADRs in each country

Table 5 Identified ADRs in the study cohort classified according to WHO-ART classification

System/organ class	Frequency (% of total[a])	Examples
Gastro-intestinal system	118 (36)	Diarrhoea, constipation, vomiting, nausea
Skin and appendages	43 (13.1)	Rash macula-papular, angioedema, itching
Heart rate and rhythm disorders	34 (10.4)	Bradycardia, tachycardia
Metabolic and nutritional disorders	30 (9.2)	Hypokalaemia, hyperglycaemia, hyponatraemia
Cardiovascular disorders, general	16 (4.9)	Hypertension, hypotension
Psychiatric disorders	15 (4.6)	Appetite lost, hallucination
White cell and RES disorders	14 (4.3)	Leukocytosis, eosinophilia
Central and peripheral nervous system disorders	10 (3.1)	Headache, tremor, convulsions
Respiratory system disorders	10 (3.1)	Respiratory distress, hypoventilation
Body as a whole, general disorders	9 (2.7)	Fever, oedema peripheral
Liver and biliary system	8 (2.4)	ALT increased, bilirubin increased, GGT increased
Resistance mechanism disorders	7 (2.1)	Candidiasis, thrush
Platelet, bleeding and clotting disorders	3 (0.9)	Bruise, thrombocytopenia
Urinary system disorders	3 (0.9)	Nephropathy toxic, urine discolouration
Vascular (extracardiac) disorders	3 (0.9)	Thrombophlebitis
Vision disorders	2 (0.6)	Conjunctivitis, vision blurred
Endocrine disorders	1 (0.3)	Cushing's syndrome
Red blood cell disorders	1 (0.3)	Haemoglobin decreased
Reproductive disorders, female	1 (0.3)	Genital ulceration

RES Reticuloendothelial system, *GGT* gamma-glutamyltransferase, *ALT* alanine aminotransferase

[a] Total number of ADRs = 328

The use of five or more low-risk drugs per patient and the use of three or more high-risk drugs were strong predictors for the occurrence of ADRs (OR 4.7, 95% CI 2.4–9.3; OR 6.5, 95% CI 2.7–16.0 respectively; $p<0.001$).

In the full model adjusted by country, diagnoses which significantly predicted an ADR were diagnosis of a nervous system disorder or of blood-forming organs and certain disorders involving the immune mechanisms or certain conditions originating in the perinatal period.

The univariable analysis showed that older children aged between >11 years and 18 years were more likely to experience ADRs than younger children aged less than 11 years (OR 1.7, 95% CI 1.0–2.8; $p=0.031$). This remained significant in the full model adjusted by country.

The univariable analysis for the associations between ADR occurrence and the potential risk factors and the results of the full model of multivariable analysis are shown in Table 6.

We also considered another regression model including the above predictors plus length of hospital stay to see the influence of hospital stay as predictor. We obtained the same conclusion from the model about statistical significance of the included variables except for the disease variables ('D50–D89' and 'P00–P96') which became not significant. In addition there was a lot of interaction between length of stay and other variables. Therefore we choose to report the model without length of stay.

Discussion

This international multicentre study investigated risk factors associated with ADRs from a large prospective cohort of international paediatric hospitalised patients. The overall ADR incidence in this cohort was 16.7% (95% CI 14.5–19.0). Our previous paper (ADVISE) [12] discussed the differences among countries with regards to ADR incidences as well as details on the characteristics of identified ADRs.

The early detection of ADRs is important to prevent unnecessary harm to patients. Knowledge of factors predisposing a patient to ADRs is important to develop appropriate prevention strategies. Moreover, improvements in the education of prescribers emphasising identification of risk factors for ADRs and the importance of risk benefit assessments before any medicine is prescribed are crucial to improve the safety of pharmacological treatments in paediatric hospital departments.

This study shows that ADR incidence can be influenced by several factors, which should be considered as key points for healthcare professionals to identify and so minimise the risk of ADRs, as the early detection of an ADR is most likely to depend on the clinical observation of patients.

We considered the length of stay (LOS) as a consequence of having an ADR but not as a risk to predispose to an ADR. Many previous studies have considered length of hospital stay as a risk factor for ADRs [25]. After comparing the

Table 6 Risk factors of ADRs in hospitalised children in the study cohort adjusted by country[a]

Risk factors	Univariable OR (95% CI)	*p*-value	Full model[b] OR (95% CI)	*p*-value
Age				
0 to ≤2 years	1.1 (0.79–1.6)	0.498	1.2 (0.80–1.9)	0.351
>2 to ≤11 years	1.00 (reference)		1.00 (reference)	
>11 to ≤18 years	1.7 (1.0–2.8)	0.031	2.1 (1.1–3.8)	0.020
Gender (female vs. male)	0.96 (0.70–1.3)	0.776	0.94 (0.65–1.4)	0.739
Number of low-risk drugs prescribed				
0	1.00 (reference)		1.00 (reference)	
1–4	1.4 (0.91–2.2)	0.129	2.3 (1.4–4.0)	0.002
5–10	4.8 (2.8–8.2)	<0.001	4.7 (2.4–9.3)	<0.001
>10	18.4 (7.6–44.5)	<0.001	11.5 (3.6–36.3)	<0.001
Number of high-risk drugs prescribed				
0	1.00 (reference)		1.00 (reference)	
1	1.2 (0.48–3.0)	0.690	0.91 (0.35–2.4)	0.855
2–3	3.5 (1.6–7.7)	0.002	2.4 (1.0–5.6)	0.045
>3	12.1 (5.4–27.3)	<0.001	6.5 (2.7–16.0)	<0.001
ICD 10 code				
A00–B99 (yes/no)	0.33 (0.16–0.68)	0.003	0.61 (0.30–1.4)	0.225
D50–D89 (yes/no)	3.9 (2.0–7.5)	0.001	2.3 (1.0–5.1)	0.043
G00–G99 (yes/no)	2.2 (1.4–3.7)	0.001	2.3 (1.3–4.2)	0.006
P00–P96 (yes/no)	2.2 (1.0–4.9)	0.053	2.6 (1.0–6.5)	0.049
E00–E90 (yes/no)	0.13 (0.02–0.93)	0.042	0.20 (0.02–1.6)	0.132

A00–B99 Certain infections and parasitic diseases (e.g. enteroviral meningitis, tuberculosis), *D50–D89* diseases of the blood and blood-forming organs and certain disorders involving the immune mechanisms (e.g. sickle-cell anaemia, agranulocytosis), *G00–G99* diseases of the nervous system (e.g. epilepsy, sleep apnoea), *P00–P96* certain conditions originating in the perinatal period (e.g. congenital hypotonia, bacterial sepsis of newborn), *E00–E90* endocrine, nutritional and metabolic diseases (e.g. nutritional deficiency, insulin-dependent diabetes mellitus)

[a] Risk factors are presented as crude and adjusted odds ratios (ORs) with 95% confidence intervals (95% CI)

[b] Full model adjusted for possible confounding factors (age, gender, number of drugs prescribed, and above disease groups)

length of hospital stay for patients with an ADR with patients who did not experience an ADR (median 6 vs. 4 days; $p<0.05$), we cannot exclude the possibility that a longer hospital stay could be the consequence of ADRs rather than a risk factor predisposing to an ADR. Previous studies conducted in adults showed that ADRs could be a cause of a longer LOS for patients [26, 27].

Polypharmacy

Undoubtedly polypharmacy is an important risk factor for ADRs. Previous data showed that it is significantly associated with the occurrence of ADRs in adults and children [9, 25, 26, 28]. Our study confirmed these findings showing a relationship between the number of drugs prescribed and the occurrence of ADRs. This relationship remained significant in the multivariable analysis in the overall study cohort as well as in each individual country cohort except HK, where the total number of prescribed drugs per patient was very small compared to other countries and the majority of patients with ADRs had fewer than five drugs prescribed.

Patients with five or more drugs prescribed during their hospital stay had the highest risk of developing an ADR—three times higher compared to patients receiving between one and four drugs as shown in the multivariable analysis. One possible explanation might be that polypharmacy may increase the chances of drug-drug interaction, which leads to increased possibilities for an ADR to occur [29].

Similar findings of polypharmacy as a risk factor for ADR occurrence were reported in a study by Zopf et al. (2008) conducted in an adult population [28].

The drug combinations (polypharmacy) which were associated with ADRs in the present study are commonly seen in all types of paediatric wards. For example, antibiotics, analgesics and drugs for obstructive airways diseases were most often associated with ADRs and most commonly prescribed together.

Age

When looking into the predefined age groups in the univariable logistic regression analysis, the ORs indicated that

older children were more prone to have ADRs than younger children. This was confirmed in the multivariable analysis which revealed the age group '>11 to ≤18 years' as an independent risk factor. A previous study by Gonzalez-Martin et al. showed that, although there was no statistically significant difference among age groups, older children (10–16 years) had a tendency to have higher ADR frequency [8].

Similar findings were reported from other studies [7, 30]. However, these findings should be interpreted with caution. Human physiology is constantly changing from birth to adolescence, resulting in different responses to drugs among age groups. These differences in pharmacokinetics and pharamcodynamics are particularly significant in neonates and very young children [31]. Therefore a higher ADR incidence would be expected in very young children such as neonates. The question remains whether there is an association because more high-risk drugs are given to older children causing more ADRs because of the nature of the drugs.

Gender

Some studies in adults have shown that female patients are more prone to develop ADRs than male patients whereas other studies have not [26, 27, 32]. However, a recent paediatric study published in 2011 which used the WHO VigiBase database found that a high proportion of ADR reports among children were for boys [33]. In our study, we found that almost equal proportions of ADRs were identified for female and male patients (17.0 and 16.4% respectively). Also, univariable and multivariable analyses showed that gender was not a predisposing factor in the overall study cohort or in any country cohort. Our results could be explained by the fact that due to the unique physiology and immature systems of children, especially in young children, gender might not be a predisposing factor for ADRs in children. A study by Zopf et al. (2008) found that females were at higher ADR risk compared to males except for children and young adults [34].

Although an impact of other socioeconomic factors on the occurrence of ADRs has been reported in adults and children, it was not investigated in our study [35, 36] because it would have been very difficult to get comparable information from different countries and hence a bias could be introduced. Nevertheless, it is an interesting area for further research.

A study by Knopf and Du (2010) showed no significant difference in the occurrence of ADRs between boys and girls with regards to their social status (defined by parents' education level, household incomes and profession) [29]. However, another study examining drug-related hospitalisation in both adults and children in Lebanon found that socioeconomic status was a risk factor for increased ADR incidence in children [36]. It did not comment however on any difference between males and females with regard to socioeconomic status.

Drugs involved

Other factors we investigated as potential risk factors for ADRs were the use of certain drug groups which we had predefined as high-risk drugs. There was a significant association between the use of high-risk drugs (analgesics, antiepileptics, systemic corticosteroids, immunosuppressive agents and systemic antibacterials and antimycotics) and the risk of ADRs. Bates et al. (1999), using univariable analysis, reported that in adults diuretics, electrolyte concentrates, antitumor agents and anticoagulants are associated with the occurrence of ADRs [32]. However, the majority of drugs seen as high risk in adults were not commonly prescribed in our paediatric study cohort. Therefore, data from adults are not necessarily applicable to children.

In our study antibacterials, analgesics and drugs for obstructive airways diseases were most often reported to be associated with ADRs. This is in line with what has been reported by Turner et al. and Neubert et al. [37, 38]. Gill et al. (1995) also reported similar drugs (morphine, salbutamol) as being most frequently involved in ADRs [39]. Anti-infective and respiratory drugs were found to be the most commonly prescribed medications to children in primary care in the UK, Italy and the Netherlands [40]. Therefore, it is important for both primary care and secondary care physicians and pharmacists to be vigilant in monitoring potential ADRs.

Associated diagnosis

In this study, the univariable analysis showed that the risk of ADRs is higher if the patient has one of the following four ICD diagnoses: 'certain infections and parasitic diseases' (A00–B99), 'diseases of the blood and blood-forming organs and certain disorders involving the immune mechanisms' (D50–D89), 'diseases of the nervous system' (G00–G99) and 'endocrine, nutritional and metabolic diseases' (E00–E90). However, in the multivariable regression model only two types of diseases were independent and remained statistically significant (Table 6).

These two diagnosis groups, independently associated with the occurrence of ADRs, involve an impairment of biological defense mechanisms which may predispose patients to the development of adverse reactions as the body has less capacity to compensate. This is especially applicable to patients with suppressed immune systems and metabolic diseases [41]. On the other hand these findings could be due to caregivers/healthcare professionals using one or more of the high-risk drugs to treat such conditions, which in turn predisposes a patient to an ADR. Comparisons with previous studies

are difficult to make as none has investigated diagnosis as a potential predictor for ADRs.

Strengths and weaknesses

This study used multiple logistic regression which allows us to better understand the relationship between independent ADR predictors. This study was conducted on an international level and involved five hospitals from five countries in Europe, Asia and Australia which, we believe, overcomes variations reported in previous studies [9], such as study setting, patient group, method used to identify ADRs, statistical methods used and ADR definition used. This gives the study results generalisability to other health care settings in other countries and/or hospitals. Moreover, this study allows us to get a clear picture regarding the effect of different treatment strategies and different study populations on ADR occurrence.

A limitation of this study is that the effect of unlicensed and off-label use of the medications as potential risk factors for ADR occurrence was not analysed. Another limitation was that the sample size from two hospitals, Australia and HK, was small. This was due to resource limitations in Australia which resulted in only 1 month of data collection. The spread of pandemic flu (influenza A H1N1) during the second half of 2009 in HK led to restrictions in ward visits for research.

Conclusion

This study conducted in general paediatric medical wards in European and non-European countries showed that the following were independent predictors of ADRs: number of drugs prescribed per patient; older age; presence of diseases of the blood and blood-forming organs and certain disorders involving the immune mechanisms, diseases of the nervous system, or certain conditions originating in the perinatal period. Gender, however, did not appear to play such an important role in paediatric ADR epidemiology as it does in the adult population.

These findings indicate that in order to minimise the risk of ADRs, healthcare professionals should keep the number of prescribed drugs as low as possible, pay particular attention to children prescribed five drugs or more and also to those children at high risk, such as immuno-compromised patients.

Acknowledgements Asia Rashed was funded by the Yamani Cultural and Charitable Foundation, London, United Kingdom. In addition, authors wish to thank Professor Stephen Evans for his statistical advice Dr Lynda Wilton for reviewing the manuscript and Ben Cross for developing the database.

Contributors I.C.K.W. and A.N. created the idea of the study. I.C.K.W. revised methodology and supervised the study. A.N. was the chief investigator of the study and supervised the analysis and data collection. A.N.R. was responsible for the management and analysis of the data from all sites, data collection and assessment in the UK and entering the data into the database. N.C., W.R., S.T. were responsible for study implementation, data collection and assessment at their sites. A.N.R. produced the first draft of the manuscript and all authors approved the final draft. I.C.K.W. is guarantor for the study.

Conflicts of interest All authors declared that they have no financial interests that may be relevant to the submitted work.

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