

ROBERT KOCH INSTITUT



Originally published as:

Knopf, H., Du, Y.

Perceived adverse drug reactions among non-institutionalized children and adolescents in Germany

(2010) British Journal of Clinical Pharmacology, 70 (3), pp. 409-417.

DOI: 10.1111/j.1365-2125.2010.03713.x

This is an author manuscript.

The definitive version is available at <http://www3.interscience.wiley.com>

Perceived adverse drug reactions among non-institutionalized children and adolescents in Germany

Hildtraud Knopf, Yong Du

RKI 22, Robert Koch Institute, General-Pape-Strasse 64-66, 12101 Berlin

What is already known about the subject?

Drug safety in paediatric medication is a public health concern. According to previous studies, the incidence of adverse drug reactions (ADRs) varies greatly from 0.7% to 2.7% among paediatric outpatients and from 2.6% to 18.1% among paediatric inpatients. Little has been reported on the risks of drug use in the general child population.

What this study adds

Our study showed that the prevalence of perceived ADRs in Germany was 0.9% among non-institutionalized children in general and 1.7% among children who had used at least one medicine within the 7 days before the medical interview. Perceived ADRs in the general child population were clustered with gastrointestinal disorders and subcutaneous tissue disorders. They appeared to be mild and at the lower limits of the range reported in other studies. Health surveys covering the use of a diverse range of drugs might be suitable for computing ADR prevalence and for identifying risk factors among non-institutionalized children. They should be taken into account together with other pharmacovigilance systems.

Aims: Little has been reported on the risks of drug use in the general child population. This study investigated perceived adverse drug reactions (ADRs) among non-institutionalized children in Germany.

Methods: All medicines used in the last 7 days before the medical interview were recorded among the 17 450 children aged 0–17 years who participated in the 2003–06 German Health Interview and Examination Survey for Children and Adolescents (KiGGS). Perceived ADRs were reported by the children's parents and confirmed by trained medical professionals during the medical interview.

Results: One hundred and fifty-seven medicines were involved in the occurrence of 198 perceived ADRs in 153 patients. This corresponded to 1.1% of total used drugs, 0.9% (95% confidence intervals 0.7, 1.1%) of all children, and 1.7% (1.4, 2.1%) of children treated with medications. About 40% of all perceived ADRs involved gastrointestinal disorders and 16% involved skin tissue disorders. Perceived ADRs were most frequently reported in relation to drugs acting on the nervous system (25.8%), followed by systemic anti-infectives (18.7%) and drugs acting on the respiratory system (16.2%). Risk factors for perceived ADRs included older age groups, polypharmacy (≥ 2) and a poor health status.

Conclusion: Perceived ADRs in the general child population were clustered with gastrointestinal disorders and subcutaneous tissue disorders. They appeared to be mild and at the lower limits of the range reported in other studies. Health surveys covering the use of a diverse range of drugs might be suitable for computing ADR prevalence and identifying risk factors among non-institutionalized children. They should be taken into account together with other pharmacovigilance systems.

Introduction

For a long time now, adverse drug reactions (ADRs) have been recognized as one of the main causes of paediatric morbidity in the USA and some European countries [1–3]. Many studies on paediatric ADR occurrence have been published since then. Most of them are based on an analysis of data on hospitalized children [4–9], outpatient paediatric clinics or drug consumption [10–14]. Results on ADR incidence vary greatly in these studies, between 0.7% [10] and 2.7% [11] for paediatric outpatients and between 2.6% [10] and 18.1% [9] for paediatric inpatients. An earlier meta-analysis of 17 prospective studies published between 1973 and 2000 estimated that the overall incidence of ADRs was 1.46% for paediatric outpatients and 9.53% for paediatric inpatients [15] and a recent metaanalysis of eight prospective studies published between 2001 and 2007 reported weighted average ADR incidence rates of 1.0% for paediatric outpatients and 10.9% for paediatric inpatients [16].

In Germany, ADR incidence has been investigated by means of intensive monitoring in hospital. In a 10-bed paediatric isolation ward of a German university hospital in Erlangen, the ADR incidence was estimated at 17.4–21.5% [17–19] using this method. Another study conducted in the HELIOS Klinikum Wuppertal teaching hospital reported that 14.1% of inpatient children experienced an ADR over a period of 3 months [20]. These studies were conducted in paediatric wards. Few results have been reported in Germany from non-clinical settings on epidemiological aspects of the risks of paediatric drug use. An early regional ADR monitoring programme in the federal state of Brandenburg estimated that ADR incidence was approximately 1% among children given medications [21]. This study was conducted 10 years ago. More up-to-date population-representative national data on noninstitutionalized children not necessarily using medical services have so far been very rare both in Germany and worldwide. Against this background, we investigated the perceived ADRs reported by children's parents among non-institutionalized children and adolescents in Germany using the drug-use data from the latest German Health Interview and Examination Survey for Children and Adolescents (KiGGS).

Methods

Data source and study population

The German KiGGS survey was conducted by the Robert Koch Institute from 2003 to 2006. KiGGS investigated 0- to 17-year-old children and adolescents usually resident in Germany with the aim of providing comprehensive and representative data on their health status [14].

The design, sampling strategy and study protocol of KiGGS have been described in detail elsewhere [14]. Briefly, two-stage sampling procedures were applied. In the first stage, a sample of 167 German municipalities (112 in the former West Germany, 55 in the former East Germany) was drawn which was representative of municipality sizes and structures in Germany. In the second stage, the addresses of all 28 299 children and adolescents were chosen randomly from the local population registers. Children and adolescents with a foreign nationality were also included. Excluded were children who were currently in institutions such as hospitals, medical and nursing stations [22]. The overall percentage of non-deliverable survey contacts was 5.3%. The final survey sample included 17 641 children and adolescents with a response rate 66.6% [22]. One hundred and ninety-one children did not provide drug-use data and were therefore excluded from the present study, resulting in a study population of 17 450 children (8880 boys, 8570 girls; see Table 1). All survey participants were informed of the purpose of the study and other relevant concerns. Informed consent was obtained prior to the medical examination either from the children's parents or from the children themselves if they were over the age of 14 years [14].

Data collection and assessment

All the children's parents/guardians and all children aged 11 years or older were asked to fill in a standard parents' or children's questionnaire. These questionnaires were used to collect information on socio-demographic data, family backgrounds, parents-rated children's health status, and health-

related living conditions and behaviour patterns. In addition, trained physicians conducted a standardized, computer-assisted personal interview with the children's parents and the children themselves on medical history, health problems and all medicines used within the 7 days prior to the interview [23]. Parental social status was defined as lower, intermediate or upper according to the total scores of a composite social-status index integrating the parents' levels of education, household incomes and professions [24]. Children who themselves (or whose mother/father) did not have German nationality or were not born in Germany were defined as having an immigration background [25].

Medicine use was investigated by asking the following question:

'Has your child taken any medicines in the last 7 days? Please also mention the use of any ointments, liniments, contraceptive pills, vitamin and mineral supplements, medicinal teas, herbal medicines or homoeopathic medicines'.

Children aged 14 years and older were encouraged to add data on the use of medicines themselves. All prescription or over-the-counter (OTC) medicines used in the 7 days before the interview were recorded in the answers to this question. The definition of 'medicines' here was broader than that used by the German Medicines Act [26].

We collected the following information on every medicine mentioned by parents or the children themselves:

brand name: as free text;

indications: as free text;

form of administration: i.e. tablets, dragees, drops, ointments, injections, liniments, etc.;

frequency of intake: 'several times a day', 'every day', 'regularly but not daily' or 'every week';

origin of the medicine: 'prescribed by a doctor', 'prescribed by a non-medical practitioner', 'bought over the counter', or 'obtained from other sources';

duration of use: '<1 week', '1–4 weeks', '1–12 months' or '1 year or longer';

improvement in the condition(s) treated: 'great', 'partial', 'not much', 'not at all' or 'does not apply';

We also asked the children's parents or the children themselves whether or not the medicine used was well tolerated and to describe the degree of tolerability ('very good/good', 'partial', 'not good' or 'poor'). Another question was whether any ADRs/side effects were noticed following the use of the medicine ('yes' or 'no'). If the answer was 'yes',

the ADRs/side effects reported were documented and confirmed informally by interviews conducted by physicians with medical knowledge. No standardized causality/ severity assessment was made on the reported ADRs, however.

The free texts on medicine brand names were coded according to WHO ATC (Anatomical Therapeutic-Chemical) codes [27] as follows: A00 (alimentary system and metabolism), B00 (blood and blood-forming organs), C00 (cardiovascular system), D00 (dermatologicals), G00 (genito-urinary system and sex hormones), H00 (systemic hormonal preparations excluding sex hormones and insulin), J00 (anti-infectives for systemic use), L00 (antineoplastic and immunomodulating agents), M00 (musculoskeletal system), N00 (nervous system), P00 (antiparasitic products, insecticides and repellents), R00 (respiratory system), S00 (sensory organs) and V00 (various). Homoeopathic preparations, which were commonly used among children and adolescents in Germany [28], were given an additional new code 'Z00' as they were not covered by the ATC classification system. Indications of medicines were coded according to WHO ICD-10 [29] and ADRs according to MedDRA (Medical Dictionary for Regulatory Activities, version 10.1); the so-called 'preferred terms' [PT System Organ Class (SOC)] were assigned [30, 31].

Statistical analysis

All statistical analyses were performed using SPSS statistical software (release 17.0). Descriptive statistics were used to analyze characteristics of the study population including the prevalence of perceived ADRs. Associations of the perceived ADRs with socio-demographic and health-related characteristics were quantified by using odds ratios (OR) and their 95% confidence intervals (95% CIs), which were derived from multiple logistic regression models among children who had taken medications. The complex sample method was used to obtain the 95% CIs by the SPSS procedure [22]. Group differences were considered statistically significant if a *P* value was less than 0.05 or if

the 95% CIs for two rates did not overlap.

Results

Table 1 lists the main characteristics of the study sample by gender. The vast majority of boys and girls had a good/very good health status, came from families with no immigration background and resided in the former West Germany and in cities. Nearly half of boys and girls lived in a family with an intermediate social status, one quarter, respectively, in a family with a low or high social status. No significant difference was found between boys and girls with regard to these characteristics.

Eight thousand eight hundred and ninety-nine children (51%) had used at least one medicine during the last 7 days before the interview (Table 1), with girls showing a higher proportion than boys ($P < 0.05$). One hundred and fifty-three children reported perceived ADRs, corresponding to a population prevalence rate of 0.9% (95% CIs 0.7, 1.1%) with no difference between boys and girls ($P = 0.835$). Among children who used at least one medicine, the prevalence of perceived ADRs was 1.7% (1.4, 2.1%) (data not shown in Table 1).

Among children who had used medications, no significant difference in the prevalence of perceived ADRs was found in subgroups stratified by gender, regions of residence, immigration background and parental social status (Table 2). Along with age, the prevalence of perceived ADRs showed a J-shape curve; the highest rate was found in the 14–17 year age group, the lowest in the 3–6 and 7–10 year age groups ($P < 0.001$). A significant difference was also found in the number of concomitantly used medicines and the children's parents-rated health status. The prevalence of perceived ADRs was seven times higher in children using four or more medicines than in children using only one. This association was found in both sexes and all age groups (data not shown). The difference was significant within users of one to four medicines, but disappeared when stratified by age and sex (data not shown). The prevalence of perceived ADRs was more than nine times higher among children with a bad/very bad health status than among children with a good/very good health status. The risks of perceived ADRs were confirmed in the multivariate regression analysis. The interaction between the number of drugs and children's health status was not statistically significant (data not shown in Table 2).

A total of 14 588 medicines were recorded in the study sample; 157 medicines (1.1%) were reportedly involved in the occurrence of perceived ADRs (Table 3). A significantly lower proportion was found among the non-prescription medicines, medicines obtained from other sources, and preparations used for a short term (<1 week) or irregularly. By contrast, a significantly higher proportion was found in prescription medicines, medicines used for a medium period (from 1 week to 12 months) and in medicines that were used regularly.

Medicines from the classes N00, J00, R00, G00, D00 and A00 (representing 82% of the total medicines) covered the vast majority of suspected drugs (Table 4). The proportion of suspected drugs in each of these medication classes varied from 0.4% for A00 to 5.7% for J00. The same was true for the medications in the subgroups. The highest proportion was recorded in psychoanaleptics (12.1%, particularly methylphenidate 11.9%), followed by antibiotics 6.0% and contraceptives 2.8%. Although P00 (antiparasitic products, insecticides and repellents) showed the highest proportion of 10%, the number of medicines in this class was very low, being only 20 (Table 4).

Most perceived ADRs were recorded in drugs acting on the nervous system (N00), followed by systemic anti-infectives (J00), drugs acting on the respiratory system (R00), and drugs acting on the genitourinary system and sex hormones (G00) (Table 5). According to MedDRA terminology, 40.4% of all perceived ADRs related to gastrointestinal disorders such as nausea, vomiting and diarrhoea, while 16.2% were skin and subcutaneous tissue disorders such as rashes and dry skin.

Discussion

In a population-representative sample of children aged 0 to 17 years, we found that 0.9% (1.7% of children who had used medications in the last 7 days) reportedly experienced an ADR. Similar findings have been reported in previous pharmacovigilance studies conducted among children in Germany and other European countries.

A 3 month German ADR monitoring project estimated the incidence of mild to moderate ADRs as about 1% in children who had been given medications [21]. An Italian active ADR monitoring program reported an ADR incidence rate of 15.1 per 1000 children [3]. A prospective 1 week monitoring study in France found that 1.53% of children consulted a regional hospital and 0.67% a private paediatrician because of ADRs [10]. Another French prospective pharmacovigilance survey of drug prescribing by office-based paediatricians reported an ADR incidence rate of 1.41% [32]. The results of two meta-analysis studies estimated that the ADR incidence rate was 1.0 (95% CI 0.3, 1.7) for outpatient children [16] and 1.46% (95% CI 0.7, 3.03) for children undergoing outpatient care [15]. Our finding on the prevalence of perceived ADRs was well below the 95% CIs of the two studies [15, 16]. However, the children in our study were non-institutionalized and sampled from the general child population; most of them were in good/very good health. Since most outpatient children were being treated for a specific condition and more likely to be given medications, there was a greater possibility of ADRs. This may be one of the reasons why the prevalence rates of perceived ADRs in the total sample and among drug users were close to the lower and upper 95% CIs, respectively, of the two meta-analysis studies [15, 16].

In the Italian ADR monitoring programme, the highest ADR incidence rate was found in the youngest infant group, the lowest among children aged 8 to 14 years [3]. In a retrospective study conducted in Singapore, in which age and sex were independent ADR risk factors among hospitalized children, ADRs were more likely to occur at higher ages and among boys [33]. Data from the Sweden Medical Products Agency on the mandatory reporting of ADRs also showed a higher ADR frequency among boys than among girls over the period from 1987 to 2001, particularly among children under 5 years of age [34]. Our study, however, found no difference between boys and girls, but a significant difference between age groups, which largely showed a J-shaped curve, the highest rate being found in the 14–17 year age group. This may be due to the fact that many ADRs reported in our study related to oral contraceptives and Ritalin, which were used mainly by older adolescents.

Polypharmacy was a well-established ADR risk factor in both adult and child patients [15, 35]. As the number of concomitantly used drugs increases, so does the likelihood of drug–drug interactions, leading to a greater possibility of ADRs. We found a significant correlation between perceived ADRs and the number of concomitantly used drugs. This finding has been consistently observed previously in a prospective study of spontaneous ADR reporting among hospitalized children in Spain [6], in an ADR monitoring study of outpatient infant and preschool children in the Zagreb region [11] and in a retrospective study in Singapore [33]. Self-rated health status was an important indicator of morbidity; a poor state of health may imply a greater possibility of medication use [36] and therefore be a predictive risk factor of ADRs.

In our study gastrointestinal disorders such as nausea, vomiting and diarrhoea accounted for 40% of perceived ADRs, followed by skin/subcutaneous tissue disorders and general disorders/administration site conditions. These ADRs accounted for two thirds of the total number of perceived ADRs. One reason for such a clustering may be that the ADRs in our study were reported by the children's parents or the children themselves. It may be easier for them, as non-professionals, to perceive such ADRs. Our study sample consisted of non-institutionalized children in outpatient care; serious ADRs needing hospitalization may therefore have been excluded in advance. In addition, ADRs such as hepatotoxicity and pathological laboratory abnormalities induced by drug use were less likely to be reported in such a survey. Though we did not assess the severity of perceived ADRs, we presumed that most of the patients-perceived ADRs were mild to moderate and possibly at the lower limits of the range usually reported. Intensified ADR monitoring may identify a higher number of ADRs and more severe ADRs. However, this would require personnel and involve the cost of medical examinations [20].

Perceived ADRs were reported most frequently in relation to drugs acting on the nervous system, systemic anti-infectives, drugs acting on the respiratory system, genito-urinary and sex hormones,

dermatologicals, and drugs acting on alimentary system and metabolism. Medicines from these classes were also the paediatric medicines that accounted for the vast majority of all medicines used. The prevalence rates of perceived ADRs varied between these classes. The lowest rate was found in drugs acting on the alimentary system and metabolism; in our study most of the medicines in this class were hydrosoluble vitamins and mineral supplements. In the class of drugs acting on the nervous system, suspected drugs were mainly those of the psychoanaleptics subgroup (methylphenidate in particular). Analgesics aspirin and paracetamol were reported less often, even though they accounted for a substantial proportion of the medicines in this class (data not shown). As for drugs acting on the respiratory system, perceived ADRs were mostly recorded in the subgroup of cough and cold medicines, the safety of which was recently reviewed by the UK Medicines and Healthcare products Regulatory Agency (MHRA), which called for their rational use and intensive monitoring [37]. 5.7% of all systemic anti-infectives were involved in the occurrence of perceived ADRs (mainly the antibiotics subgroup). Similar findings were also reported previously in both prospective studies [6] and the analysis of data from ADR spontaneous reporting [38], as well as in the pilot study on ADR monitoring among children by community pharmacies in Aberdeen, UK [39].

Most medicines that were used regularly were prescription medicines, which, as found in our study, were more likely to cause an ADR than OTC medicines. Interestingly, we found that medicines that were used for a medium period of time were more likely to cause an ADR. Repeated use of medicines for a medium period (from 1 week to 12 months) meant rechallenges and dechallenges, so it was easy for parents/adolescents to perceive any ADR. Longterm use of medicines over 1 year, however, may induce tolerance. In addition, patients may choose not to report what they may think is 'normal' when it occurs repeatedly. As a matter of fact, the characteristics of perceived ADRs relating to the suspected medicines and symptoms found in our study were very similar to those found by means of the yellow card system in Spain [38], among outpatient children in the Netherlands [40] and in the US [41], and in the regional ADR monitoring study conducted in Brandenburg, Germany [21]. A recent review revealed that the quality of patient ADR reports seemed not to differ very much from that of reports by health professionals [42].

A major strength of our study is that we used population-representative data to collect and analyze the perceived ADRs among non-institutionalized children. The results provide a clear picture of the frequency and spectrum of perceived ADRs that were not necessarily related to medical treatment in hospitals or outpatient facilities. There are several limitations, however. First, the ADRs reported in this study were perceived by children's parents or the patients themselves. It may be difficult for them to distinguish between an ADR and a symptom of the disease being treated, resulting in over- or under-reporting. Second, although all perceived ADRs were documented and confirmed by medical professionals with medical knowledge, a standardized causality and severity assessment was not carried out. Nevertheless, since parents may understand their own children better and can observe their health status more closely and perceive any changes after the intake of medicines, parental reporting of perceived ADRs can be regarded as an effective method in paediatric pharmacovigilance [42, 43]. Finally, drug use was measured in the past 7 days before the medical interview. This method is less likely to capture ADRs following longterm medicine use.

In conclusion, the perceived ADRs in the generally healthy child population were clustered with gastrointestinal disorders and skin and subcutaneous tissue disorders. They appeared to be mild and at the lower limits of the range usually reported. This, however, should be interpreted in conjunction with methodological limitations. The results of the KiGGS survey on medicine use provided a significant contribution to the quantification of perceived ADRs in the general child population. A comparison of our findings with those of national and international studies suggests that health surveys covering a diverse range of drug use may be suitable for computing perceived ADR prevalence and identifying risk factors and should be taken into account together with other pharmacovigilance systems. This applies in particular to population representative statements on drug use and potential hazards.

Competing interests

There are no competing interests to declare.

This study received financial support from the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfARM). The German Health Interview and Examination Survey for Children and Adolescents (KiGGS) was funded by the Federal Ministry of Health and the Federal Ministry of Education and Research.

References

- 1 Whyte J, Greenan E. Drug usage and adverse drug reactions in paediatric patients. *Acta Paediatr Scand* 1977; 66: 767–75.
- 2 Mitchell AA, Goldman P, Shapiro S, Slone D. Drug utilization and reported adverse reactions in hospitalized children. *Am J Epidemiol* 1979; 110: 196–204.
- 3 Menniti-Ippolito G, Raschetti R, Da CR, Giaquinto C, Cantarutti L. Active monitoring of adverse drug reactions in children. Italian Paediatric Pharmacovigilance MultiCentre Group. *Lancet* 2000; 355: 1613–4.
- 4 Le J, Nguyen T, Law AV, Hodding J. Adverse drug reactions among children over a 10-year period. *Pediatrics* 2006; 118: 555–62.
- 5 Mitchell AA, Lacouture PG, Sheehan JE, Kauffman RE, Shapiro S. Adverse drug reactions in children leading to hospital admission. *Pediatrics* 1988; 82: 24–9.
- 6 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: 681–8.
- 7 dos Santos DB, Coelho HL. Adverse drug reactions in hospitalized children in Fortaleza, Brazil. *Pharmacoepidemiol Drug Saf* 2006; 15: 635–40.
- 8 Fattahi F, Pourpak Z, Moin M, Kazemnejad A, Khotaei GT, Mamishi S, Siadati A, Tabatabaei P. Adverse drug reactions in hospitalized children in a department of infectious diseases. *J Clin Pharmacol* 2005; 45: 1313–8.
- 9 Buajordet I, Wesenberg F, Brors O, Langslet A. Adverse drug events in children during hospitalization and after discharge in a Norwegian university hospital. *Acta Paediatr* 2002; 91: 88–94.
- 10 Jonville-Bera AP, Giraudeau B, Blanc P, Beau-Salinas F, Autrec-Leca E. Frequency of adverse drug reactions in children: a prospective study. *Br J Clin Pharmacol* 2002; 53: 207–10.
- 11 Cirko-Begovic A, Vrhovac B, Bakran I. Intensive monitoring of adverse drug reactions in infants and preschool children. *Eur J Clin Pharmacol* 1989; 36: 63–5.
- 12 Sanz E, Boada J. Adverse drug reactions in paediatric outpatients. *Int J Clin Pharmacol Res* 1987; 7: 169–72.
- 13 Kramer MS, Hutchinson TA, Flegel KM, Naimark L, Contardi R, Leduc DG. Adverse drug reactions in general pediatric outpatients. *J Pediatr* 1985; 106: 305–10.
- 14 Kurth BM, Kamtsiuris P, Hölling H, Schlaud M, Dölle R, Ellert U, Kahl H, Knopf H, Lange M, Mensink GB, Neuhauser H, Rosario AS, Scheidt-Nave C, Schenk L, Schlack R, Stolzenberg H, Thamm M, Thierfelder W, Wolf U. The challenge of comprehensively mapping children's health in a nation-wide health survey: design of the German KiGGS Study. *BMC Public Health* 2008; 8: 196.
- 15 Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol* 2001; 52: 77–83.
- 16 Clavenna A, Bonati M. Adverse drug reactions in childhood: a review of prospective studies and safety alerts. *Arch Dis Child* 2009; 94: 724–8.
- 17 Weiss J, Krebs S, Hoffmann C, Werner U, Neubert A, Brune K, Rascher W. Survey of adverse drug reactions on a pediatric ward: a strategy for early and detailed detection. *Pediatrics* 2002; 110: 254–7.
- 18 Neubert A, Dormann H, Weiss J, Egger T, Criegee-Rieck M, Rascher W, Brune K, Hinz B. The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. *Drug Saf* 2004; 27: 1059–67.
- 19 Neubert A, Dormann H, Weiss J, Criegee-Rieck M, Ackermann A, Levy M, Brune K, Rascher W. Are computerised monitoring systems of value to improve pharmacovigilance in paediatric patients? *Eur J Clin Pharmacol* 2006; 62: 959–65.

- 20** Haffner S, von LN, Wirth S, Thurmann PA. Detecting adverse drug reactions on paediatric wards: intensified surveillance versus computerised screening of laboratory values. *Drug Saf* 2005; 28: 453–64.
- 21** Lewis MA, Kuhl-Habich D, von Rosen J. Drug use and adverse event monitoring in German children. *Int J Clin Pharmacol Ther* 2001; 39: 507–12.
- 22** Kamtsiuris P, Lange M, Schaffrath RA. Der Kinder- und Jugendgesundheitsurvey (KiGGS): Stichprobendesign, Response und Nonresponse-Analyse [The German Health Interview and Examination Survey for Children and Adolescents (KiGGS): sample design, response and non-response analysis]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2007; 50: 547–56.
- 23** Knopf H. Arzneimittelanwendung bei Kindern und Jugendlichen. Erfassung und erste Ergebnisse beim Kinder- und Jugendgesundheitsurvey (KiGGS) [Medicine use in children and adolescents. Data collection and first results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2007; 50: 863–70.
- 24** Winkler J, Stolzenberg H. [Social class index in the Federal Health Survey]. *Gesundheitswesen* 1999; 61: S178–83.
- 25** Schenck L, Ellert U, Neuhauser H. [Children and adolescents in Germany with a migration background. Methodical aspects in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2007; 50: 590–9.
- 26** Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz – AMG) Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), das durch Artikel 1 der Verordnung vom 28. September 2009 (BGBl. I S. 3172) geändert worden ist. Berlin: Bundesministerium der Justiz; 2009.
Available at http://www.gesetze-im-internet.de/amg_1976/BJNR024480976.html
- 27** WIdO, GKV-Arzneimittelindex im Wissenschaftlichen Institut der AOK (WIdO). Anatomisch-Therapeutisch-Chemische-Klassifikation Mit Tagesdosen Amtliche Fassung Des ATC-Index Mit DDD-Angaben Für Die Bundesrepublik Deutschland Im Jahr 2007. Köln: Deutsches Institut für Medizinische Dokumentation und Information (DIMDI), 2009.
- 28** Du Y, Knopf H. Paediatric homoeopathy in Germany: results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). *Pharmacoepidemiol Drug Saf* 2009; 18: 370–9.
- 29** WHO. International Statistical Classification of Diseases and Health Related Problems (The) ICD-10, 2nd edn. Geneva: World Health Organisation, 2009.
- 30** Journot V, Tabuteau S, Collin F, Molina JM, Chene G, Rancinan C. About the necessity to manage events coded with MedDRA prior to statistical analysis: proposal of a strategy with application to a randomized clinical trial, ANRS 099 ALIZE. *Contemp Clin Trials* 2008; 29: 95–101.
- 31** MedDRA MSSO Comment on the Primary System Organ Class (SOC) Allocation in MedDRA. MSSO-DI-9745-1.0.0. 6 August 2007. Available at http://www.meddramsso.com/files_acrobat/Primary_SOC_Allocation_in_MedDRA.pdf
- 32** Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. *Br J Clin Pharmacol* 2002; 54: 665–70.
- 33** Kidon MI, See Y. Adverse drug reactions in Singaporean children. *Singapore Med J* 2004; 45: 574–7.
- 34** Kimland E, Rane A, Ufer M, Panagiotidis G. Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. *Pharmacoepidemiol Drug Saf* 2005; 14: 493–9.
- 35** Bates DW, Miller EB, Cullen DJ, Burdick L, Williams L, Laird N, Petersen LA, Small SD, Sweitzer BJ, Vander Vliet M, Leape LL. Patient risk factors for adverse drug events in hospitalized patients. ADE Prevention Study Group. *Arch Intern Med* 1999; 159: 2553–60.
- 36** Du Y, Knopf H. Self-medication among children and adolescents in Germany: results of the National Health Survey for Children and Adolescents (KiGGS). *Br J Clin Pharmacol* 2009; 68: 599–608.
- 37** Sharfstein JM, North M, Serwint JR. Over the counter but no longer under the radar – pediatric cough and cold medications. *N Engl J Med* 2007; 357: 2321–4.
- 38** Morales-Olivas FJ, Martinez-Mir I, Ferrer JM, Rubio E, Palop V. Adverse drug reactions in children reported by means of the yellow card in Spain. *J Clin Epidemiol* 2000; 53: 1076–80.
- 39** Stewart D, Helms P, McCaig D, Bond C, McLay J. Monitoring adverse drug reactions in children using community pharmacies: a pilot study. *Br J Clin Pharmacol* 2005; 59: 677–83.
- 40** Schirm E, Tobi H, van Puijenbroek EP, Monster-Simons MH, de Jong-Van den Berg LT. Reported adverse drug reactions and their determinants in Dutch children outside the hospital. *Pharmacoepidemiol Drug Saf* 2004; 13: 159–65.

- 41** Bourgeois FT, Mandl KD, Valim C, Shannon MW. Pediatric adverse drug events in the outpatient setting: an 11-year national analysis. *Pediatrics* 2009; 124: e744–50.
- 42** Blenkinsopp A, Wilkie P, Wang M, Routledge PA. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. *Br J Clin Pharmacol* 2007; 63: 148–56.
- 43** Oshikoya KA, Senbanjo IO, Njokanma OF. Parental reporting of suspected adverse drug reactions in children in Lagos, Nigeria. *Arch Dis Child* 2009; 94: 469–73.

Tables

Table 1

Socio-demographic and health-related characteristics of survey participants by gender. German Health Interview and Examination Survey for Children and Adolescents (KiGGS), 2003–06

	Boys <i>n</i>	%	95% CI	Girls <i>n</i>	%	95% CI
Total	8880	100		8570	100	
Age groups (years)						
0–2	1397	13.6	13.2, 13.9	1373	13.6	13.2, 14.0
3–6	1925	21.0	20.7, 21.3	1907	21.1	20.8, 21.4
7–10	2103	21.7	21.4, 22.1	2004	21.8	21.4, 22.1
11–13	1572	17.3	17.0, 17.6	1468	17.3	17.0, 17.7
14–17	1883	26.4	25.8, 27.0	1818	26.3	25.7, 26.9
Region						
East	2889	16.5	12.3, 21.9	2847	16.5	12.3, 21.9
West	5991	83.5	78.1, 87.7	5723	83.5	78.1, 87.7
Urbanicity						
Rural town	1958	17.9	12.6, 24.8	1939	17.9	12.6, 24.7
Small town	2337	27.6	20.9, 35.6	2229	27.2	20.5, 35.1
Medium-sized town	2498	29.0	22.2, 37.0	2475	29.3	22.4, 37.2
Large city	2087	25.5	19.0, 33.3	1927	25.6	19.1, 33.5
Immigrant background*						
Yes	1350	17.4	15.4, 19.6	1230	16.9	14.9, 19.1
No	7498	82.6	80.4, 84.6	7292	83.1	80.9, 85.1
Social class*						
Low	2454	27.7	26.1, 29.4	2306	27.3	25.9, 28.8
Intermediate	4011	45.2	43.7, 46.8	3890	45.7	44.1, 47.2
High	2185	27.0	25.2, 29.0	2181	27.1	25.2, 29.0
Parent-rated health status*						
Very good	3407	38.2	36.8, 39.6	3466	40.1	38.7, 41.6
Good	4759	54.7	53.2, 56.1	4491	53.6	52.2, 55.0
Moderate	567	6.9	6.2, 7.6	486	5.9	5.3, 6.6
Bad	19	0.2	0.1, 0.4	18	0.3	0.2, 0.5
Very bad	7	0.1	0, 0.2	5	0.1	0, 0.1
Children who used medications	4362	48.7	47.2, 50.3	4537	53.1	51.5, 54.7
Children with perceived ADRs	77	0.8	0.6, 1.1	76	0.9	0.7, 1.3

*The amounts in each category may not add up to the total because of missing data. ADRs, adverse drug reactions.

Table 2

Prevalence rates and risk factors of perceived ADRs among children who used medications. German Health Interview and Examination Survey for Children and Adolescents (KiGGS), 2003–06

	Prevalence (%)	95% CI	Odds ratio*	95% CI	P value
Gender					0.799
Boys	1.7	1.3, 2.2	1.1	0.7, 1.5	
Girls	1.8	1.4, 2.4	1		
Age groups (years)					<0.001
0–2	1.6	1.1, 2.4	1		
3–6	1.0	0.6, 1.6	0.5	0.3, 1.1	
7–10	1.1	0.7, 1.8	0.7	0.4, 1.4	
11–13	2.0	1.3, 3.1	1.5	0.8, 2.6	
14–17	2.7	2.0, 3.7	1.8	1.0, 3.0	
Region					0.716
East	2.0	1.2, 3.2	1.1	0.6, 1.9	
West	1.7	1.3, 2.1	1		
Immigrant background					0.924
Yes	1.6	1.0, 2.6	1.0	0.6, 1.9	
No	1.8	1.4, 2.2	1		
Social status					0.495
Low	1.5	1.0, 2.2	0.9	0.5, 1.5	
Intermediate	1.9	1.5, 2.5	1.2	0.7, 1.8	
High	1.7	1.1, 2.4	1		
Number of drugs used					<0.001
1	1.00	0.8, 1.3	1		
2	1.8	1.2, 2.7	1.8	1.1, 2.8	
3	3.4	2.2, 5.1	3.5	2.1, 5.9	
4+	7.2	4.7, 10.2	6.7	4.1, 11.0	
Parent-rated children's health status					<0.001
Very good/good	1.5	1.2, 1.8	1		
Moderate	4.4	3.0, 6.6	2.2	1.4, 3.5	
Bad/very bad	13.8	4.8, 33.9	8.7	2.6, 28.7	

*Adjusted for age group, gender, region, immigrant background, social status, number of drugs, parents-rated children's health status.

Table 3

Perceived ADRs among children in Germany by origin of drugs, duration and frequency of use. German Health Interview and Examination Survey for Children and Adolescents (KiGGS), 2003–06

	Number of drugs n (%)	Suspected drugs n	Proportion % (95% CI)	P value
Origin of the medicine				<0.001
Prescription	8 565 (59.2)	135	1.6 (1.3, 1.9)	
Over the counter (OTC)	3 579 (24.7)	14	0.4 (0.2, 0.7)	
Other sources	2 042 (14.1)	8	0.4 (0.2, 0.8)	
Total*	14 470 (100)	157	1.1 (0.9, 1.3)	
Duration of use				<0.001
<1 week	7 984 (55.5)	57	0.7 (0.6, 0.9)	
1–4 weeks	2 099 (14.6)	36	1.7 (1.2, 1.4)	
1–12 months	2 431 (16.9)	39	1.6 (1.2, 2.2)	
≥1 year	1 869 (13.0)	23	1.2 (0.8, 1.9)	
Total*	14 383 (100)	155	1.0 (0.9, 1.3)	
Frequency of use				0.019
Regular	9 588 (65.9)	111	1.2 (1.0, 1.4)	
Irregular	2 518 (17.3)	14	0.6 (0.3, 0.9)	
Other frequency	2 441 (16.8)	31	1.3 (0.9, 1.8)	
Total*	14 547 (100)	156	1.1 (0.9, 1.3)	

*The amounts in each category may not add up to the total because of missing data. P value: chi-square test for the difference within the subgroup.

Table 4

Perceived ADRs among children in Germany by medication classes. German Health Interview and Examination Survey for Children and Adolescents (KiGGS), 2003–06

ATC-codes	Number of drugs used <i>n</i>	Suspected drugs <i>n</i>	Proportion %	95% CI
N00	1 289	37	2.87	2.1, 4.0
-N06	190	23	12.1	8.2, 17.6
-N06BA04	160	19	11.9	7.7, 17.9
J00	475	27	5.7	3.9, 8.2
-J01	434	26	6.0	4.1, 8.7
R00	4 412	31	0.7	0.5, 1.0
-R05	1 864	14	0.8	0.4, 1.3
G00	507	16	3.2	1.9, 5.1
-G03A	429	12	2.8	1.6, 4.9
D00	1 956	14	0.7	0.4, 1.2
A00	3 310	12	0.4	0.2, 0.6
B00	86	3	3.5	0.8, 10.3
L00	90	3	3.3	0.8, 9.9
H00	298	3	1.0	0.2, 3.1
P00	20	2	10.0	1.8, 31.6
V00	234	2	0.9	0.1, 3.3
S00	236	2	0.9	0.1, 3.3
M00	602	2	0.3	0.0, 1.3
Z00	951	2	0.2	0.0, 0.8
C00	82	1	1.2	0, 7.4
Missing	40	0	-	-
Total	14 588	157	1.1	1.0, 1.3

A00, Alimentary system and metabolism; B00, Blood and blood-forming organs; C00, Cardiovascular system; D00, Dermatologicals; G00, Genito-urinary system and sex hormones; G03A, Oral contraceptives; H00, Systemic hormonal preparations excluding sex hormones and insulin; J00, Anti-infectives for systemic use; J01, Antibiotics; L00, Antineoplastic and immunomodulating agents; M00, Musculoskeletal system; N00, Nervous system; N06, Psychoanaleptics; N06BA04, Methylphenidate (Ritalin); P00, Antiparasitic products, insecticides and repellents; R00, Respiratory system; R05, Cough and cold medications; S00, Sensory organs; V00, Various; Z00, Homoeopathics.

Table 5

Perceived ADRs among children in Germany by ATC classes and MedDRA SOC. German Health Interview and Examination Survey for Children and Adolescents (KiGGS), 2003–06

ATC-codes	MedDRA-SOC																								Total	
	1		2		3		4		5		6		7		8		9		10		11		12			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%		
A00			1	0.5					10	5.1			1	0.5											12	6.1
B00									4	2.0															4	2.0
C00									1	0.5															1	0.5
D00	1	0.5	16	8.1																					17	8.6
G00			1	0.5			8	4.0	7	3.5			2	1.0			3	1.5	4	2.0					25	12.6
H00			1	0.5									1	0.5									1	0.5	3	1.5
J00	3	1.5	2	1.0			2	1.0	26	13.1	1	0.5	1	0.5							2	1.0			37	18.7
L00									3	1.5			1	0.5											4	2.0
M00			1	0.5					2	1.0															3	1.5
N00	10	5.1	2	1.0	1	0.5			11	5.6			6	3.0			7	3.5	12	6.1	2	1.0			51	25.8
P00									3	1.5															3	1.5
R00	6	3.0	6	3.0	3	1.5			12	6.1			2	1.0	1	0.5	1	0.5					1	0.5	32	16.2
S00			1	0.5																			1	0.5	2	1.0
V00									1	0.5	1	0.5													2	1.0
Z00			1	0.5	1	0.5																			2	1.0
Total	20	10.1	32	16.2	5	2.5	10	5.1	80	40.4	2	1.0	14	7.1	1	0.5	11	5.6	16	8.1	5	2.5	2	1.0	198	100.0

MedDRA SOC: 1 General disorders and administration site conditions; 2 Skin and subcutaneous tissue disorders; 3 Respiratory, thoracic and mediastinal disorders; 4 Reproductive system and breast disorders; 5 Gastrointestinal disorders; 6 Immune system disorders; 7 Nervous system disorders; 8 Infections and infestations; 9 Psychiatric disorders; 10 Metabolism and nutrition disorders; 11 Others; 12 Not classified. ATC Codes: A00, Alimentary system and metabolism; B00, Blood and blood-forming organs; C00, Cardiovascular system; D00, Dermatologicals; G00, Genito-urinary system and sex hormones; H00, Systemic hormonal preparations excluding sex hormones and insulin; J00, Anti-infectives for systemic use; L00, Antineoplastic and immunomodulating agents; M00, Musculoskeletal system; N00, Nervous system; P00, Antiparasitic products, insecticides and repellents; R00, Respiratory system; S00, Sensory organs; V00, Various; Z00, Homoeopathics. ATC, Anatomical-Therapeutic-Chemical; MedDRA, Medical Dictionary for Regulatory Activities; SOC, System Organ Class.