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Allergy-like Immediate Reactions with Herbal Medicines in Children: A Retrospective Study Using Data from Vigibase®

Ricarda Meincke, MSc ^a; Jitka Pokladnikova, PharmD, PhD ^a; Julie Straznicka ^a, PharmDr; Ronald H.B. Meyboom MD, PhD ^{b,c}; David Niedrig, PhD ^d; Stefan Russmann, MD^{e,f}, Ludek Jahodar^g

a. Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, Hradec Kralove, Czech Republic

b. WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Uppsala, Sweden

c. Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, The Netherlands

d. University Children's Hospital Zurich, Zurich, Switzerland

e. drugsafety.ch, Küsnacht, Switzerland

f. Institute of Pharmaceutical Sciences, ETH Zurich, Zurich, Switzerland

g. Department of Pharmaceutical Botany and Ecology, Faculty of Pharmacy, Charles University in Prague, Hradec Kralove, Czech Republic

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Corresponding author:

Julie Straznicka, PharmD

Faculty of Pharmacy in Hradec Kralove, Charles University in Prague

Department of Social and Clinical Pharmacy

Heyrovského 1203, CZ-500 05 Hradec Kralove, Czech Republic

Phone: +420 495 075 216

E-mail: straj7aa@faf.cuni.cz

Meinke R; Pokladnikova J; Straznicka J; Meyboom RHB; Niedrig D; Russmann S;

Jahodar L

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Pediatr Allergy Immunol

Abstract

Background: The use of herbal medicines in children and the general population is continually on the rise with an overall herbal lifetime and current use ranging between 0.8–85.5 % and 2.2–8.9 %, respectively. Although acute hypersensitivity reactions are generally considered to be rare, little knowledge exists on the frequency and type of these reactions especially in specific populations like children.

Objectives: To assess the patterns of acute hypersensitivity reactions to herbal medicines reported to the WHO global individual case safety report (ICSR) database Vigibase® in children.

Study design: From the original Vigibase® extract for the time between 1968 and 2014, we included all reports with adverse drug reactions (ADR) associated with herbal medicines in children where WHO-ART reaction terms were indicative of acute hypersensitivity reactions.

Results: Vigibase® contained 2,646 ICSRs with 14,860 distinct adverse reactions reported in association with herbal medicine in children. Among those, 79 cases with 107 *allergy-like* reactions met our inclusion criteria. The most commonly reported WHO-ART terms were urticaria or rash/rash erythematous (59.8 %), and allergic reaction (8.4 %). The most frequently reported suspected herbal medicines were mixed herbal products (51.4%), *Hedera helix* (15.0 %), and *Echinacea purpurea* (5.6 %). Most frequent routes of administration were oral (75.9 %), topical (8.9%), and rectal (3.8 %). Over 30 % of cases were reported in the age group from 7 to 12 years. The majority of reports were received from Germany (29.1 %), Thailand (21.5 %), and Australia (11.4 %).

Conclusion: Vigibase® contains a considerable number of acute hypersensitivity reactions in children associated with herbal medicines, including life-threatening reactions such as anaphylactic shock.

Keywords

adverse drug reactions, allergy, drug safety, herbal medicine, hypersensitivity, children, pediatric, pharmacovigilance, phytotherapy.

Corresponding author:

Julie Straznicka, PharmD

Faculty of Pharmacy in Hradec Kralove, Charles University in Prague

Department of Social and Clinical Pharmacy

Heyrovského 1203, CZ-500 05 Hradec Králové, Czech Republic

Phone: +420 495 075 216

E-mail: straj7aa@faf.cuni.cz

Introduction

Contrary to popular belief, herbal remedies can cause severe adverse drug reactions (ADRs) and interactions with other herbal products or medicines. (1, 2) The lack of similar regulations for herbal medicines that are already in place for conventional drugs leaves the so-called spontaneous reporting systems (SRSs) as the sole and principal source of adverse event data for herbal drugs. Therefore, for a newly introduced herbal preparation, the reporting of ADRs plays a critical role in determining its overall adverse event profile. (3) Especially in children who require different dosage and treatment regimens and whose immune system is in an earlier stage of exposure and adaptation, adverse events may vary in their frequency and manifestation. (4)

With regard to herbal medicine use in paediatric patients, a recently published systematic review found overall herbal lifetime use to be between 0.8–85.5 % and current use to range from 2.2 to 8.9 %. (5) Studies investigating the relationship between herbal medicines and hypersensitivity reactions in children are rare in the literature. A review of Ernst summarized the findings of serious ADRs in children and adults, based mostly on case series. (6) The most frequently reported serious ADRs were 149 cases of allergic reactions due to Eucalyptus. Studies regarding pharmacovigilance in children have predominantly been published in North America, making up 64.8 % of all studies included in a systematic review of Black et al. Only 16.9 % of the included studies used SRSs as an ADR data source. (7)

The objective of this study was therefore to identify herbal medicines associated with hypersensitivity reactions in children and adolescents as reported in Vigibase®. Analysis of

the data aimed to provide information about herbal medicines most commonly related to *allergy-like* and *asthma-like* symptoms, as well as factors such as gender, reporting frequency by country and year, reaction outcomes, reporter qualification.

Methods

Data sources

The WHO's global individual case safety report (ICSR) database Vigibase[®] reporting system counted over 10 million reports as of April 2015. (8) In this study, a data extract provided by the Uppsala Monitoring Center (UMC) in Sweden for the period between the start of the WHO's international pharmacovigilance program in 1968 and August 2014 was used. (2) The UMC manages the WHO's global individual case safety report (ICSR) database Vigibase[®].

Herbal medicine definition

This study uses the WHO definition of herbal medicines: "Herbal medicines include herbs, herbal materials, herbal preparations, and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations". (9) All substances of natural origin in Vigibase[®] are grouped by HATC (Herbal Anatomical-Therapeutic-Chemical) codes. (10)

Case selection

Patient age was limited to < 18 years and time of ADR onset to ≤ 1 day to distinguish reports of immediate hypersensitivity (Type I) reactions from delayed onset hypersensitivity reactions (Type IV). (11) Substances not classified as *suspect* or with non-HATC codes were omitted. The WHO-ART preferred terms indicating symptoms of an immediate hypersensitivity reaction were selected manually. Reaction terms less suggestive of

hypersensitivity or more likely to have a different etiology than the suspect herbal such as cough, dyspnoea, larynx pain, stridor, pruritus ani or genital were excluded from the reaction terms. Gastrointestinal (GIT) symptoms were excluded altogether. The terms were divided into two groups, *allergy-like* and *asthma-like*, with the WHO-ART preferred terms *asthma* and/or *bronchospasm* comprising the *asthma-like* group, all remaining terms constituting the *allergy-like* group (Table 1).

Table 1 Example of manually selected WHO-ART terms indicating immediate hypersensitivity reactions

Causality assessment

Only the cases where the relationship between a herbal and an adverse drug reaction was classified according to the WHO standardised case causality assessment criteria and rated as either *certain*, *probable*, or *possible* (12) were included in this study. Figure 1 summarizes the selection process.

Statistical analysis

Data analysis was descriptive and was carried out using the statistical data analysis software STATA[®] MP 13.1 (StataCorp., College Station, TX, USA)

Confounders

The confounders that may have influenced study results are primarily co-medications. Children with diseases such as cystic fibrosis, attention deficit disorder, asthma, atopic dermatitis, allergic rhinitis, cancer, inflammatory bowel disease, and rheumatoid arthritis have been shown to use Chinese herbal medicine, Ginkgo, Echinacea, and St. John's wort more frequently than children who are not affected by these diseases. (13) Likewise, co-

medications may confound the data since a suspect herbal can no longer be considered the only possible source of a reported hypersensitivity reaction. However, the analysis of the presence of diseases and intake of co-medications is beyond the scope of this study, and co-medications are not often stated by the primary reporter in the first place as they are not among the four minimum criteria (Reporter ID, patient, drug, ADR) needed to submit an individual case safety report.

Fig. 1: Flowchart depicting the case selection process and exclusion/inclusion criteria.

¹ Herbal medicines coded as “concomitant”, “interacting”, “null” and “not converted” were not included in the study cohort

² Manual selection, classification, and revision of ADRs indicating high specificity regarding allergic reactions

³ Calculation of latency time in STATA[®] based on “onset date” (of ADR) and “start date” (of herbal drug)

Results

This study used a data extract of Vigibase[®] from 1968 to August 2014, which contains 26,909 unique ICSRs relating to herbal medicines from 42 different countries. The total number of adverse drug reactions was 237,496, coded according to the WHO Drug Dictionary Enhanced (Version June 1, 2014) in the WHO-ART adverse reaction terminology. Of the total data set, 79 cases met our inclusion criteria. The final cohort in our study consists of 107 ADRs indicative of an allergic reaction following the use of one or more herbal medicines in children under 18 years of age. This represents 0.05 % of ADRs of the original Vigibase[®] extract.

Table 2: Case report characteristics

Adverse drug reactions

The total number of reported ADRs divided into *allergy-like* and *asthma-like* in our study population of 79 cases was 107, representing 1.35 reported ADRs per unique case report ID and suspect herbal. *Allergy-like* reactions accounted for 97.5 % of reports and *asthma-like* reactions for 2.5 %.

Geographical distribution

All 107 reports (79 cases) meeting our inclusion criteria were reported from 16 countries, with seven being in Europe, four in Asia, two in Oceania, one in the Caribbean, and two in South America. The majority of ADRs came from Germany (29.1 %), followed by Thailand (21.5 %) and Australia (11.4 %), representing over half of all cases included in this study (62.0 %).

Reports by gender and age

Gender was reported in all 79 cases and was evenly distributed in the study population. The age group with the highest frequency of reported *allergy-like* ADRs to herbal medicines was 7-12 years. The mean age was 8.3 years, and the standard deviation was ± 5.4 years, median 8 years (Table 2). The most frequently reported ADRs were rash (22.4 %), urticaria (22.4 %), and rash erythematous (15.0 %), accounting for 59.8 % of all reported ADRs (Table 2).

Reporter qualification

The category hospital was the most frequent reporter qualification and accounted for 24.1 % of all cases. Physicians are the second most important group (Table 2).

Reaction outcomes

At the time of reporting, most cases had an outcome where recovery of the patient from one or more ADRs was achieved (72.0 %); there were no reports of fatal ADR to herbals. In the nine ADRs reported as “not recovered”, rash and urticaria were most commonly caused by various herbal medicines.

Fig. 2: Number of ADRs reported per year (n = 79)

Analysis of reports by year of reporting showed that there were no reports which met our inclusion criteria before 1992. A significant gap can be observed in 2012 (Figure 2).

Suspect herbal medicines

The most commonly reported suspect herbal medicines were mixed herbals (51.4 %), *Hedera helix* (15.0 %), and *Echinacea purpurea* (5.6 %), all together contributing to 71.6 % of all reported ADRs in this study.

Table 3: Ten most reported suspect herbal medicines associated with ADRs and 10 preferred base names of suspect mixed herbal medicines (n = 107)

Discussion

This descriptive study analyzed a VigiBase[®] extract from 1960 to August 2014 and is the first to report global ADR data associated with hypersensitivity reactions due to herbal medicines

in children. A comparatively small number of ICSRs, namely 0.09 % of the original data set, were associated with herbal-induced hypersensitivity reactions in pediatric patients under the age of 18 years.

The use of herbal medicine has consistently been increasing worldwide, as has the total number of herbal ADR reports. The growing global popularity of herbal use was also reflected in our study by the increasing number of reports from 1986 until 2011.

With regard to the likely diagnosis of immediate allergic reactions, we used a restrictive study design emphasizing high specificity and, consequently, excluded the majority of reports from the extracted original data set.

The majority of ADRs in our study were either skin or hypersensitivity reactions, with urticaria (22.4 %), rash/rash erythematous (22.4 %/15.0 %), and allergic reaction (8.4 %) accounting for most reports. This is largely consistent with previous studies that investigated ADRs in adults and pediatric patients due to complementary and alternative medicines which include herbal products. (14) Most studies investigating ADRs in children have focused on conventional medicines. In those studies, the skin was reported to be the most commonly affected organ system, followed by the GIT. (15, 16)

In our study, the incidence of ADRs was the highest in the age group 7 – 12 years. It has been shown before that children and teenagers may be more prone to suffer from hypersensitivity reactions than the rest of the population. (17) We did not further analyze reports by age group and country of origin; however, the majority of reports came from Germany (29.1 %). The German health care system covers herbal remedies for children under 12 years of age. In our study, 57 of 79 cases occurred in children aged 0-12 years. The use of herbal medicines in this age group due to insurance coverage may also pose an incentive for German parents to choose alternative medicine options for their underage children.

Regarding gender distribution, overall, evidence is contradictory, with some studies reporting higher percentages of ADRs occurring in male pediatric patients (18, 19, 20) even though female pediatric and adolescent patients use more complementary and alternative medicines including herbal products. (5) Our study results showed no gender differences, which is in accordance with previous studies. (18, 19, 20) However, these studies mainly discussed the overall ADR incidence in children, without a focus on herbal medicines or hypersensitivity reactions. It has previously been reported that boys seem to be at a higher risk of suffering from allergic diseases in childhood than girls, but girls are more affected by asthma, food allergies, and anaphylaxis once puberty is reached. (21)

Of all single-ingredient herbal drugs, the most frequently reported herbal preparation leading to *allergy-like* as well as *asthma-like* symptoms was *Hedera helix* (15.0 %). It has been reported to cause occupational contact dermatitis. (22) We can speculate about the complete absence of cases with eucalyptus as a suspected drug. Although it was the most frequently reported drug in severe ADRs with herbal medicines in adults, (2) due to the limitation of use in children under 12 years old according to EMA, (23) there was only one case of a four-years old boy's reaction to eucalyptus oil in our data set. This boy came from Mexico and therefore it is possible that there were no restrictions on the use of eucalyptus oil in this country or the reaction occurred due to inappropriate use of the product.

The largest group of reporter type in our study were physicians, followed by pharmacists. A review of Inch et al. showed that, generally, more reports are submitted by female physicians and that pharmacists report substantially less than physicians. (24) Since we do not know if any of the physicians who reported the ADRs in this study are allergist or CAM specialists, it is not clear in how far reporter type might confound the data.

Apart from the important contribution health care professionals have in pharmacovigilance, there is a growing understanding of the role that patients and consumers

play in post-marketing surveillance of conventional and herbal medicines. Now required by law in the EU, consumer reporting was already practiced in Sweden and the Netherlands long before the law was implemented, and the results show that it has been a highly valuable tool in signal detection. (25)

Despite the various limitations spontaneous reporting as a means of post-marketing surveillance has, the importance of SRSs in ADR detection has been acknowledged widely. (26) The main drawbacks of using SRSs as a source for pharmacovigilance data remain the problem of underreporting, duplicate reports, a certain background incidence of a particular ADR in the population, and unknown exposure of a patient to a drug. (27) Some studies have found that under-reporting for non-serious ADRs is even greater than that for serious ADRs, leading to only 4 % of non-serious and 10 % of serious ADRs being reported, (24, 28) which most likely extrapolates to even greater numbers for herbal medicines. Likewise, factors such as insect bites, increased exercise regimen, mastocytosis, uncontrolled asthma, food hypersensitivities, or latex allergy may have confounded the data. (17) Semantics have also been shown to influence ADR selection of MedDRA reaction terms by reporters used to code an adverse event (29), and the same may be presumed for WHO-ART, which was used in this study. Another limitation might have been the manual selection process of reaction terms that indicate hypersensitivity and the overall exclusion of all GIT related symptoms. Since food allergies often cause GIT symptoms that can be either IgE-mediated, non-IgE mediated, or mixed IgE and non-IgE mediated, (30) we decided to exclude GIT symptoms from the list of selected reaction terms altogether. Other symptoms such as cough, dyspnoea, larynx pain, pruritus ani or genital were excluded from the reaction terms as the probability of a non-herbal related etiology appeared relatively more likely than with other selected terms. Ultimately, the small number of cases included in this study do not allow for any generalizations or further quantitative pharmacoepidemiological interpretations. It should be

noted that the ICSRs that comprised the data extract used for this study came from a variety of sources and the likelihood that the suspected adverse reactions are drug-related is not the same in all cases. Our results suggest that while herbal medicines for oral use in children and adolescents are generally regarded as safe, international pharmacovigilance data indicates that many such products carry a risk of causing acute allergy-like adverse reactions. The recognition of the possibility of such reactions - with the use of e.g. *Hedera helix*, *Pelargonium* roots and *Echinacea purpurea* - is needed for a timely diagnosis as well as for the prevention of potentially severe ADRs.

Conclusion

The results highlighted the potential of herbal medicines to cause serious allergic reactions in children. The global increase in herbal medicine use calls for improved, standardized, and more consistent reporting of ADRs associated with herbal medicines to ultimately provide safer treatment options for children and adolescents. Due to the lack of clinical studies in pediatrics for both conventional and herbal medicines, it is also important to realize the potential of pharmacovigilance data as a tool in signal detection for pediatric patients, and improvements at all levels of the pharmacovigilance process need to be made. The reporting rate and awareness of the public and medical staff of the importance of pharmacovigilance needs to be raised.

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Table 1 Example of manually selected WHO-ART terms indicating immediate hypersensitivity reactions

Allergic reaction	Angioedema	Face oedema	Oedema periorbital	Skin reaction local
Allergy	Asthma*	Flushing	Oedema pharynx	Stridor*
Anaphylactic reaction	Bronchospasm*	Larynx oedema	Rash	Tongue oedema
Anaphylactic shock	Dermatitis	Oedema generalized	Rash erythematous	Urticaria
Anaphylactoid reaction	Erythema multiforme	Oedema mouth	Rash maculo- papular	Urticaria acute

Table 2: Characteristics of reported cases

Gender (n = 79)	n	%
Female	38	48.1
Male	41	51.9
Age group (years) (n = 79)		
0-2	15	19.0
3-6	18	22.8
7-12	24	30.4
13-17	22	27.8
Reporting country (n = 79)*		
Germany	23	29.1
Thailand	17	21.5
Australia	9	11.4
Spain	5	6.3
Switzerland	4	5.1
Korea, Republic of	4	5.1
Malaysia	3	3.8
Ukraine	3	3.8
Cuba	2	3.8
Netherlands	2	3.8
Reporting source (n = 79)		
Hospital	19	24.1
Physician	14	17.7
Pharmacist	13	16.5
Other	8	10.1
General practitioner	6	7.6
Specialist physician	5	6.3
Not converted	5	6.3
Other Health Professional	3	3.8
Manufacturer	3	3.8
NULL	2	2.5
Consumer/Non Health Professional	1	1.3
Type of ADR (n = 79)		
Allergy-like	77	97.5
Asthma-like	2	2.5
Most frequently reported WHO-ART preferred terms (n = 107)		
Rash	24	22.4
Urticaria	24	22.4
Rash erythematous	16	15.0
Allergic reaction	9	8.4
Anaphylaxis	7	6.5
Dermatitis	5	4.7
Face oedema	4	3.7
Oedema periorbital	3	2.8
Rash maculo-papular	3	2.8
Angioedema	2	1.9
Oedema generalised	2	1.9
Oedema mouth	2	1.9
Allergy	1	0.9
Asthma	1	0.9
Bronchospasm	1	0.9
Erythema multiforme	1	0.9
Flushing	1	0.9
Larynx oedema	1	0.9

* 10 most frequently reporting countries

Table 3: Ten most reported suspect herbal medicines associated with ADRs and 10 preferred base names of suspect mixed herbals (n = 107)

Suspect herbal	n	%
Mixed herbals	55	51.4
<i>Hedera helix</i>	16	15.0
<i>Echinacea purpurea</i>	6	5.6
<i>Andrographis paniculata</i>	5	4.7
<i>Thymus vulgaris</i>	3	2.8
<i>Calendula officinalis</i>	2	1.9
<i>Carica papaya</i>	2	1.9
<i>Hamamelis virginiana</i>	2	1.9
<i>Matricaria recutita</i>	2	1.9
<i>Senna alata</i>	2	1.9
Preferred base name		
Pelargonium reniforme root/ <i>Pelargonium sidoides</i> root	11	20.0
<i>Elettaria cardamomum</i> oil/ <i>Zingiber officinale</i> extract/ <i>Capsicum annuum</i>	10	18.2
<i>Hedera helix</i> leaf/ <i>Coptis</i> spp. rhizome	4	7.3
<i>Primula veris</i> root extract/ <i>Thymus vulgaris</i> herb extract/ <i>Hedera helix</i> leaf extract	4	7.3
<i>Chelidonium majus</i> herb/ <i>Melissa officinalis</i> leaf/ <i>Silybum marianum</i> fruit/ <i>Angelica archangelica</i> root/ <i>Carum carvi</i> fruit/ <i>Glycyrrhiza glabra</i> root/ <i>Matricaria recutita</i> flower/ <i>Mentha x piperita</i> leaf/ <i>Iberis amara</i>	3	5.5
<i>Mentha x piperita</i> oil/ <i>Ulmus rubra</i> bark powder	3	5.5
<i>Sambucus nigra</i> flower/ <i>Scutellaria baicalensis</i> root/ <i>Salix alba</i> stem bark/ <i>Armoracia rusticana</i> root	3	5.5
<i>Thymus vulgaris</i> extract/ <i>Drosera rotundifolia</i> extract	3	5.5
<i>Aloe vera</i> gum/ <i>Aloe ferox</i> gum	2	3.6
<i>Panax ginseng</i> root/ <i>Schisandra chinensis</i> fruit	2	3.6

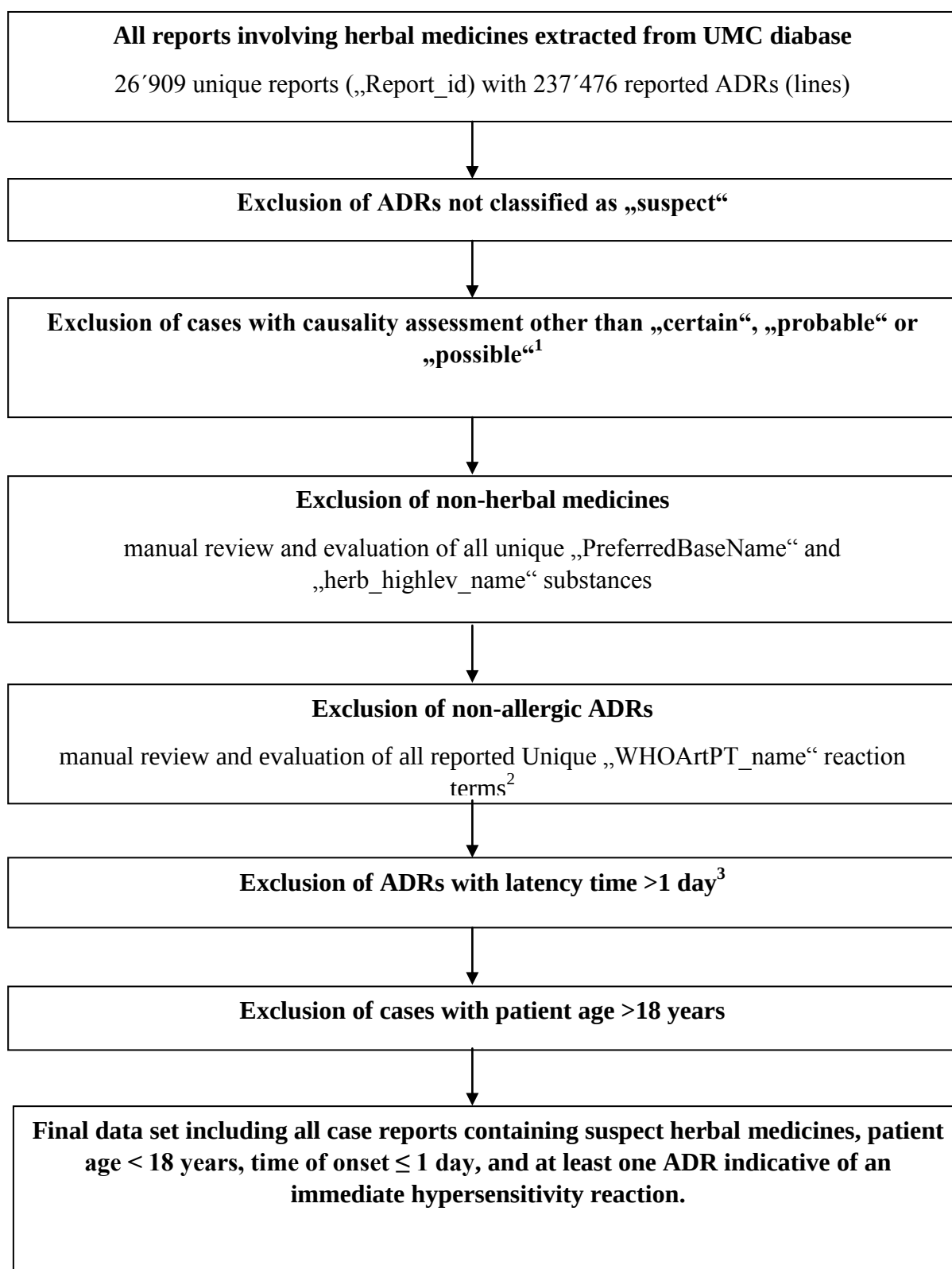


Fig. 1: Flowchart depicting case selection process and exclusion/inclusion criteria.

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²Manual selection, classification and revision of ADRs indicating high specificity regarding allergic reactions

³Calculation of latency time in STATA[®] based on “onset date” (of ADR) and “start date” (of herbal drug)

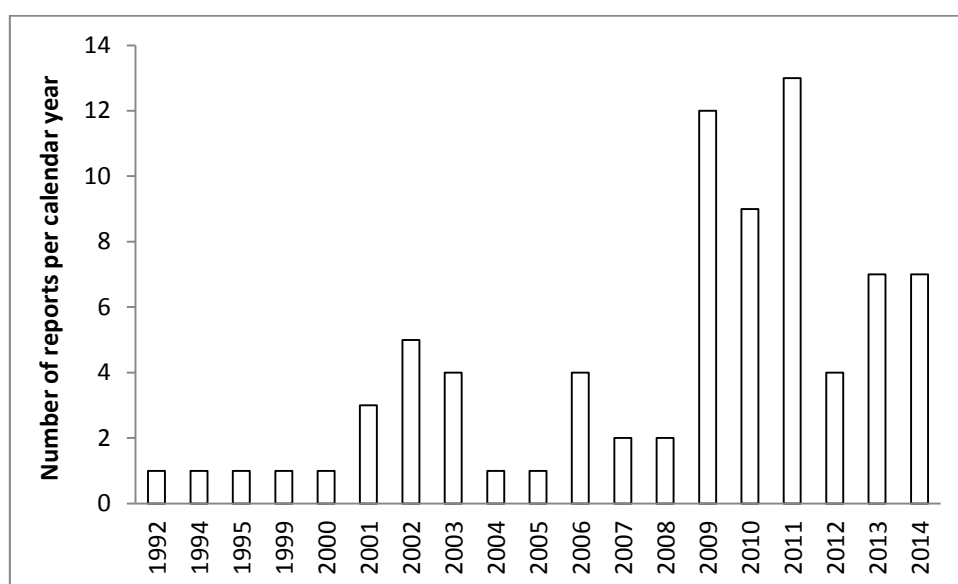


Fig. 2: Number of ADRs reported per year (n = 79)