Charles University in Prague
Faculty of Pharmacy in Hradec Králové
Department of Clinical and Social Pharmacy

Master‘s Thesis

Allergic Reactions to Herbal Medicines in Children

Supervisor: Ph.D. Jitka Pokladnikova, PharmD.

Hradec Králové, 2015 **Ricarda Meincke**

Statement of Originality

I declare that the research presented here is my own original work, created with the guidance of my supervisor Ph.D. Jitka Pokladnikova, and has not been submitted to any other institutions for the award of a degree. All information sources and publications used are properly cited.

Date: Signature:

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1 Abstract

Background: The use of herbal medicines in children and adolescents is continually on the rise. Contrary to popular belief, herbal products (HPs) are not always a safe alternative to conventional drugs and can cause a variety of adverse events such as severe and fatal allergic reactions. In regards to herbal medicine use in children, a recently published systematic review that searched PubMed, Embase, PsycINFO and AMED included 58 studies from 19 countries and found overall herbal lifetime use to be between 0.8–85.5 % and 2.2–8.9 % for current use. Unlike most synthetically produced drugs, the adverse event profile of such "natural" preparations in children has rarely been studied. To this date, effective systems that monitor adverse drug events (ADRs) and long term side effects associated with HPs are either non-existent or still developing in many countries. Due to insufficient and inconsistent ADR reporting, little is known about the ADR spectrum of herbals in pediatric patients. Awareness of the potential of HPs to cause ADRs, particularly in children and adolescents, needs to be increased and reporting to national pharmacovigilance centers (PVCs) reinforced.

Objectives: This project analyzed the worldwide adverse event data for herbal drugs related to hypersensitivity reactions as recorded in the WHO's global individual case safety report (ICSR) database VigiBase® between 1968 and August 2014, focusing on pediatric patients under the age of 18 years.

Methods: From the original VigiBase® extract, only drugs with an herbal ATC code (HATC), classified as "suspect" with a *certain*, *possible* or *probable* causality assessment, a time of ADR onset of "0-1 day", patient age less than 18 years and ADRs suggesting hypersensitivity, were included in this study. WHO-Art preferred terms indicating allergy were further divided into *allergic* and *asthma-like*.

Results: 26,909 ICSRs relating to herbal drugs worldwide, accounting for a total of 237,496 reported ADRs, comprised the original dataset. Of these 150 cases, representing 222 ADRs, met our study's inclusion criteria. Out of 222 ADRs, 202 were classified as *allergic* and 20 as *asthma-like*. The most frequently reported WHO-ART terms in the allergic group were urticaria (22.1 %), rash (11.7 %) and anaphylactoid reaction (9.0 %). The most common reported terms of the *asthma-like* reactions were asthma (5.4 %) and bronchospasms (2.7 %). Mixed herbals were the most frequently reported suspect herbal causing almost equally as many *allergic* (60.9 %) as *asthma-like* reactions (70.0%). Anaphylactic shock was reported in 12 cases (5.4 %) and no case was lethal. Most reports occurred in those 13-17 years of age.

Males (54 %) were slightly more affected than females (46 %). The majority of cases were reported in Germany (28 %), Sweden (15.3 %) and Thailand (11.3 %).

Conclusion: Data analyzed as reported in VigiBase® showed that herbal medicines can cause severe hypersensitivity reactions and anaphylaxis in children and adolescents. To further optimize the usefulness of pharmacovigilance data and establish safer treatment regimens for pediatric patients, awareness of potential health threats through herbal medicines needs to be increased and the reporting of ADRs promoted.

2 Introduction

Unlike conventional medicines, herbal medicines do not undergo active clinical testing or post-marketing surveillance before or after marketing authorization. Therefore, for a newly introduced herbal preparation, the reporting of ADRs plays a critical role in determining its overall adverse event profile. For conventional medicines adverse event reporting primarily serves the purpose of determining long term ADRs that cannot be detected during the duration of clinical trials, as well as extremely rarely occurring adverse events of already established medicines.

Contrary to popular belief, herbal remedies can cause severe ADRs and interactions with other herbals or medicines [1]. The lack of similar regulations for herbals that are already in place for conventional drugs, leave so called spontaneous reporting systems (SRSs) as the sole and principal source of adverse event data for herbal drugs. Furthermore, pharmacovigilance is a valuable tool in determining efficacy and interaction potential of herbal medicines, which due to the lack of pre-marketing studies would otherwise remain unidentified [2].

Most research regarding drug safety in children has been conducted for prescription and non-prescription drugs, in particular vaccines, antidepressants, antipsychotics, other central nervous system (CNS) drugs, corticosteroids, antibiotics, antivirals and general anaesthetics [3]. Adverse events in children and adolescents associated with herbal medicines has only more recently been the subject of studies published in the literature [4-7].

For both herbal and conventional medicines, the conduction of large scale clinical trials in children raises various ethical concerns and questions. The physiological changes that a child's body undergoes until it reaches adulthood cause the pharmacodynamic and pharmacokinetic profile of a drug to differ from that in adults. Hence, paediatric patients require different dosage and treatment regimens and adverse events can vary in their manifestation [8-10]. Due to the lack of evidence based pharmacotherapy, paediatricians prescribe most medicines "off-label". Off-label use is the prescription and administration of a medicine for an indication or population group it is not officially licensed for, or via a route of administration or dosage that has not been approved. The rate of off-label and unlicensed drug use in children was found to be 71.8 % in intensive care units (ICUs), 46.0 % on wards, 33.0 % in outpatients and 10.8 % by general practitioners [11]. The U.S. FDA therefore emphasizes the importance of clinical trials in children in order to determine age dependent dosage regimens, efficacy and drug safety profiles, and points out that no more than 20-30 %

of drugs currently holding a license for the U.S. market have been approved for use in children [12].

With regard to herbal medicine use in paediatric patients, a recently published systematic review that searched PubMed, Embase, PsycINFO and AMED included 58 studies from 19 countries and found overall herbal lifetime use to be between 0.8–85.5 % and 2.2–8.9 % for current use. Percentages representing lifetime use and current use for CAM (Complementary and Alternative Medicine) and homeopathy were analysed separately and ranged from 10.9–87.6 % and 0.8–39 % (lifetime) and 8–48.5 % and 1–14.3 % (current) respectively. Use of both herbal drugs and homeopathy in paediatric patients was highest in Germany [13].

Overall, little evidence of the efficacy of most herbal medicines in children and adults exists. If positive results are reported these are usually attributed to a placebo effect rather than a pharmacological effect of the herbal preparation [14]. However, an example of an herbal that has recently been studied in a clinical trial and was found to be effective is *Ginkgo biloba*. The study by Shakibaei et al. found that *G. biloba* may have a positive additive effect in complementary therapy with methylphenidate to treat ADHD/hyperactivity disorder in children [15]. On the contrary, a randomized controlled trial by Salehi et al. showed that *Ginkgo biloba* monotherapy was not superior to methylphenidate in treating ADHD in children [16]. Contradicting evidence regarding the efficacy in children and adults exists for various herbals and most frequently depends on study design.

Studies researching the relationship between herbal medicines and hypersensitivity reactions in children and adults are rare in the literature. A review by E. Ernst in 2003 summarized the findings of serious ADRs in children and adults, based mostly on case series and case reports. Results showed serious ADRs such as intravascular haemolysis, hypertension, encephalitis, myocardial infarction or toxic hepatitis, have been caused by herbal medicines [4]. The most frequently reported serious ADRs were 149 cases of allergic reactions due to Eucalyptus. For all other reactions, sample sizes were much smaller and mostly consisted of case reports. It seems the frequency with which herbal remedies cause hypersensitivity reactions is significantly underestimated and underreported. An idea of how high the prevalence of allergic disorders in children is was found in the International Study of Asthma and Allergies in Childhood (ISAAC), which was conducted in 6- to 7-year-old Canadian children, of whom 10.8 % had allergic rhinoconjunctivitis symptoms, 18.2 % asthma symptoms, and 12 % eczema symptoms[17]. A systematic review by Gardiner et al. in 2013, including 96 articles, representing 128 cases of adverse events associated with herbal

medicine use in children, found in decreasing order of frequency eucalyptus (n=12), camphor (n=10), fennel (n=6), jin bu huan (n=6), swanuri marili (n=6), kharchos suneli (n=6), tea tree (n=5), lavender (n=4), blue cohosh (n=3), buckthorn (n=3), liquorice(n=3), and garlic (n=3) to be the most frequently reported herbals, primarily causing neurological and gastrointestinal symptoms [18]. Anaphylaxis was only reported in one case concerning a chamomile-containing enema, however, the review emphasized the need for improved reporting of case reports describing herbal induced adverse events. Overall, considering the seriousness and prevalence of allergy in pediatric patients in general and the underreporting of adverse event due to herbals, in particular in children and adolescents, lead us to analyze the available international ADR data indicating hypersensitivity reactions caused by herbal preparations in those less than 18 years of age.

For adults, using electronic health care records in the form of spontaneous reports has previously shown to be a useful approach in the detection of ADRs [19]. The problem of underreporting of ADRs and the consequent lack of data is an even greater problem for children than adults, and more for herbals remedies than for conventional medicines. ADR reporting was found to occur least frequently in the age group of 5-19 year olds, and most frequently in 0- to 4-year-olds and 65- to 74-year-olds, with no significant difference in age distribution between low and high income level countries [20]. Polypharmacy, comorbidities, drug-drug or drug-herbal interactions between could explain an increased prevalence of ADRs in the elderly [21].

Due to the limited data in the group of 5-19 year olds, other means of ADR detection in children such as patient interviews, information collected on hospital ward rounds, computerized records and case reports are employed [22]. Studies regarding pharmacovigilance in children have predominantly been published in North America, making up 64.8% of all studies included in a systematic review by Black et al. in 2015. Only 16.9% of the included studies used spontaneous reporting systems as ADR data source [3]. To the best of our knowledge, studies using data from spontaneous reporting systems that analyse worldwide adverse event data for hypersensitivity reactions in paediatric patients related to herbal medicines, do not currently exist in the literature. Therefore we decided to conducted as study investigating the prevalence of allergic reactions in children and adults associated with herbals using a data extract from the WHO's international ICSR database VigiBase®.

3 Aim

The objective of this study was to analyze worldwide ADR reports of hypersensitivity reactions in children under the age of 18 related to herbal medicines between 1968 and August 2014. The scope of this Master's thesis is to identify frequently reported herbals 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 *allergic* and *asthma-like* symptoms, as well as factors such as gender, reporting frequency by country and year, reaction outcomes and reporter qualification.

4 Theoretical part

4.1 Global pharmacovigilance systems

Pharmacovigilance (PV), also known as drug safety, is a term used in the pharmacological sciences and describes the process of monitoring and preventing adverse drug reactions (ADRs). The official definition of the WHO of pharmacovigilance is "a science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [23]. An adverse drug reaction can be described as "any undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use" [24]. According to the WHO, an ADR is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function" [25]. An ADR is distinguished from a toxic reaction, which occurs at above therapeutic concentrations, and a side effect, which is dose-dependent and not associated with the therapeutic effect of a drug. Compared to ADRs, side effects can be beneficial in nature e.g. some antihistamines also have antiemetic and sedative properties that can reduce nausea and help with falling asleep. The term "adverse effects" or "adverse drug reaction" on the other side implies solely undesirable effects. The WHO ADR definition therefore excludes reactions due to contaminants which are often found in herbal products [26] and are the main focus of this study.

Between 1950-1960, thalidomide, back then known as Contergan, was heavily used as a medication to treat morning-sickness in pregnant women, particularly in Germany. As a result of its teratogenic effect, an estimated 10,000 children in 46 countries were born with congenital abnormalities and malformations of the limbs [27]. In response to what is now known as the biggest post-marketing tragedy of the pharmaceutical industry in the 20th century and to prevent such disasters from recurring, the WHO initiated its international ADR monitoring program in 1968 with the goal of creating a global ADR database. Today the WHO's global individual case safety report (ICSR) database, VigiBase®, is located at the UMC (Upsalla monitoring centre) in Sweden [28]. VigiBase® is a spontaneous reporting system (SRS) for individual case safety reports (ICSRs) with the purpose to detect drug safety signals. Since the foundation of the program, the number of participating nations has continually been on the rise, and as of December 2014, counts 120 member countries and 29 associate members which are currently waiting for compatibility approval of their ADR

reporting systems [29, 30]. In 2013 the leading country in terms of ADR reports per 1mio inhabitants was Singapore, followed by the U.S. [21]. Currently, VigiBase® holds a total of over 10 million ICSRs that have been reported by member countries the start of the operation of the international pharmacovigilance program in 1968 [31].

Apart from the WHO, many countries started establishing their own ADR databases. In the United States the Adverse Event Reporting System (AERS) of the US Food and Drug Administration (FDA) implemented the reporting of ADRs under the name of the MedWatch program [32]. In the U.K. the GPRD (General Practitioners Research Database) is operated by the National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA) [33], and in Spain adverse drug reactions are reported to the Sistema Español de Farmacovigilancia (SEFV) (Spanish Pharmacovigilance System) [34]. However, the problem of underreporting of adverse events, in particular in relation to herbals, is not an issue of only a few nations but a global challenge. A good example explaining the reason for the lack of evidence and studies for herbal medicines is TCM (traditional Chinese medicine). Herbals are one of the fundamental therapy approaches used in TCM, along with acupuncture, which has been gaining increasing popularity in Western countries such as Europe and the U.S. In the United States the approval of acupuncture needles as medical devices by the U.S. Food and Drug Administration (FDA) [9], lead to the cost of acupuncture being covered by some insurance policies. However, traditionally used Chinese herbals are viewed and regulated as dietary supplements and the cost is not covered by most insurance providers. This conflict of interest between government funding for drug research and the questionable categorization of herbal remedies as supplements may contribute to the gap between scientific evidence-based medicine and human use-based practice.

Dietary supplements according to the FDA are “safe until proven unsafe”, where the evidence to disprove their safety can only be supplied through case reports or retrospective studies. On the contrary, conventional medicines are subject to strict distribution criteria and undergo vigorous testing during all clinical trial phases, before market authorization is granted. Sometimes ADRs only occur decades after sales and marketing of a medicinal product. Hence, in PV the discovery of previously unknown and serious ADRs through signal detection is of greatest interest [21]. The goal of SRSs is to generate ADR signals that can ultimately lead to a drug being withdrawn from the market. One of the most commonly used examples to illustrate the importance of SRSs is the market withdrawal of Rofecoxib (Vioxx®) or Cerivastatin (Baycol®) [32, 35]. Rofecoxib, a non-steroidal anti-inflammatory

drug, was withdrawn due to an increased risk of cardiovascular morbidity through stroke and/or heart attack. Cerivastatin, a cholesterol lowering agent, showed repeatedly more cases of rhabdomyolysis than for other members of the statin group. However, not can only rare or long term ADRs be detected through SRSs but adverse events that occur more frequently. These can remain undiscovered during the testing phases as trials can fail to represent the actual future patient population in size or exclude the presence of certain co-morbidities [36].

Before the establishment of SRSs in 1960, pharmacovigilance data was collected through phase VI clinical trials sponsored by the industry or prospective clinical registries. Today SRSs depend on patients, health care workers and pharmaceutical companies to report adverse events for both conventional and herbal medicines. Since health care practitioners are not legally entitled to report ADRs outside of clinical trials, the entire PV system relies on medical staff reporting ADRs to meet their own personal ethical and moral obligations. Furthermore, many health care professionals forward patient reports long after the occurrence of an ADR, sometimes because of lack of time and inconvenience of the process. This delay in information transfer to national and regional centres further defers the data analysis process at the WHO and possibly protracts signal detection. A signal as defined by the WHO is “reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”[37]. The slowness and incompleteness of SRSs is their main drawback [36]. The inconsistency that accompanies non-mandatory reporting regulations in most countries results in underreporting and underutilization of pharmacovigilance as a tool for ADR detection and post-marketing surveillance [36] because data is submitted voluntarily and no systematic monitoring strategy is in place [32]. Data mining of electronic medical record (EMR) systems have emerged as an alternative option to phase IV trials and clinical registries [38]. There are various statistical measures that are used in signal detection from EMR data that along with biostatistical algorithms are the most common form of analyzing pharmacovigilance data [6].

4.2 Adverse event reporting

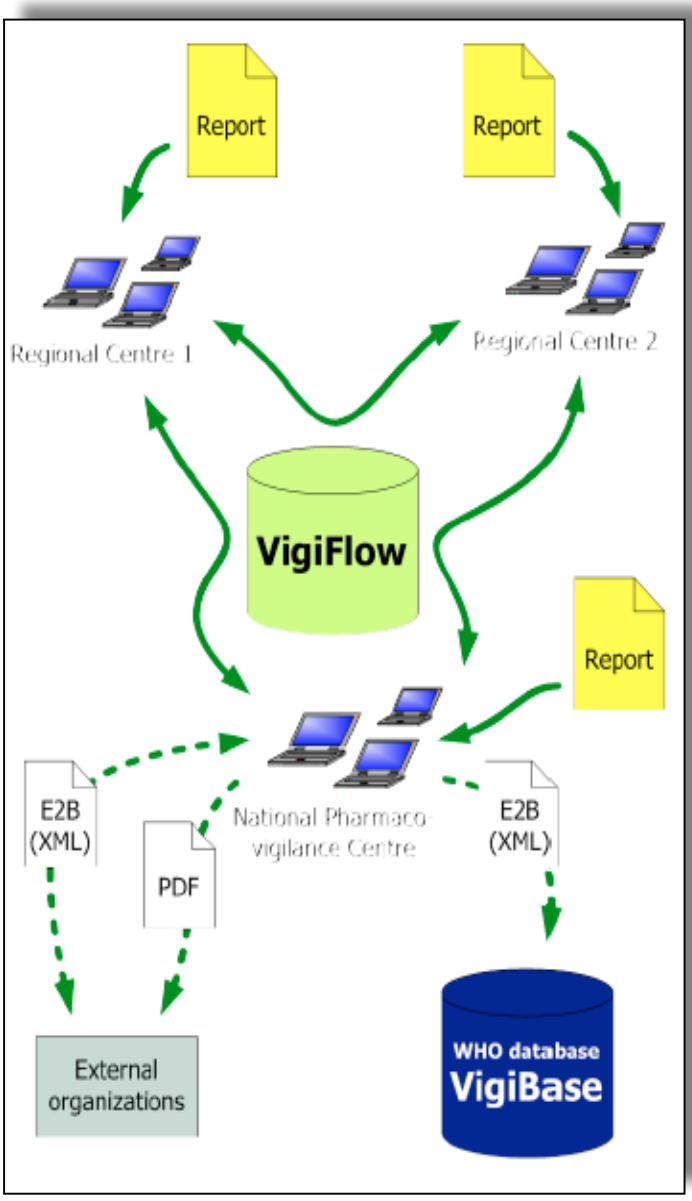

Fig 1 Flow of ICSRs

Reports arriving at the WHO are coded in E2B format, a messaging standard used to send and receive ADR reports in ICSR format. Source: WHO-UMC. VigiFlow® The complete ICSR management system from the UMC

Different countries use different pharmacovigilance systems. Since we are using data extracted from VigiBase® in this study, the systems used by all member countriess of the WHO's international ICSR monitoring program will serve as an example to illustrate the process of adverse event reporting. All member countries and their national and regional pharmacovigilance centres can obtain access to VigiFlow®. VigiFlow® is "a complete Individual Case Safety Report (ICSR) management system for pharmacovigilance (PV) at a national level"[39] and can be used by any country that is part of the WHO international pharmacovigilance program. Once a national or regional PV centre receives an ADR report from e.g. a doctor or pharmacist, the data is entered into VigiFlow®. ADR terminology is coded in either MedDRA or WHO-ART and ICSRs are compatible with the international standard ICH-E2B format. Herbal medicine are assigned an herbal ATC code (HATC) [40].

Once entered into VigiFlow®, the information is forwarded for further assessment to the central national PV centre and analysed for completeness. The national centre verifies the information in the ICSR, including the causality assessment, and reports are forwarded to the UMC (Uppsala Monitoring Centre) and stored in VigiBase®. VigiBase® is the WHO's

international ICSR database. ADRs can directly be reported to national or regional PV centres by pharmaceutical companies, health care professionals and in some countries such as the U.S. also by consumers [33]. Figure 1 shows a diagram of the ICSR report flow [39]. The data mining tool VigiLyze™ can be used to search and analyse reports stored in VigiBase® [41]. The WHO also provides a statistical analysis tool called VigiMine. All drug-ADR pairs as reported in VigiBase® can be statistically analysed according to various criteria. Stratification by age, gender, country and year of reporting is also possible [42]. Each case concerns a single patient and can have only one suspect drug but more than one reported ADR. . If an interaction was suspected, multiple drugs can be coded as interacting.

Despite the WHO's international ADR monitoring program, collaborating countries vary in their reporting strategy. In some countries, for example Sweden, health care providers are compelled to report any ADRs to the national pharmacovigilance centres within the first two years after market authorization and particularly serious, rare and unknown ADRs at any time after approval [43]. However, generally there is no legal obligation in most countries that requires medical staff to report ADRs to a drug safety agency.

Guo et al showed in their study that in China serious and less serious ADRs are reported equally frequent, whereas in the U.K. reporting of serious ADRs is actively being encouraged. As a result a higher proportion of ADRs in the U.K. is classified as such, not because more serious ADRs occur in the United Kingdom than in China. The study also discussed the varying proportion of reporter type by country. In some countries pharmaceutical companies provide the main source of ADR reports, in others health care professionals and patients primarily take on this role. This shows that there is a substantial difference in awareness of the public by country to be able to report ADRs [21] and the need to educate people about pharmacovigilance.

4.3 Causality assessment

Spontaneous ICSRs are assed according to their causality between the reported ADR(s) and drug(s). The WHO has defined certain criteria that a report has to meet to be classified as belonging to one of the 6 assessment groups as shown in Table 1 [26]. To be classified as *certain*, a positive re-challenge must have occurred, i.e. the reported ADR must recur after repeated administration of the suspect herbal, and the temporal relationship needs to be plausible. *Certain* differs from the definition of *probable/likely*, which also requires a temporal connection but only a positive de-challenge, meaning the ADR subsided after discontinuation of the drug. Lastly, for a case to be defined as *possible*, the most important criteria is an existing temporal relationship between drug intake and occurrence of an ADR. Due to missing information from the primary reporter, many cases can only be classified as *possible*. Pharmacovigilance officers at regional and national centres will often follow up with the primary reporter to obtain sufficient information and provide the most accurate causality assessment as possible. An example of a case where even a positive rechallenge will not lead to a *certain* causality assessment is the occurrence of thromboembolic disorders with combined oral contraceptives (COCs). The reason for this is that there is a certain background incidence of e.g. thromboembolisms in women who do not take COCs. Therefore, in such cases the causality can never be classified as *certain*.

Table1: **Causality assessment of suspected adverse drug reactions. *Source:* Adapted from Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnoses and management. Lancet 2000: 356:**

Certain
- A clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals
- The response to withdrawal of the drug (dechallenge) should be clinically plausible
- The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary

Probable/likely
- A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge)
- Rechallenge information is not required to fulfil this definition

Possible
- A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals
- Information on drug withdrawal may be lacking or unclear

Unlikely
- A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations

Conditional/unclassified
- A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are being examined

Unassessable/unclassifiable
- A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified

4.4 Safety of herbal medicines

The annual use of herbal medicines in the general population has been estimated to lie between 20-54 % according to different population studies [44]. Impurity, contamination and counterfeit products are a major concern for children, adolescents and adults alike. Use of complementary and alternative medicines (CAM) such as herbal preparations are also frequently used by pregnant women, and most women self-treat without consultation of their doctor [45]. For the same reasons adults may choose to use herbal supplements, parents might be inclined to give them to their children. Ernst and Hung summarized in their review of 73 articles the following expectations that users of complementary and alternative medicines had (in order of highest to lowest reported response): Hope to influence the natural history of the disease; disease prevention and health/general well-being promotion; fewer side effects; being in control over one's health; symptom relief; boosting the immune system; emotional support; holistic care; improving quality of life; relief of side effects of conventional medicine; good therapeutic relationship; obtaining information; coping better with illness; supporting the natural healing process; and availability of treatment [46]. The third most frequent response was "fewer side effects" and the tenth "relief of side effects of conventional medicines". This shows how widespread the misconception is that herbal medicines are a health risk free alternative to standard pharmacotherapy. Many parents naively believe that herbal remedies do not contain "chemicals". However, little data regarding the safety profile of herbal medicines exist [44]. By assuming to choose a better alternative for their children, parents can actually harm their children by delaying or replacing conventional medical treatment [1, 47]. Even deaths due to CAM use in favour of conventional medicines in children have been reported [5].

Unlike conventional medicines, herbal products can easily be acquired in pharmacies, supermarkets, drugstores and on the internet. Due to less strict regulations regarding the production of herbal products, quality of the preparations is frequently an issue. Batches may vary in concentration and composition or contain contaminants [48]. Counterfeit products that can easily be acquired on the internet pose another threat to consumers. Presence of impurities as well as dubiety about actual ingredients, potency and purity are a concern and may have negative health implications [44]. Hepatotoxicity is a frequently studied serious adverse reaction associated with herbal drug use. Examples of single ingredient herbals that have been shown to cause liver damage are different Chinese herbals, *Teucrium* species and Kava, as well as multi-ingredient preparations such as Hydroxycut that is advertised to aid in

weight loss [48]. Alongside TCM, Indian Ayurvedic medicine also use predominantly herbal remedies. A study by Saper et al. found that 14 out of 70 selected ayurvedic herbals contained lead, mercury and/or arsenic. Some of the tested herbals were specifically designated for paediatric patients and contained a 2 to 3 fold higher mercury content than references doses suggested by the EPA (Environmental Protection Agency); at least 55 cases of heavy metal intoxication associated with ayurvedic herbals in children and adults have been reported in the U.S. and elsewhere since 1978 [49]. Examples of herbals for which severe toxicities or interactions are known are St. John's wort, Kava-kava, Wormwood, Nutmeg, Valerian, Catnip, Ginseng, Ginkgo biloba, Comfrey, Blue cohosh, Pennyroyal oil from *Mentha pulegium*, apricot kernels, podophyllin from *Podophyllum peltatum*, Kan-mokutsu (*Aristolochia manshuriensis*) and Aristolochia fangchi, Chuen-lin (*Coptis chinensus* or *C. japonicum*) and yin-chen (*Artemisia scoparia*) or Danshen (*Salvia miltiorrhiza*) [6].

An example of a serious but not allergic reaction gives the study by Halicioglu et al. who reported two cases of generalized tonic-clonic seizures in an infant and a toddler after oral intake of sage oil (*Salvia officinalis*). Substances contained in sage oil such as 1,8-cineole, camphor, a-thujone, b-thujone, borneol, and viridiflorol have been shown to have epileptogenic properties [50]. This is a good example of how a plant based medicinal product that would be considered safe by consumers and parents can unexpectedly provoke severe adverse drug reactions in paediatric patients.

4.5 Hypersensitivity reactions associated with herbal medicines

Initially classified by Coombs and Gell in 1963, immediate allergic reactions, also known as type A or type I allergic reactions, refer to the IgE mediated process that causes the onset of symptoms soon after exposure to an allergen [51]. Type I reactions are characterized by rhinitis, headache, dermatitis (hives), and/or anaphylactic shock whereas Type 4 allergic reactions are known as delayed hypersensitivity and are associated with contact dermatitis [52]. Hard to distinguish from anaphylactic reactions are anaphylactoid reactions, which are not governed by immunological processes but due to mast cell degranulation. Anaphylactoid is now considered to be an outdated term by the World Allergy Organisation and the term non-allergic anaphylaxis or non-immune anaphylaxis should be used instead [53]. Anaphylaxis in childhood is most commonly triggered by hypersensitivity to allergens contained in food [54]. Wheat, milk, eggs, fish, soy and peanuts most frequently lead to an anaphylactic shock in children and adolescents [55]. Herbal medicine use is not just increasing amongst the adult population but also in adolescents. Results of an online survey found that 41% of 520 adolescents stated they had used herbal or green tea, zinc, echinacea or echinacea/goldenseal, ginseng, ginger, ginkgo biloba, soy supplements, omega 3 fatty acids or fish oil, creatine, weight loss supplements, St. John's wort, valerian, ephedra, or feverfew before [56].

Data regarding hypersensitivity reactions associated with herbal drug use in children is particularly rare in the literature [56] and case reports are the main source of information. More evidence is available regarding the occurrence of allergic reactions in the general population. For example, a study by Wechwithan et al. previously reported the occurrence of allergic reaction such as anaphylaxis, angioedema, urticaria and facial oedema due to different Thai herbal preparations [57]. In the study analysis of all reports in the Thai ADR database between 2002 and 2013 yielded 502 reports of ADRs associated with Thai traditional medicines (TTM). The highest percentage of ADRs classified as serious was reported for *Andrographis paniculata* (24.6 %), *Derris scandens* Benth (19.2 %) and *Curcuma longa* Linn. (14.6 %). Six reports of anaphylactic shock, 47 of urticaria and 11 of facial oedema were reported for *A. paniculata*. Five reports of angioedema were found for *D. scandens* whereas *C. longa* (Tumeric) was associated with gastrointestinal symptoms such as nausea, vomiting, diarrhoea or dizziness.

Another example of an herbal induced hypersensitivity reaction is a case report by Engebretsen et al. which discusses the case of a 20-year old man that had repeatedly been

suffering from facial oedema after taking Echinaforce®, an herb and root extract from *Echinacea purpurae*. After extensive testing a positive reaction to sesquiterpene lactones was detected, which are commonly found in the *Asteraceae/ Compositae* family [58]. Cross reactions within the *Asteracea* family are known to occur and result in hypersensitivity type 1 reactions when other plants of this family are used [52]. Cases of anaphylaxis for *Echinacea purpurae* have been reported, but are also known to occur for other members of the *Asteracea* family that are commonly used such as chamomile (*Chamaemelum nobile*) and milk thistle (*Silybum marianum*); long-term use of Echinacea, Evening primrose (genus *Oenothera*) and Ginkgo are associated with allergy [52].

With regards to Chinese herbal medicines Ji et al. report cases of sever and fatal anaphylaxis associated with the use of nine different Chinese herbal injections used to treat upper respiratory tract infectionsor the common cold.Out of 150 cases, 27 concerned children under the age of 12, of which 6 were lethal. Injections used contained one or more herbal ingredient and included Shuanghuanglian (*Scutellaria baicalensis*, *Flos lonicerae*, *Forsythia suspense*), Qingkailing (Cholic acid, *Conchamargaritifera,* Hyodesoxycholic acid, *Bubalus bubalis, Gardenia jasminoides, Isatis indigotica, Scutallaria baicalensis, Flos lonicerae*), Chaihu (*Radix Bupleuri*), Banlangen (*Isatis indigotica*), Chuanhuning (*Androrgraphis paniculata, Nees* leaf extract, potassium sodium dehydroandroan drographolide succinate), and Yuxingcao (*Houttuynia cordata*); allergic reactions constitute 44.6-50.49 % of all reported ADRs for Chinese erbal injections [59].

The described studies are just examples of studies that have been published in the literature and comprise the current evidence base. Likely most allergic reactions and cases of anaphylactic shock have never been reported in first place and the actual extent of hypersensitivity reactions in children associated with herbal medicines remains significantly underrepresented and underestimated. One of the largest challenges remains changing the common misconception people have that herbal medicines are “natural” and “safer” than conventional drugs [60] to develop a more sensible approach to their use.

4.6 Cost of adverse drug reactions

Not only impact drug associated adverse events, for herbal and conventional medicines alike, patient health but required medical treatments needed for recovery require to use health care funds for health problems that could have potentially been avoided altogether. Overall, cost and adverse events associated with herbal medicine use in children are infrequently discussed in the literature [61] but some studies show that they impose substantial financial expenses on health care systems worldwide. The importance of post marketing surveillance becomes evident considering that, depending on the study, about 6.2 % off all hospital admission are attributed to adverse drug reactions [24, 32, 62]. Apart from the cost of treatment, patients seeking immediate medical attention at emergency departments further contribute to the problem of long waits at ERs that are already being operated at full capacity. Investigating this problem, Patel et al. found in their study that approximately 28 % of all visits to emergency departments are due to ADRs, illustrating the impact on the health care system [63]. Looking at fatal outcomes, a study by Juntti-Patinen and Neuvonen, found that 5% of all deaths at a Helsinki hospital were probably or certainly due to an adverse drug reaction. However, most of the patients were severely ill and treated with drugs known to have frequent and serious side effects [62].

In the UK alone up to 50 % of people are thought to have used an herbal medicinal product at least once in their life [64]. In 2009, global expenditures on herbals amounted to 62 billion dollars [65]. In relation to herbal remedies, a study by Engebretsen et al. showed that approximately 5-10 % of patient visits to dermatological clinics are related to plants and plant products [58]. Kimland et al report that 5 % of hospital admissions of children are related to ADRs [43] whereas results of a review by Clavenna and Bonati found that 1.8% of hospital admission in children were caused by ADRs [66]. An idea of just how much adverse drug reactions in paediatric patients can cost the health care system per year showed a prospective observational cohort study by Kunac et al. in 2009. The authors found that the annual cost of 67 ADRs, of which 38 could have been prevented, added up to 235, 214 New Zealand dollar (2002 values), with roughly two thirds being attributed to preventable ADRs ($NZ 148, 287) [67]. This shows that many adverse events could be prevented and the financial resources that required for treatment could be allocated and used more effectively elsewhere.

5 Methods

5.1 Data sources

The WHO's global individual case safety report (ICSR) database VigiBase® reporting system counted over 10 million reports as of April 2015 [31]. In this study, a data extract provided by the Uppsala Monitoring Center (UMC) in Sweden for the period of the start of the WHO's international pharmacovigilance program in 1968 and August 2014 was used. The UMC manages the WHO's global individual case safety report (ICSR) database VigiBase®.

5.2 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" [68]. All substances of natural origin in VigiBase® are grouped by HATC (Herbal Anatomical-Therapeutic-Chemical) codes [69].

5.3 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). Substances not classified as *suspect* or with non-HATC codes were omitted. WHO-ART preferred terms indicating to be a symptom of an immediate hypersensitivity reaction were selected manually (WHO Drug Dictionary Enhanced (Version June 1, 2014). Reaction terms less suggestive of hypersensitivity or more likely to have a different etiology than the suspect herbal such as cough, dyspnoea, larynx pain and pruritus ani or genital were excluded from the reaction terms. GIT symptoms were excluded altogether. Terms were divided into two groups, those considered as *allergic* and those as *asthma-like*, where WHO-ART preferred terms *asthma, stridor and/or bronchospasm* comprise the group *asthma-like*, all remaining terms constitute the group *allergic* (Table 2)

Table 2 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 8	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

* reactions terms classified as *asthma-like*

5.4 Causality assessment

Only Cases where the relationship between an herbal and an adverse drug reaction was classified according to WHO standardised case causality assessment as either *certain, probable* and *possible* [70] were included in this study. Figure 2 summarizes the selection process.

5.5 Statistical analysis

Data analysis was carried out using the statistical data analysis software STATA® and descriptive statistics.

5.6 Confounders

Confounders that may have influenced study results are primarily co-morbidities and co-medications. Children with co-morbidities 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 [56]. 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, analysis of the presence of co-morbidities and intake of co-medications is beyond the scope of this study and frequently co-medications are not stated by the primary reporter in the first place as

they do not belong to the four minimum criteria (Reporter ID, patient, drug, ADR) needed to submit an individual case safety report.

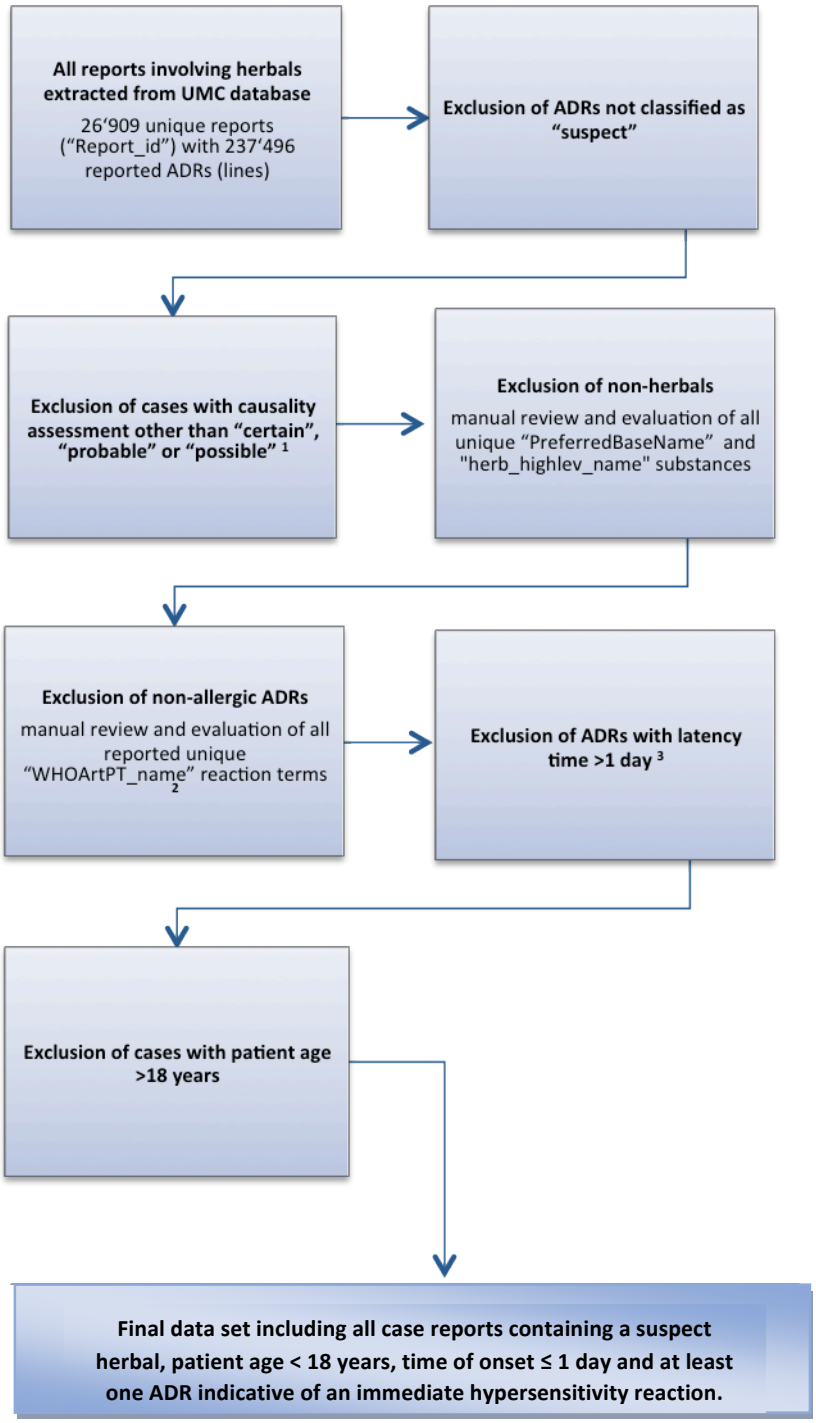

Figure 2: Flowchart depicting case selection process and exclusion/inclusion criteria.

[1]Herbals 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)

6 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 (lines), coded according to the WHO Drug Dictionary Enhanced (Version June 1, 2014) in WHO-ART adverse reaction terminology. The final cohort in our study consists of 150 ICSRs with 222 ADRs indicative of an allergic reaction following the use of one or more herbal medicines in children under 18 years of age. This represents 0.56 % of all ICSRs and 0.09 % of ADRs of the original VigiBase® extract.

6.1. Reports by gender

From the total data set, 150 cases met our inclusion criteria. Gender was reported in all 150 cases, with male paediatric patients accounting for 54 % and females for 46 % of the study population (Table 3). Overall, the average number of ADRs reported per case by gender was 1.5 for both males and females. The three most frequently reported ADRs by gender were urticaria, rash and anaphylactoid reaction (Figure 3) of which 63.3%, 42.3% and 70.0 % occurred in males and 36.7 %, 57.7 % and 30.0 % in females respectively.

Table 3 Cases reports by gender (n=150)

Gender	Frequency	Per cent %[1]	Cumulative %
Male	81	54	54
Female	69	46	100
Total	150	100	

[1] Percentage of 150 unique report IDs by gender

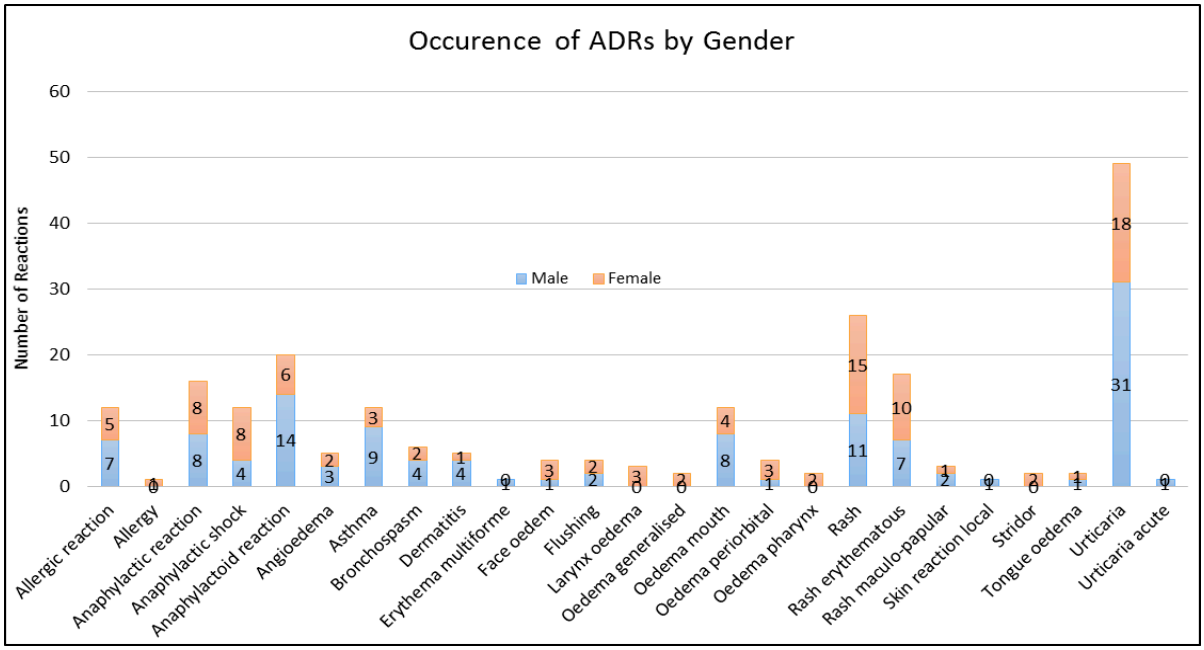

Figure 3 Occurrence of ADRs by Gender (n=222)

Overall, 81 male and 69 female pediatric patients were included in this study for which 120 and 102 ADRs were reported respectively. More cases of males suffering from urticaria and anaphylactoid reaction were reported. Females were also more frequently affected by rash. Two thirds of case with anaphylactic shock occurred in females.

6.2 Reports by age

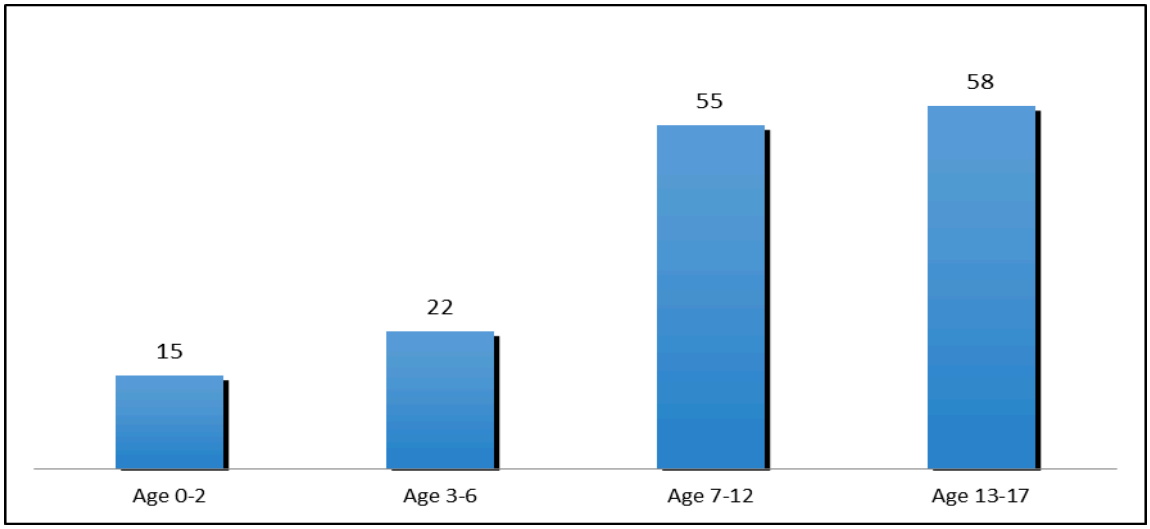

Figure 4 Reports of allergic ADRs to herbals by age group (n=222)

Patient age with the highest frequency of reported allergic ADRs to herbals was age 16; only one report exists for age 0-1. The mean age was 8.5 years and the standard deviation ± 3.9 years. Numbers of ICSRs increased with age and most cases occurred in the group age 13-17 years (Figure 4).

6.3 Geographical distribution

All 150 reports meeting our inclusion criteria were reported in 23 countries with 14 being in Europe, 4 in Asia, 2 in Oceania, 2 in North America and 1 in South America. The majority of ICSRs came from Germany (28 %), followed by Sweden (15.3 %) and Thailand (11.3 %), representing over half of all cases included in this study (54.7 %) (Table 4).

Table 4 Occurrence of allergic ADRs related to herbal drugs by country (n=222)

Country	Frequency	Per cent %	Cumulative %
Germany	42	28.0	28.0
Sweden	23	15.3	43.3
Thailand	17	11.3	54.7
Australia	9	6.0	60.7
Spain	8	5.3	66.0
Denmark	7	4.7	70.7
Switzerland	7	4.7	75.3
Norway	6	4.0	79.3
Austria	5	3.3	82.7
Korea, Republic of	4	2.7	85.3
Malaysia	3	2.0	87.3
Netherlands	3	2.0	89.3
Ukraine	3	2.0	91.3
Cuba	2	1.3	92.7
New Zealand	2	1.3	94.0
United Kingdom	2	1.3	95.3
Croatia	1	0.7	96.0
Czech Republic	1	0.7	96.7
Indonesia	1	0.7	97.3
Mexico	1	0.7	98.0
Peru	1	0.7	98.7
Portugal	1	0.7	99.3
Slovakia	1	0.7	100.00

[1] Percentage of occurrence by country of origin in a total of 23 countries

6.4 Annual distribution

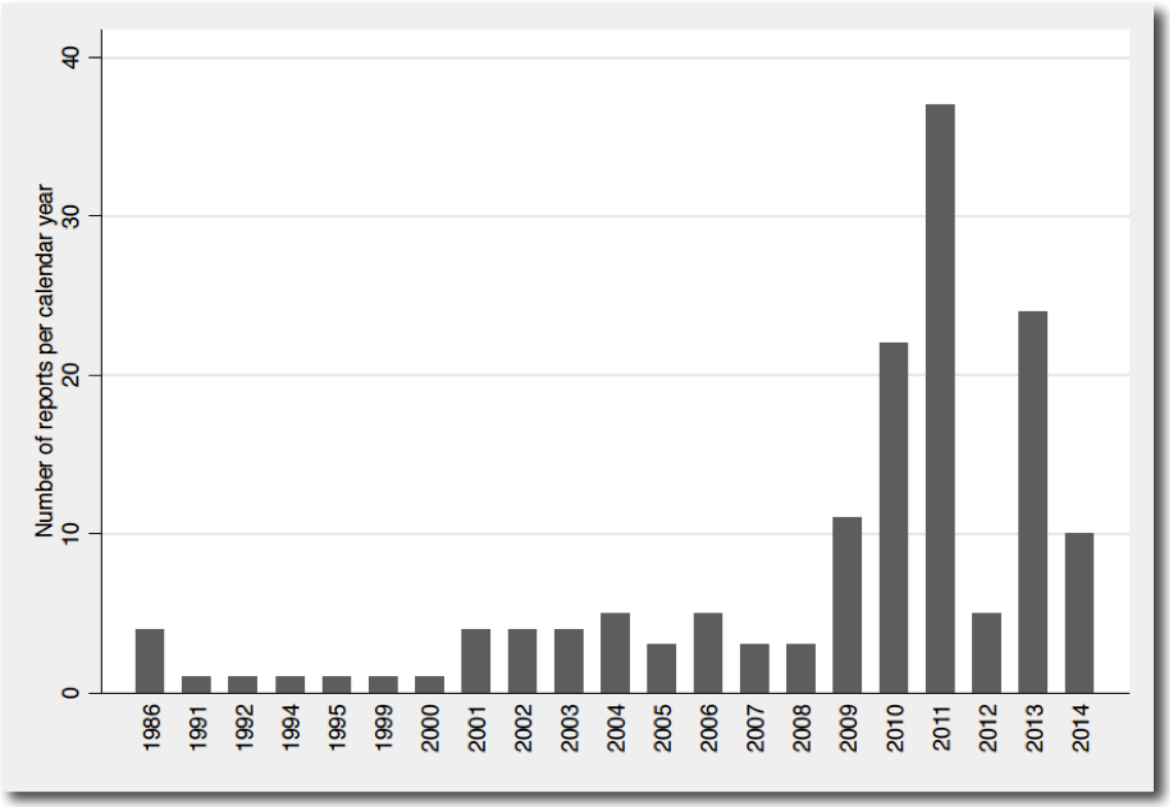

Figure 5 Number of ADRs reported per year (n=222)

Analysis of reports by year of reporting showed that no report that met our inclusion criteria was reported before 1986. The majority of 150 cases included in this study were reported after 2008. A significant gap can be observed in 2012 (Figure 5).

6.5 Causality assessment

All cases with a WHO causality assessment category of *certain, probable* and *possible* were included, with less than one fifth indicating a definite relationship between an ADR and a herbal medicine (Table 5). Due to rounding, percentages may not always appear to add up to 100 %.

Table 5 ADRs by causality assessment (n=222)

Causality assessment	Frequency	Percent %[1]	Cumulative %
Possible	92	41.4	41.4
Probable	91	41.0	82.4
Certain	39	17.6	100.0
Total	222	100.0	

[1] Percentage of ADR by case causality

6.6 Adverse drug reactions

The total number of reported ADRs divided into *allergic* and *asthma-like* in our study population of 150 cases was 222, representing 1.48 reported ADRs per unique case report ID and suspect herbal. *Allergic* reactions accounted for 91.0% of all ADRs, *asthma-like* reactions for 9.0% of all ADRs (Table 6).

Table 6 Type of ADR (n=222)

ADR type	Frequency	Percent %[1]	Cumulative %
Allergic	202	91.0	91.0
Asthma-like	20	9.0	100.0
Total	222	100.0	

[1] Percentage of ADR type of 150 cases

The most frequently reported ADRs were urticaria (22.1 %), rash (11.7 %), anaphylactoid reaction (9.0 %) and rash erythematous (7.7 %), accounting for 56.8 % of all reported ADRs (Table 7). About one third of ADRs (80 of all 222 ADRs) were reported as serious. It should be noted that this is not a complete list of the manually selected reaction terms but only those for which ADRs were reported.

Table 7 Most frequently reported WHO-ART preferred terms (n=150)

WHO-ART PT	Frequency	Percent %[1]	Cumulative %
Urticaria	49	22.1	22.1
Rash	26	11.7	33.8
Anaphylactoid reaction	20	9.0	42.8
Rash erythematous	17	7.7	50.5
Anaphylactic reaction	16	7.2	57.7
Allergic reaction	12	5.4	63.1
Anaphylactic shock	12	5.4	68.5
Asthma[2]	12	5.4	73.9
Oedema mouth	12	5.4	79.3
Bronchospasm[2]	6	2.7	82.0
Angioedema	5	2.3	84.2
Dermatitis	5	2.3	86.5
Face oedema	4	1.8	88.3
Flushing	4	1.8	90.1
Oedema periorbital	4	1.8	91.9
Larynx oedema	3	1.4	93.2
Rash maculo-papular	3	1.4	94.6
Oedema generalized	2	0.9	95.5

Oedema pharynx	2	0.9	96.4
Stridor[2]	2	0.9	97.3
Tongue oedema	2	0.9	98.2
Allergy	1	0.5	98.7
Erythema multiforme	1	0.5	99.1
Skin reaction localized	1	0.5	99.6
Urticaria acute	1	0.5	100.0
Total	222	100.0	

[1] Percentage of ADR by case causality

[2] Reaction terms classified as asthma-like

6.7 Suspect herbals

The most commonly reported suspect herbals were mixed herbals (61.7 %), *Phleum pratense* (13.1 %), also known as Timothy-grass, and *Hedera helix* (7.2 %), the common Ivy, all together contributing to 82.0 % of all reported ADRs in this study (Table 8).

Table 8 Suspect herbals associated with all ADRs (n=222)

Herbal high level classification	Frequency	Percent %[1]	Cumulative %
Mixed herbals	137	61.7	61.7
Phleum pratense	29	13.1	74.8
Hedera helix	16	7.2	82.0
Echinacea purpurea	6	2.7	84.7
Andrographis paniculata	5	2.3	86.9
Thymus vulgaris	4	1.8	88.7
Artemisia vulgaris	3	1.4	90.1
Calendula officinalis	2	0.9	91.0
Carica papaya	2	0.9	91.9
Hamamelis virginiana	2	0.9	92.8
Matricaria recutita	2	0.9	93.7
Senna alata	2	0.9	94.6
Arachis hypogaea	1	0.5	95.1
Arctostaphylos uva-ursi	1	0.5	95.5
Arnica montana	1	0.5	96.0
Atropa belladonna	1	0.5	96.4
Avena sativa	1	0.5	96.9
Eucalyptus globulus	1	0.5	97.3
Melaleuca alternifolia	1	0.5	97.8
Mentha x piperita	1	0.5	98.2
Papaver somniferum	1	0.5	98.7
Pelargonium sidoides	1	0.5	99.1
Styrax benzoin	1	0.5	99.6

Symphytum officinale	1	0.5	100.0
Total	222	100.0	

[1] Percentage of suspect herbals associated with allergic and asthma-like ADRs (n=222)

Of suspect herbals associated with *allergic* reactions 60.9 % were mixed herbals, 12.4 % *Phleum pratense* and 7.9 % *Hedera helix* (Table 9). Similarly, *asthma-like* reactions were mostly associated with mixed herbals (70.0 %) and *Phleum pratense* (20.0 %) (Table 10).

Table 9 Reported suspect herbal associated with *allergic* reactions (n=202)

Suspect herbal	Frequency	Percent %[1]	Cumulative %
Mixed herbals	123	60.9	60.9
Phleum pratense	25	12.4	73.3
Hedera helix	16	7.9	81.2
Echinacea purpurea	6	3.0	84.2
Andrographis paniculata	5	2.5	86.6
Thymus vulgaris	3	1.5	88.1
Artemisia vulgaris	2	1.0	89.1
Calendula officinalis	2	1.0	90.1
Carica papaya	2	1.0	91.1
Hamamelis virginiana	2	1.0	92.1
Matricaria recutita	2	1.0	93.1
Senna alata	2	1.0	94.1
Arachis hypogaea	1	0.5	94.6
Arctostaphylos uva-ursi	1	0.5	95.1
Arnica montana	1	0.5	95.5
Atropa belladonna	1	0.5	96.0
Avena sativa	1	0.5	96.5
Eucalyptus globulus	1	0.5	97.0
Melaleuca alternifolia	1	0.5	97.5
Mentha x piperita	1	0.5	98.0
Papaver somniferum	1	0.5	98.5
Pelargonium sidoides	1	0.5	99.0
Styrax benzoin	1	0.5	99.5
Symphytum officinale	1	0.5	100.0
Total	202	100.0	

[1]Percentage of suspect herbals associated with allergic reactions (n=202)

Table 10 Reported suspect herbal associated with *asthma-like* reactions (n=20)

Suspect herbal	Frequency	Percent %[1]	Cumulative %
Mixed herbals	14	70.0	70.0

Phleum pratense	4	20.0	90.0
Artemisia vulgaris	1	5.0	95.0
Thymus vulgaris	1	5.0	100.0
Total	20	100.0	

[1]Percentage of suspect herbals associated with asthma-like reactions (n=20)

Of 137 suspect mixed herbals, 48.2 % were reported as WHO-ART lower base name *herbal pollen*, followed by 8.0 % *Pelargonium reniforme root/Pelargonium sidoides root* and 7.3 % *Elettaria cardamomum oil/Zingiber officinale extract/ Capsicum annuum* (Table 11).

Table 11 Preferred base name of suspect mixed herbals

Suspect mixed herbal	Frequency	Percent %[1]	Cumulative %
Herbal pollen nos	66	48.2	48.2
Pelargonium reniforme root/ Pelargonium sidoides root	11	8.0	56.2
Elettaria cardamomum oil/ Zingiber officinale extract/ Capsicum annuum	10	7.3	63.5
Alnus glutinosa pollen extract/ Betula pendula pollen extract/ Corylus avellana pollen extract	7	5.1	68.6
Phleum pratense/ Dactylis glomerata/ Anthoxanthum odoratum/ Lolium perenne/Poa pratensis	7	5.1	73.7
Hedera helix leaf/Coptis spp. rhizome	4	2.9	76.6
Primula veris root extract/ Thymus vulgaris herb extract/ Hedera helix leaf extract	4	2.9	79.6
Chelidonium majus herb/ Melissa officinalis leaf/ Silybum marianum fruit/ Angelica archangelica root/ Carum carvi fruit/ Glycyrrhiza glabra root/ Matricaria recutita flower/ Mentha x piperita leaf/ Iberis amara	3	2.2	81.8
Mentha x piperita oil/ Ulmus rubra bark powder	3	2.2	83.9
Sambucus nigra flower/	3	2.2	86.1

Scutellaria baicalensis root/ Salix alba stem bark/ Armoracia rusticana root			
Thymus vulgaris extract/ Drosera rotundifolia extract	3	2.2	88.3
Aloe vera gum/Aloe ferox gum	2	1.5	89.8
Panax ginseng root/ Schisandra chinensis fruit	2	1.5	91.2
Pinus mugo oil/ Eucalyptus globulus oil/ Pinus nigra oil	2	1.5	92.7
Alnus glutinosa pollen extract/ Betula pendula pollen extract/ Corylus avellana pollen extract	1	0.7	93.4
Althaea officinalis extract/ Matricaria recutita extract/ Equisetum arvense extract/ Taraxacum officinale extract/ Achillea millefolium extract/ Quercus robur extract/ Juglans regia extract	1	0.7	94.2
Arachis hypogaea oil/ Prunus dulcis oil/ Cinnamomum camphora oil	1	0.7	94.9
Cocos nucifera oil/Illicium verum oil/ Cananga odorata flower oil	1	0.7	95.6
Echinacea angustifolia/ Aconitum napellus/ Baptisia tinctoria/ Bryonia alba/ Eupatorium perfoliatum/ Psychotria ipecacuanha/ Cinchona spp.	1	0.7	96.4
Ferula assa-foetida/ Rhamnus purshiana dry extract/ Strychnos nux-vomica extract/ Zingiber officinale rhizome Primula veris root extract/	1	0.7	97.1
Thymus vulgaris herb extract/ Hedera helix leaf extract	1	0.7	97.8
Lavandula angustifolia oil/ Eucalyptus globulus oil/ Pinus sylvestris oil/	1	0.7	98.5

Cupressus sempervirens oil/ Hyssopus officinalis oil			
Pinus mugo oil/ Eucalyptus globulus oil/ Pinus nigra oil/ Pinus sylvestris	1	0.7	99.3
Spirulina spp.	1	0.7	100.0
Total	137	100.0	

[1]Percentage of mixed herbal preparations for 137 reported ADRs

6.8 Reporter qualification

The category physician was the most frequent reporter qualification and was selected in 72 % of all cases. Pharmacists are the second most important group (Table 12).

Table 12 Case reports by reporter type (n=150)

Reporter qualification	Frequency	Percent %[1]	Cumulative %
Physician[2]	108	72.0	72.0
Pharmacist	13	8.7	80.7
Other	8	5.3	86.0
Other Health Professional	7	4.7	90.7
Not Converted	5	3.3	94.0
NULL	4	2.7	96.7
Manufacturer	3	2.0	98.7
Nurse	1	0.7	99.4
Consumer/Non Health Professional	1	0.7	100.0
Total	150	100.0	

[1] Percentage of total number of reports (n=150) by reporter type

[2] The reporter types "General practitioner", "Hospital", "Physician" and "Specialist physician" as originally reported in VigiBase® were summarized as reporter type "Physician"

6.9 Reaction outcomes

At the time of reporting, most cases had an outcome where recovery of the patient from one or more ADRs was reported (84.7 %); in no case was an ADR to an herbal fatal (Figure 6). Of the 9 ADRs reported as "not recovered" rash and urticaria were most common (Table 13) caused by various herbals (Table 14). The specific category "anaphylaxis" was most commonly associated with mixed herbals and *Phleum pratense* (Table 15). Of the mixed herbals, herbal pollen was most frequently reported (Table 16).

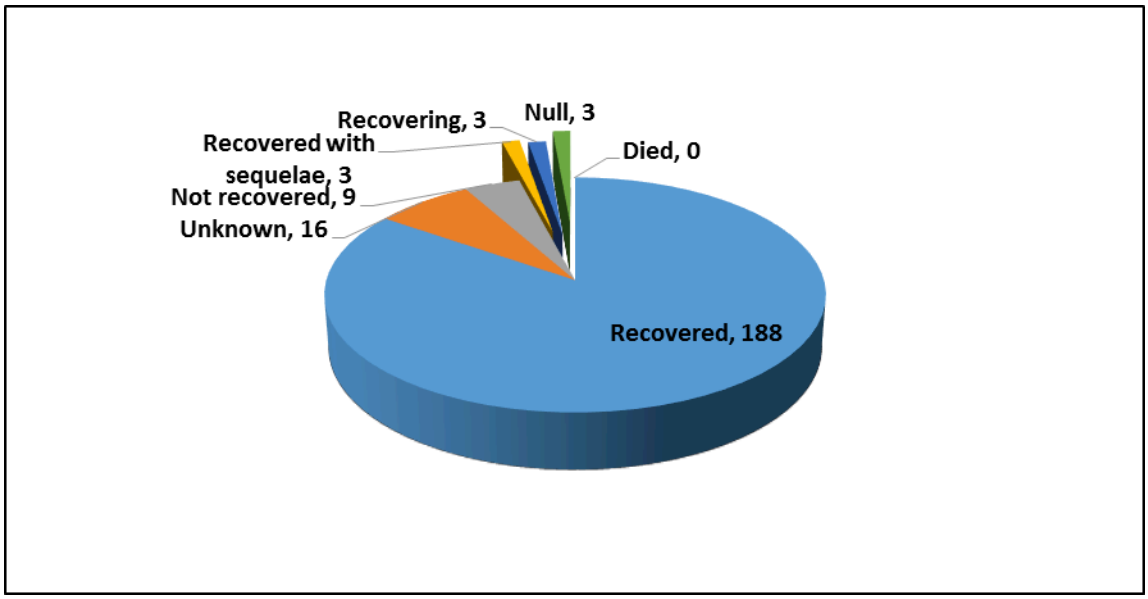

Figure 6 Reaction outcomes (n=222)

The vast majority of patients were able to fully recover by the time of reporting, 12 patients had not yet recovered and 3 developed a chronic condition as a result of exposure to an herbal medicine. In no case did a reaction lead to a lethal outcome (Figure 6).

Table 13 ADRs associated with reaction outcome "not recovered" (n=9)

ADR[1]	Frequency	Percent %[1]	Cumulative %
Urticaria	3	33.3	33.3
Rash	3	33.3	66.6
Rash erythematous	1	11.1	77.7
Bronchospasm	1	11.1	88.8
Angioedema	1	11.1	100.0
Total	9	100.0	

[1] WHO-ART preferred term name

The most frequent reactions associated with an outcome classified as "not recovered" were rash and urticaria (Table 13).

Table 14 Herbals associated with reaction outcome "not recovered" (n=9)

Herbal[1]	Frequency	Percent %[1]	Cumulative %
Andrographis paniculata	2	22.2	22.2
Panax ginseng root/Schisandra chinens..	2	22.2	44.4
Hedera helix	1	11.1	55.5
Elettaria cardamomum oil/Zingiber off..	1	11.1	66.6
Ferula assa-foetida/Rhamnus purshiana..	1	11.1	77.7

Pelargonium reniforme root/Pelargoniu..	1	11.1	88.8
Pinus mugo oil/Eucalyptus globulus oi..	1	11.1	100.0
Total	9	100.0	

[1] WHO-ART preferred base name

In 4 of the 6 cases reported with an outcome as "not recovered" two were caused by *Andrographis paniculata* and two by *Panax ginseng/ Schisandra chinensis* (Table 14).

Table 15 Herbals associated with anaphylaxis (n=48)

Herbal[1]	Frequency	Percent %	Cumulative %
Mixed herbals	38	79.2	79.2
Phleum pratense	5	10.4	89.6
Andrographis paniculata	1	2.1	91.7
Arachis hypogaea	1	2.1	93.8
Arnica montana	1	2.1	95.8
Artemisia vulgaris	1	2.1	97.9
Hedera helix	1	2.1	100.0
Total	48	100.0	

[1] WHO-ART high level name

The WHO-ART term mixed herbals was associated with the majority of cases reporting anaphylaxis (Table 15).

Table 16 Mixed herbals associated with anaphylaxis (n=38)

Herbal[1]	Frequency	Percent %	Cumulative %
Herbal pollen nos	31	81.6	81.6
Alnus glutinosa pollen extract/Betula..	4	10.5	92.1
Primula veris root extract/Thymus vul..	1	2.6	94.7
Sambucus nigra flower/Scutellaria bai..	1	2.6	97.4
Spirulina spp.	1	2.6	100.0
Total	38	100.0	

[1] WHO-ART preferred base name

Of the mixed herbals, herbal pollen nos (not otherwise specified) was the most frequently reported term followed by *Alnus glutinosa* pollen extract/ *Betula pendula* pollen extract/ *Corylus avellana* pollen extract (Table 16).

6.10 Case example 1

Our initial VigiBase® data set contained 68 variables per case in total plus 7 variables generated during analysis with Stata® data analysis and statistical software. Table 17 shows a good example of an ICSR where the minimum requirement of information was provided by the reporter but several details that could have allowed for a more precise causality assessment were lacking.

The case concerns a 2 year-old girl in Australia who was given an extract of *Echinacea purpurea* and subsequently developed facial oedema. The causality was assessed as *possible* i.e. a plausible temporal relationship between the use of the herbal preparation and the occurrence of the ADR were present. If a dechallenge or rechallenge occurred is unknown, which therefore excludes the causality assessment options *probable* or *certain*. The start date of the ADR was April 6th 1999, and the case was first entered into the Australian pharmacovigilance database on November 22nd 1999. This illustrates the previously discussed problem of information delay within spontaneous reporting systems (SRSs). Resolution date and outcome were also not specified, however, facial oedema is not a chronic condition and abatement of the symptoms upon withdrawal of the herbal extract or with medical treatment would be expected, all the more because the reaction was not classified as serious. Route of administration was also not specified and we do not know what the indication was. Amount of the extract that was administered is also unknown. This would be of particular interest since dosages for children can vary greatly from those used for adults, and ADRs can be coded as accidental or deliberate overdose in Vigiflow®. The reporter of the reaction was a general practitioner, which falls under the group physicians in our results and also constitutes the largest reporter group. Overall, the report presents a rather common ADR associated with a commonly used herbal and the occurrence of allergic reactions due to *Echinacea purpurea* has been described before [71].

Table 17 Raw data ICSR example 1

Variable	Result	Variable	Result
Report_id	2281333	**AmountCode**	-
DateDatabase	19991122	**AmountUnit**	NULL
FirstDateDatabase	19991122	**Frequency**	-
CountryCode	AUS	**FrequencyCode**	-
CountryText	Australia	**FrequncyUnit**	NULL

SafetyReportId	AU-AUNC-140808	**RouteCode**	SY
CompanyNumb	-	**Route**	Other
Serious	-	**IndicationSupText**	NULL
Seriousness	NULL	**IndicationText**	NULL
Died	-	**ReportedTermOriginal**	Not available
ReportTypeCode	S	**ReportedTerm**	Face oedema
ReportType	Spontaneous report	**ReactionSerious**	N
NotifierTypeCode	14	**ReactionSeriousness**	-
NotifierType	General practitioner	**WhoArtSocCode**	1300
AgeReaction	2	**WhoArtArecno**	602
agereacnum	2	**WhoArtSeq**	1
AgeU	6	**WhoArtSOC_name**	URINARY SYSTEM DISORDERS
AgeUnit	Year(s)	**WhoArtPT_name**	Face oedema
GenderCode	2	**WhoArtLLT_name**	Face oedema
Gender	Female	**CausalityCode**	3
ReOutcome	Unknown	**Causality**	Possible
onsetdate2	6/04/1999	**Dechallenge1**	5
OnsetDate	19990406	**DechallengeAction**	Unknown
ResolutionDate	-	**Dechallenge2**	5
MedProd_ID	34853	**DechallengeOutcome**	Effect unknown
ReportedDrug	ECHINACEA EXTRACT	**Rechallenge1**	4
MAH	0	**RechallengeAction**	Unknown
MAHolder	None	**Rechallenge2**	3
PreferredBase	1323501	**RechallengeOutcome**	Effect unknown
PreferredBaseName	Echinacea purpurea	**herbal012***	1
herb_highlev_name	Echinacea purpurea	**adrcat012***	1
PreferredSalt	1323502	**jitkaadrcat012***	1
PreferredSaltName	Echinacea purpurea extract	**ADRtype***	1
BasisCode	1	**Latencytime***	0
Basis	Suspect	**lattime3cat***	1
startdate2	6/04/1999	**Anaphylaxis***	0
StartDate	19990406		

StopDate	19990406
Amount	-

* Categories created during Stata® analysis

6.11 Case example 2

The second case example concerns a 17 year-old girl who suffered from an immediate type hypersensitivity reaction grade IV (WHO preferred term anaphylactic shock) after a single oral administration of *Arachis hypogaea* (peanut) oil. Information for several variables such as seriousness, notifier type and amount taken are missing. However, the case still meets the specified minimum requirements for ICSRs that are report ID, reporter, patient, suspect medicine and ADR [72]. In this case the causality was classified as *probable* i.e. indicating a plausible temporal relationship as well as a "positive dechallenge" (symptoms resolved after discontinuation of the peanut oil). Date of onset was May 9th 2000 and the outcome was reported as recovered (Table 18).

In Western countries the number of children affected by peanut allergy has doubled in the last decade and is the most frequent cause of anaphylaxis and death associated with food allergies [73]. Compared to milk and egg allergy, only few children outgrow their peanut allergy and 1-2 % of children in the UK are thought to be affected [74].

Table 18 Raw data ICSR example 2

Variable	Result	Variable	Result
Report_id	2644331	**AmountCode**	-
DateDatabase	20010821	**AmountUnit**	NULL
FirstDateDatabase	20010821	**Frequency**	1
CountryCode	NZL	**FrequencyCode**	10
CountryText	New Zealand	**FrequncyUnit**	Time(s)
SafetyReportId	NZ-NZNC-044334	**RouteCode**	PO
CompanyNumb	-	**Route**	Oral
Serious	-	**IndicationSupText**	NULL
Seriousness	NULL	**IndicationText**	NULL
Died	-	**ReportedTermOriginal**	Not available
ReportTypeCode	S	**ReportedTerm**	Immediate type hypersensitivity reaction grade IV
ReportType	Spontaneous report	**ReactionSerious**	N

NotifierTypeCode	-	**ReactionSeriousness**	-
NotifierType	NULL	**WhoArtSocCode**	1810
AgeReaction	17	**WhoArtArecno**	713
agereacnum	17	**WhoArtSeq**	2
AgeU	6	**WhoArtSOC_name**	BODY AS A WHOLE - GENERAL DISORDERS
AgeUnit	Year(s)	**WhoArtPT_name**	Anaphylactic shock
GenderCode	2	**WhoArtLLT_name**	Immediate type hypersensitivity reaction grade IV
Gender	Female	**CausalityCode**	2
ReOutcome	Recovered	**Causality**	Probable
onsetdate2	########	**Dechallenge1**	1
OnsetDate	20000509	**DechallengeAction**	Drug withdrawn
ResolutionDate	-	**Dechallenge2**	1
MedProd_ID	33779	**DechallengeOutcome**	Reaction abated
ReportedDrug	ARACHIS OIL	**Rechallenge1**	3
MAH	0	**RechallengeAction**	No rechallenge
MAHolder	None	**Rechallenge2**	4
PreferredBase	1646801	**RechallengeOutcome**	Not applicable
PreferredBaseName	Arachis hypogaea	**herbal012***	1
herb_highlev_name	Arachis hypogaea	**adrcat012***	1
PreferredSalt	1646802	**jitkaadrcat012***	1
PreferredSaltName	Arachis hypogaea oil	**ADRtype***	1
BasisCode	1	**Latencytime***	0
Basis	Suspect	**lattime3cat***	1
startdate2	########	**Anaphylaxis***	1
StartDate	20000509		
StopDate	20000509		
Amount	-		

* Categories created during Stata® analysis

7 Discussion

This descriptive study analyzed a VigiBase® extract from 1960 to August 2014 and is the first study 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. The initial data set containing 26,909 ICSRs related to herbals represent roughly 0.27 % of over 10 million reports that have been reported in VigiBase® to this date [31]. In 1999, the UMC database reached 2 million reports of which 0.5 % were related to herbals [75]. However, this decrease in percentage of herbal reports contributing to the entire database does not reflect a decrease in herbal medicine use. In 1999, the WHO international pharmacovigilance program counted far less member countries than the current 120 permanent and 29 associate members as of December 2014 [29, 30]. Quite the opposite holds true and herbal medicine use has consistently been increasing worldwide as has the total number of herbal ADR reports. Hence, an overall a faster increase in the number of reported ADRs due to conventional medicines than herbals could explain this disproportionality. The growing global popularity of herbal use was also reflected in our study by the increasing number of reports from 1986 until 2011. However, increased number of member countries as well as possible policy changes regarding herbal medicines in some countries and increased awareness of their health risks may have influenced reporting over the years. We currently do not have an explanation for the decrease in number of reports in this study after 2011. It has been shown that the rate at which an ADR is reported can vary among drugs and can change for the same drug over a period of time [32].

Regarding gender distribution, overall evidence is contradictory with some studies reporting higher percentages of ADRs occurring in male pediatric patients [34, 67, 76, 77] even though female pediatric and adolescent patients use more complementary and alternative medicines including herbals [13, 78]. Our study results showed 54 % of pediatric patients affected by ADRs were male, which agrees with previous studies [34, 67, 76, 77, 79]. However, these studies mainly discussed the overall ADR incidence in children, without a focus on herbals or hypersensitivity reactions. Whether this is an actual indication that male pediatric patients suffer more frequently from hypersensitivity reactions than girls, or simply that more reports concerning boys than girls are submitted, remains unclear at this point. However, 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 and sex hormones are thought to play a role in this change in prevalence [80].

In our study urticaria was the most frequently reported ADR (22.1 %) in children using an herbal medicine and who were under the age 18. This is consistent with a previous study by Jacobsson et al. where all ICSRs with at least one suspect complementary and alternative medicine (CAM) reported to the Swedish Medical Products Agency between 1987 and 2006 were analyzed [44]. Here urticaria was reported as the most common ADR (8.3 %), followed by exanthema (7.4 %) and contact dermatitis (5.7 %). On the other hand, an anaphylactic reaction was reported in 7.2 % of all cases in our study whereas Jacobsson et al. reported anaphylaxis in 2.0 % of all cases. Their study however did not focus on pediatric patients but analyzed 778 cases of ADRs related to CAM products with an average patient age of 53 years. A study by Kimland et al. found that between 1987 and 2001 46 % of all ADRs in children under the age of 18 were skin related. Of these 24 % accounted for application site reactions, 12 % fever, 6.7 % exanthema and 6.2 % for urticaria [43]. In our study, urticaria was the most commonly coded WHO-ART preferred term (22.1 %), followed by rash (11.7 %) and anaphylactoid reaction (9.0 %). This could suggest that the skin is the most common organ system affected by adverse drug reactions in general in children and adolescents or for herbal medicine use independent of patient age.

The most common reported suspect herbal was coded with the WHO-ART preferred term “mixed herbal” (60.9 %). Herbal pollen nos (not otherwise specified) constituted the majority of mixed herbals with 48.2 %. Herbal pollen are commonly used for subcutaneous or sublingual allergen-specific immunotherapy to treat allergic rhinitis, which if left untreated, can develop into asthma [81]. Allergic rhinitis with or without conjunctivitis is one of the most common hypersensitivity reactions in pediatric patients. About 40 % of children are thought to be affected [82, 83]. This explains the high percentage of reports being associated with herbal pollen (see case example 1). However, it is known that a history of allergy is a risk factor for suffering from anaphylactic reactions and severe anaphylaxis [84]. Our study did not further analyze route of administration but intravenous injections logically pose the greatest risk of inducing severe allergic reactions and anaphylaxis due to immediate systemic absorption. A Chinese study showed that in 2013, 17.3 % of all ADR reports in China were related to TCM, with over 70% of all serious reports ocurring when an intravenous route of administration was used [21].

Reports in VigiBase® indicative of hypersensitivity reactions and even circulatory failure due to *Pelargonium reniforme* and *Pelargonium sidoides* have been described before

[85] and agree with the results found in our study where *P. reniforme root/ P. sidoides* root was the second most frequently reported mixed herbal, accounting for ADRs in 8 % of all cases. Timmer et al. describe in their Cochrane review that the root of *P. reniforme* and *P. sidoides* is used in various dosage forms such as syrups, tablets and ethanolic solutions for the treatment of acute respiratory infections and known under brand names such as Umckaloabo®, a particularly popular herbal preparation in Germany used to treat bronchitis in children. However, the Cochrane review concluded that the overall evidence for *P.reniforme* and *P. sidoides* root was either low or very low for different respiratory tract infections in adults and children [86].

Out of all herbal drugs, the second and third most frequently reported herbal preparation leading to *allergic* as well as *asthma*-like symptoms were *Phleum pratense* (13.1 %) and *Hedera helix* (7.2 %). *P. pratense*, also known as Timothy grass, and its pollen are common aeroallergens causing allergic rhinitis with or without conjunctivitis [87, 88]. Subcutaneous and sublingual forms of allergen specific immunotherapy (SLIT) are available for various grasses such as Thimothy grass but serious side effects and anaphylaxis have been reported before [89]. *H. helix*, known as the common Ivy, has antitussive properties and has traditionally been used to treat various respiratory diseases but solid evidence of its usefulness is still lacking [90]. It is known that *H. helix* can cause occupational contact dermatitis and asthma [91].

For all other single suspect herbals found in this study, with the exception of Senna alata, Arctostaphylos uva-ursi, Atropa belladonna and Symphytum officinale, hypersensitivity reactions have been reported previously. A study by Suwankesawong et al. analyzed a Thai Vigibase® extract from February 2001 to December 2012 and found 106 cases in which Andrographis paniculata was the suspect herbal and caused at least one ADR indicative of a hypersensitivity reaction, with anaphylactic shock being reported in five cases and anaphylactic reaction in 4 cases [92]. A case study by Benito et al. described the occurrence of facial edema, respiratory difficulties and pruritus after ingesting food seasoned with thyme or oregano; ingestion of the same foods without the herbs caused no symptoms [93]. A study by Kurzen et al. describes the case of a florist who suffered from life-threatening glottal oedema after working with Artemisia vulgaris [94] and a report of anaphylactic shock after gargling with an infusion of Calendula officinalis exists in the literature [95]. Carica papaya is known to be a food allergen and to cause immediate hypersensitivity reactions [96]. Reactions to witch hazel, Hamamelis virginiana are rather uncommon but have been reported [97]. A case study describing a severe anaphylactic

reaction in an 8-year-old boy after drinking a tea containing Matricaria recutita exists in the literature [98]. Another of the more common herbals causing allergic reactions is Arnica montana [99]. Documentation regarding anaphylaxis due to the common oat, Avena sativa, is sparse but a case report of a 7-year-old boy who developed cough, pruritus, and wheezing after consuming oats exists in the literature [100]. Allergic contact dermatitis caused by Eucalyptus globulus has been reported [101] and hypersensitivity reactions are known to occur with Melaleuca alternifolia (Tea tree) [102]. A case study describing anaphylaxis due to Mentha piperita can be found in the literature [103] and IgE mediated allergic reactions have been documented for Papaver somniferum [104]. Contact allergy for Styrax benzoin has also been reported previously [105].

The majority of ADRs in our study concerned either the skin or hypersensitivity reactions, with urticaria (22.1 %), rash (11.7 %) and anaphylactoid reaction (9.0 %) accounting for the majority of reported ADRs. This is largely consistent with previous studies that investigated ADRs to herbals in adults and pediatric patients due to complementary and alternative medicines which include herbals [44, 106]. Most studies investigating ADRs in children have focused on conventional medicines. However, even in those studies the skin was reported to be the most commonly affected organ system followed by the gastrointestinal tract [43, 66, 107].

In our study the occurrence of ADRs was highest in those age 13-17. It has been shown before that children and teenagers may be more prone to suffer from hypersensitivity reactions than the rest of the population [108]. We did not further analyze reports by age group and country of origin, however, the majority of reports came from Germany (n=42), a country with a long history and tradition of herbal and homeopathic medicine use. The German health care system covers herbal remedies for children under 12 years of age [78]. In our study 92 of 150 cases occurred in children 0-12 years. Use of herbal medicines in this age group due to insurance coverage may pose an incentive for German parents to choose alternative medicine options for their underage children. However, we do not know in how far this is reflected in the age group to country of origin relationship in our study and further investigations would be necessary. Apart from Germany, Sweden has also been a member country of the WHO Program for International Drug Monitoring (PIDM) since its start in 1968, and contributed the second highest number of reports in our study. Thailand was the third most significant contributor and has been one of the most actively participating new member countries since it joined as 26th member in 1984 [28].

As reported in previous studies [34, 44], the largest group of reporter type in our study were physicians, followed by pharmacists. A review by Inch et al. showed that generally more reports are submitted by female physicians and that pharmacists report substantially less than physicians [109]. On the other hand, in a Portuguese study by Inácio et al., that analyzed reporter types in a region in the South of Portugal in 2004 and 2012, pharmacists were the main contributors of ADR reports, followed by hospital pharmacists [110]. This reflects the ongoing shift away from doctors being the primary reporters of ADRs as has been the case since the start of the WHO's PIDM in the 1960's [20]. Yet another study found that of 2437 reports reported to the Danish Medicines Agency between 1998 and 2007, 90 % of all reports were reported by physicians however, they only reported equally as many serious ADRs as consumer whereas other health care professionals and consumers were more likely to report serious ADRs [111]. 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 Netherland long before the law was implemented and results show that it has been a highly valuable tool in signal detection [112]. However, most countries still need to significantly increase the public's awareness of the possibility to report ADRs, considering that patient reports have been found to be an invaluable source of pharmacovigilance data [113].

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 [25]. The main drawbacks of using SRS's as a source for pharmacovigilance data remains 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 [21]. Some studies found that under-reporting for non-serious ADRs is even greater than for serious ADRs, leading to only 4 % of non-serious and 10 % of serious ADRs being reported [24, 114, 115], which most likely extrapolates to even greater numbers for herbal medicines. In our study 36 % of ADRs (n=80) related to hypersensitivity were reported as serious. Even though we did not further analyze them, the main confounders of this study are potential co-medications and co-morbidities. For now the number of cases that have been affected by these confounders remain unknown and individual inspection of case reports would need to

be done. In addition, other than for the 39 cases with a *certain* causality assessment where a "positive re-challenge" had occurred, a definite correlation between the suspect herbal and reported ADRs cannot be assumed. Cases with a *probable* and *possible* causality may be highly suggestive of a relationship between the suspect herbal and ADR(s) but do not represent certain evidence. Likewise factors such as insect bites, increased exercise regimen, mastocytosis, uncontrolled asthma, food hypersensitivities or latex allergy may have confounded the data [108]. Semantics have also been shown to influence ADR selection of MedDRA reaction terms by reporters used to code an adverse event [110] 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 gastrointestinal symptoms that can be either IgE-mediated, non-IgE mediated or mixed IgE and non-IgE mediated [116], we decided to exclude GIT symptoms from the list of selected reaction terms altogether. Other symptoms such as cough, dyspnoea, larynx pain and 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.

8 Conclusion

This descriptive study was the first study to analyze the worldwide occurrence of hypersensitivity reactions in children associated with herbal medicines as reported in VigiBase®. Results highlighted the potential of herbals to cause serious allergic reactions in children. Herbal medicines were shown not to be "safe" as perceived by many parents and consumers worldwide. The global increase in herbal medicine use calls for improved, standardized and more consistent reporting of ADRs associated with herbals 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. Reporting rate and awareness of the public and medical staff of the importance of pharmacovigilance needs to be increased. Ultimately, the small number of cases included in this study make any generalizations or pharmacoepidemiologic conclusions about the results infeasible. 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. This study focused on the occurrence of ADRs indicative of hypersensitivity in patients under 18 years of age only. Further studies need to be conducted to investigate the entire ADR spectrum reported for herbal medicines in pediatric patients.

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10 Abbreviations

ADR	Adverse drug reaction
CAM	Complementary and alternative medicine
EMR	Electronic medical records
HP	Herbal product
IC	Information component
ICU	Intensive care unit
ICSR	Individual case safety report
NC	National centres
PIDM	Program for international drug monitoring
PT	WHO-ART preferred term
PV	Pharmacovigilance
ROR	Reporting odds ratio
SLIT	Sublingual immunotherapy
SRS	Spontaneous reporting system
UMC	Uppsala monitoring centre
WHO	World health organisation

11 Czech Abstract

Úvod: Spotřeba bylinných přípravků neustále vzrůstá jak mezi dospělými, tak mezi dětmi. Na bylinné přípravky je často nahlíženo jako na bezpečnou alternativu ke klasické léčbě, ačkoliv i bylinné přípravky mohou způsobovat různé nežádoucí účinky včetně závažných a smrtelných alergických reakcí. Prevalence celoživotního užívání bylinných přípravků u dětí se pohybuje mezi 0.8–85.5 % a 2.2–8.9 %. Na rozdíl od syntetických léčiv se nežádoucí účinky u bylinných přípravků studují zřídka. V současnosti neexistují účinné systémy, jakými by se tyto nežádoucí účinky včetně dlouhodobých účinků efektivně monitorovaly, popřípadě se v řadě zemích tyto systémy budují. Vzhledem k nedostatečnému a nekonzistentnímu monitorování nežádoucích účinků bylinných přípravků u dětí, toho o nich není moc známo. Povědomí o nežádoucích účincích bylinných přípravků u dětí by se mělo zvyšovat a jejich hlášení do farmakovigilačních center podporovat.

Cíl: V rámci studie jsme analyzovali nežádoucí účinky bylinných přípravků u dětí do 18 let týkající se hypersenzitivních reakcí hlášených do databáze Světové zdravotnické organizace VigiBase® v letech 1968 – srpen, 2014.

Metody: Do studie byly zahrnuty všechna spontánní hlášení z VigiBase® obsahující HATC kód, s klasifikací „podezřelé“, s hodnocením kauzality „jistá, možná, pravděpodobná“, s nástupem nežádoucího účinku 0-1 den, s pacienty mladšími 18 let, s nežádoucími účinky naznačujícími hypersenzitivní reakci. WHO-ART terminologie naznačující alergie byly dále rozděleny na nežádoucí účinky podobné alergii a nežádoucí účinky podobné astmatu.

Výsledky: Celosvětově bylo hlášeno 26,909 případů týkajících se nežádoucích účinků bylinných přípravků a 237,496 nežádoucích účinků. Z těchto dat, 150 případů s 222 nežádoucími účinky splňovaly vstupní kritéria studie. Z 222 nežádoucích účinků, bylo 202 klasifikovaných jako nežádoucí účinky podobné alergii a 20 jako nežádoucí účinky podobné astmatu. Mezi nejčastěji hlášené WHO-ART termíny vztahující se k nežádoucím účinkům podobným alergii byly urtikarie (22.1 %), vyrážka (11.7 %) a anafylaktoidní reakce (9.0 %). Mezi nejčastější nežádoucí účinky podobné astmatu patřily astma (5.4%) a bronchospasmus (2.7 %). Nežádoucí účinky podobné alergii (60.9 %) a astmatu (70.0 %) byly nejčastěji způsobeny bylinnými směsi. Anafylaktický šok byl reportován ve 12 případech (5.4%) a v žádném případě nedošlo ke smrti. Většina hlášení nežádoucích účinků spadala do věkové kategorie 13-17 let.

Nežádoucí účinky se vyskytovaly více u chlapců (54 %) nežli u dívek (46 %). Většina hlášení pocházela z Německa (28 %), Švédska (15.3 %) a Thajska (11.3 %).

Závěr: Data analyzována z Vigibase ukázala, že bylinné přípravky mohou vést k závažným hypersenzitivním reakcím a anafylaxi u dětí a dospívajících. Je potřeba zvýšit povědomí o potenciálním riziku spojeným s užíváním bylinných přípravků a podpořit jejich hlášení z důvodu lepší využitelnosti dat v rámci farmakovigilance.