

Anaphylaxis Following Immunization of Children and Adolescents in Germany

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Abstract (Word Count: 250)

Background

Anaphylaxis is a life-threatening event. The aim of this study was to estimate the annual frequency of anaphylaxis following immunization in individuals under 18 years in Germany leading to hospitalization.

Methods

All suspected cases of postvaccination anaphylaxis involving individuals aged 0–17 years reported to the German surveillance unit for rare pediatric diseases (ESPED) from June 2008 through May 2010 as well as all suspected cases of anaphylaxis as an AEFI (adverse event following immunization) in the same age group reported to the Paul-Ehrlich-Institut (PEI) during the observational period were classified according to the Brighton Collaboration Case Definition (BCCD). Only hospitalized cases of anaphylaxis fulfilling BCCD level 1–3 criteria were eligible. Estimates for the annual frequency were calculated by using capture–recapture methods.

Results

A total of 22 reports were eligible. Median age of the affected individuals (13 males, 9 females) was 7.0 years (range: 2 months to 17 years). Anaphylaxis occurred most frequently following administration of AS03 adjuvanted A/H1N1 pandemic influenza vaccine (n=8). The annual frequency of anaphylaxis after vaccination (excluding pandemic influenza vaccine as well as monovalent measles and rubella vaccines) was estimated to be 6.8 (95% CI: 6.1–10.9). The estimated incidence of anaphylaxis following administration of specific vaccines ranged from 0.4 to 127.6 cases per 1,000,000 doses administered.

Conclusions

This study confirms that anaphylaxis following immunization in children and adolescents is a rare event. AS03 adjuvanted A/H1N1 pandemic influenza vaccine appears to be associated with a higher risk of anaphylaxis as compared to other vaccines.

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Introduction

Anaphylaxis is a systemic hypersensitivity reaction to a foreign stimulus with rapid onset and release of cytokines and inflammatory mediators which can progress rapidly to multiorgan dysfunction leading to a severe and life-threatening condition. The incidence of anaphylaxis from all causes in the UK has been estimated to be 8.4 per 100,000 person-years¹.

Anaphylaxis occurring as an adverse event following immunization (AEFI) is reported to be a very rare event, although the calculated risk in children and adolescence varied widely between 0.65 cases per 1,000,000 doses and 22.4 cases per 100,000 doses administered in previous studies²⁻⁶. The aim of this study was to estimate the annual frequency and incidence of anaphylaxis occurring within 48 hours following immunization in children and adolescents in Germany leading to hospitalization.

Anaphylaxis is a feared adverse event due to the fact that it might be life-threatening. These first estimates from Germany may help addressing many physicians' and parents' concerns.

Materials and Methods

ESPED study

Children and adolescents under 18 years of age with suspected anaphylaxis following immunization were reported to the German surveillance unit for rare pediatric diseases ESPED (Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland)⁷.

A reporting card with a list of rare disorders is sent to pediatric hospitals each month.

Alternatively, hospitals can opt for online reporting.

Pediatricians return the (electronic) card, notifying ESPED of any cases or indicating 'nothing to report'. In case of a positive notification, follow-up information is requested to complete the individual case report form regarding the case presentation, diagnosis, management and outcome.

Hospital pediatricians were asked to report all children and adolescents who may have experienced anaphylaxis within 48 hours following immunization over 24 months between 1 June 2008 and 31 May 2010. All reports were classified by medically qualified staff according to the Brighton Collaboration Case Definition (BCCD) for anaphylaxis which uses a grading according to diagnostic certainty irrespective of the probability of causal relation or of allergic etiology⁸. BCCD levels 1–3 identify events that “meet the case definition”, BCCD level 4 specifies events of “reported anaphylaxis with insufficient evidence to meet the case definition”, and BCCD level 5 excludes anaphylaxis. Cases fulfilling BCCD level 1 to 3 were eligible. If a clear alternative diagnosis was reported to account for the combination of symptoms, the case was reassigned level 5. The study was approved by the Ethics Committee at the University Hospital Mannheim (2008-274E-MA).

Spontaneous case reports of anaphylaxis following immunization

According to the German Act on the Prevention and Control of Infectious Diseases, it is mandatory for physicians to report AEFI to the local health authorities which have to notify the national competent authority, the Paul-Ehrlich-Institut (PEI). Marketing authorization holders have to report suspected serious adverse reactions to the PEI according to the German drug law. Case reports are stored in the PEI adverse drug reaction database. A broad search strategy was applied to ensure identification of all

relevant individual case safety reports. Standardized MedDRA (Medical Dictionary for Regulatory Activities) queries (SMQ) including narrow and/or broad terms have been used⁹. Narrow terms are those that are highly likely to represent the condition of interest. A SQL (Structured Query Language) database search was performed for case reports regarding pediatric and adolescent vaccinees with administration date from 1 June 2008 through 31 May 2010 matching PT (“Preferred Terms”) covered by the MedDRA SMQs (Standardized MedDRA Queries) ‘Anaphylactic reaction narrow’, ‘Anaphylactic reaction broad’, ‘Hypersensitivity narrow’ and ‘Hypersensitivity broad’. The retrieved case reports were reviewed and validated according to BCCD for anaphylaxis as an AEFI⁸ by medically qualified staff. BCCD level 1–3 case reports with an anaphylactic reaction occurring within 48 hours following immunization leading to hospitalization were eligible.

Capture–recapture method

The capture–recapture method¹⁰ is used in epidemiology to estimate the size of populations^{11–13} by utilizing data from overlapping lists of cases that originate from various sources to estimate the number of missing cases and the total affected. We used the Chapman capture–recapture methods¹⁴ which have been applied previously to evaluate the reporting completeness of a passive safety surveillance system¹⁵.

Data linkage

Data linkage of retrieved case reports from ESPED and PEI was performed manually on several variables including year and month of birth, gender, vaccination date, vaccine trade name, and reported reactions.

Denominators

For the AS03 adjuvanted A/H1N1 pandemic influenza vaccine exposure estimates were available for individuals under the age of 18¹⁶.

Health insurance in Germany is compulsory and divided between statutory and private schemes. The majority of residents are covered by statutory health insurance (Gesetzliche Krankenversicherung). Employees with a higher income, self-employed residents, students and civil servants for complementary coverage can opt for private health insurance (private Krankenversicherung). Only the statutory health insurance includes family members without own income (husband/wife and children) of the insured person free of charge.

Regarding vaccines recommended for routine childhood vaccination in Germany, figures on doses administered were derived from the 'ASHIP (Associations of Statutory Health Insurance Physicians) vaccination monitoring project' at Robert Koch-Institute (RKI). The accuracy of vaccination coverage estimated from ASHIP data was previously demonstrated in an extensive validation procedure with various primary data sources like kindergarten and school entrance examinations¹⁷.

ASHIPs receive insurance refund claims from physicians for ambulatory medical services provided to statutory health insurees. These data include vaccination specific codes for nationally recommended vaccinations. As described previously¹⁷, data is extracted from the ASHIPs' databases, anonymized, and transferred to RKI. At vaccine-type level, we calculated the total of vaccinations administered from June 2008 until May 2010 to patients <18 years of age. For a total of six months within the study period, data on claimed vaccinations were not available from two out of the 17 ASHIPs but extrapolated from other ASHIPs. Since recommended vaccinations are generally also covered by

private health insurances, we projected the estimate for the statutory health insured population to the total German population <18 years of age according to the proportion of statutory health insurees of 84.5%, as derived from statistics of statutory health insurees by the German Ministry of Health and population statistics by the Federal Statistics Office. For seasonal influenza and rotavirus vaccines exposure estimates were not available.

In addition, we estimated the proportion of anaphylaxis as an AEFI among the mean annual number of cases hospitalized from 2008 to 2010 due to anaphylaxis from all causes in children and adolescents. Data on the frequency of hospitalization due to anaphylaxis from the main causes (International Classification of Diseases ICD-10 codes T78.0 “anaphylactic shock due to adverse food reaction”; T78.2 “anaphylactic shock, unspecified”; T80.5 “anaphylactic shock due to serum”, and T88.6 “adverse effect of correct medicinal substance properly administered”) from 2008 to 2010 was provided by the Federal Statistics Office. The data were collected for age groups, i.e. “under 1”, “1-4”, “5-9”, “10-14”, and “15-19” by the hospital statistics.

Sensitivity analyses

Within the scope of sensitivity analyses, hospitalized BCCD level 4 cases with time to onset within 48 hours following immunization were included.

Statistical analysis

The capture–recapture point estimator was calculated according to Chapman et al.¹⁴. We estimated the variance of the Chapman estimate according to Seber¹⁸ and Wittens¹⁹ and hence the standard error. The 95% confidence interval based on the standard error was computed by a log transformation method (formula 12)²⁰. If no cases were captured in

either the ESPED only or the PEI only cell a continuity correction of adding 0.1 to the zero cells was performed. Exact binomial confidence intervals (Clopper-Pearson Exact confidence limits) were calculated for proportions (Tab 3). Statistical analyses were performed using the software package SAS version 9.3 (SAS Institute Inc., Cary, NC/USA).

Results

In both the ESPED and the PEI investigation the reports were checked for eligibility in the following way: After removal of duplicates, the remaining reports were validated according to the criteria of the BCCD. Cases assigned level 5 were excluded from further analysis, cases assigned level 4 were exclusively used for sensitivity analyses. Case reports with a time to symptoms onset exceeding 48 hours were excluded as well. And so were reports without recorded hospitalization. The remaining reports were eligible.

In 2008, 370 out of the 373 children's hospitals in Germany participated in ESPED (coverage 99.2%) with a total of 473 ESPED collaborators being contacted (240 of whom received a reporting card per month and 233 opted for electronic reporting). The response rate was 96% (reporting card: 96%, electronic reporting: 95%). During the study period of 24 months, ESPED received a small number (n=13) of case reports of suspected anaphylaxis following immunization the majority (n=9) of which were eligible (Fig 1).

Regarding the PEI investigation, several reports were retrieved by more than one of the four SMQs, so that the total number of unique AEFI reports identified (n=705) was smaller than the number of case reports retrieved by the 4 SMQs together (Fig 2). After removal of duplicates (n=24), exclusion of case reports assigned level 4 (n=8) and 5 (n=646), exclusion of case reports with a time to symptoms onset exceeding 48 hours

(n=3), and exclusion of case reports without recorded hospitalization (n=5) 19 eligible case reports were left.

The 5 case reports (3 males, 2 females) which were excluded because the patients had not been hospitalized were all received in 2009. In 3 cases anaphylaxis occurred following administration of a pandemic vaccine (BCCD levels 1, 2, 2), one patient had received a HPV vaccine (BCCD level 1) and another one a seasonal influenza vaccine (BCCD level 2).

Among the 22 eligible case reports, 8 (36.4%) were classified BCCD level 1, 13 (59.1%) level 2, and 1 (4.5%) level 3. Three cases had exclusively been reported to ESPED, 13 exclusively to PEI, and 6 had been reported to both ESPED and PEI (Tab. 1). The median age of the affected individuals was 7.0 years (range: 2 months – 17 years). Four individuals (18.2%) were reported to have a pre-existing allergy, of whom patient 1 had an allergy to antibiotics (amoxicillin, penicillin), patient 2 to mite, patient 3 to ambroxol hydrochloride sirup, birch, nuts, rye, and grass, and patient 4 to pollen, mite, and food. Six children and adolescents were reported to have another preexisting medical condition. In 5 cases, premedication was notified, but only in one case premedication included antiasthmatic drugs.

A total of 26 vaccines were reported to have been administrated prior to (suspected) anaphylaxis with AS03 adjuvanted A/H1N1 pandemic influenza vaccine being the vaccine with the highest number of notifications (n=8) (Tab 2). In 3 patients (13.6%), concomitant vaccinations were reported: second dose combined diphtheria-tetanus-acellular pertussis, hepatitis B, poliovirus and *Haemophilus influenzae* type b vaccine + second dose pneumococcal 7-valent conjugate vaccine (diphtheria CRM197 protein);

fourth dose combined diphtheria-tetanus-acellular pertussis, hepatitis B, poliovirus and *Haemophilus influenzae* type b vaccine + first dose pneumococcal 10-valent conjugate (protein D) vaccine; and second dose combined diphtheria-tetanus-acellular pertussis, hepatitis B, poliovirus and *Haemophilus influenzae* type b vaccine + second dose pneumococcal 7-valent conjugate vaccine (diphtheria CRM197 protein) + second dose 5-valent, live, oral rotavirus vaccine.

In half of the 26 vaccines administered, the patient received the first dose, in 9 vaccines the second dose, and in one vaccine, the fourth dose. For 3 vaccines, information on dosage was not available.

The most frequently reported symptoms were generalized urticaria (hives) or erythema, difficulty in breathing without wheeze or stridor, localized or generalized angioedema, tachycardia, and nausea (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/C391>). Median time to symptoms onset was 5 min (range 1 min – 24 hours).

In 86.4% of the reports, the patient received a specific therapy. A total of 68.2% patients were treated with corticosteroids, 50% with antihistamines, and 40.9% with intravenous fluids (Table, Supplemental Digital Content 2, <http://links.lww.com/INF/C392>). Therapy included oxygen (27.3%), catecholamines (13.6%), and beta-2 sympathomimetics (4.5%). With the exception of one patient for whom the outcome was unknown all patients had recovered at the time of reporting.

There was one non-eligible case report with a fatal outcome which was originally assigned level 4 was later on recoded level 5. This case of a 5 month-old male infant had been reported to both ESPED and the PEI. The autopsy report that had been provided to

the PEI by the public prosecutor upon request stated that histological examinations revealed a severe hemorrhagic pulmonary edema of both lungs possibly caused by an acute left heart failure. Furthermore, a mild lymphocytic inflammatory reaction at the heart possibly attributable to a pre-existing myocarditis was detected. The forensic pathologists suspected a genetic defect since a sibling of the deceased infant had died in 2007 at a similar age. An autopsy had also been performed on the brother's corpse. Main findings had included a hemorrhagic, non-reactive pneumonia and a lymphocytic myocarditis.

With respect to the AS03 adjuvanted A/H1N1 pandemic influenza vaccine, the estimated absolute number of cases with anaphylaxis as an AEFI was estimated to be 11.0 (95% CI: 8.5–26.2) which corresponds to an incidence of 11.8 (95% CI: 9.1–28.2) cases per 1,000,000 doses administered (Tab. 3). The incidence rates of anaphylaxis for all other vaccines were low, without clustering of cases for a specific vaccine (Tab. 3). Regarding vaccines other than AS03 A/H1N1 pandemic influenza vaccine excluding monovalent measles and monovalent rubella vaccine in order to avoid indication bias, the absolute annual number of anaphylactic reactions in children and adolescents leading to hospitalization within the observational period of 24 months was estimated to be 13.7 (95% CI: 12.3–21.8) cases corresponding to an annual frequency of 6.8 (95% CI: 6.1–10.9) cases. In relation to the mean ($\pm$ standard deviation) annual number of hospitalized cases of anaphylaxis from the main causes in this age group ($1,246 \pm 24.7$), this corresponds to a percentage of 0.6% (95% CI: 0.5–0.9).

Sensitivity analyses

Inclusion of BCCD level 4 case reports in the analyses resulted in a total number of 29 reports 5 of which originated exclusively from ESPED, 17 exclusively from the PEI and 7 from both ESPED and PEI.

As to the AS03 A/H1N1 pandemic influenza vaccine, the frequency of anaphylactic reactions was estimated to be 14.0 (95% CI: 10.7–33.4) which in relation to the number of individuals with uptake of pandemic vaccine under the age of 18 years translates to an estimated incidence of 15.1 (95% CI: 11.5–35.9) per 1,000,000 doses administered.

Regarding vaccines other than AS03 A/H1N1 pandemic influenza vaccine excluding monovalent measles and monovalent rubella vaccine in order to avoid indication bias, the annual frequency was estimated to be 10.5 (95% CI: 9.0–16.8). In relation to the mean annual number of hospitalized cases of anaphylaxis from the main causes in this age group, this corresponds to a percentage of 0.8% (95% CI: 0.7–1.3).

Estimates for specific vaccines calculated within the scope of the sensitivity analyses were provided in Tab 3.

Discussion

Our study supports the notion that anaphylaxis following immunization in children and adolescents is a very rare event. The strength of this study is that hospitalized children with suspected anaphylaxis were prospectively analyzed by ESPED which is an active surveillance system with an (external) coverage of 99.2 % and a very good (internal) compliance (ESPED response rate in 2008: 96%) as well as retrospectively using all BCCD classified AEFI reports received by a passive surveillance system (PEI).

Reporting of adverse events following immunization to PEI as the competent authority is mandatory in Germany. Thus, the PEI is presumably in charge of the most complete

collection of AEFI reports in Germany. Completeness of the PEI AEFI reporting system in general is unknown. Regarding this study, we used capture–recapture methods to calculate an estimator for completeness which was 78% (Nearly Unbiased Estimator, NUE) and to adjust for underreporting. Using the SMQs ‘anaphylactic reaction’ and ‘hypersensitivity’ enabled a standardized and systematic database search for “Preferred Terms” (PT) specifying signs and symptoms that may occur during an anaphylactic or hypersensitivity reaction. Thus the probability is low that eligible reports may have slipped the pre-screening process. Because numerous case reports with differential diagnoses like vaso-vagal reactions or rashes were retrieved, in a second step, the case reports identified by the SMQs were validated according to the BCCD for anaphylaxis as an AEFI. In contrast, in the ESPED study cases were prospectively identified and recorded by medical staff according to a study protocol and by using a standardized case report form (CRF) addressing the Brighton Collaboration criteria.

The BCCD for anaphylaxis as an AEFI⁸ is an established assessment tool that has been used previously to evaluate case reports of potential anaphylaxis in children and adolescents^{4–6}. Passive surveillance systems have often been blamed for underreporting and a lack of detailed information. This is why our strategy was to use the prospective active surveillance system ESPED which independently collected reports of anaphylaxis as an AEFI in individuals under the age of 18 years in the same observational period using the BCCD for anaphylaxis as an AEFI as a second data source. Adjusted for underreporting, the annual frequency of anaphylaxis as an AEFI in individuals under the age of 18 years in Germany regarding vaccines (excluding AS03 pandemic vaccines as well as monovalent measles and rubella vaccines) was estimated to be 6.8 (95% CI: 6.1–

10.9) cases, a magnitude that is in line with the number of cases of anaphylaxis following immunization in individuals under 16 detected by the British Paediatric Surveillance Unit (BPSU) (n=7) which is very similar to ESPED regarding aims (surveillance of rare pediatric disorders) and methods (reporting cards, follow up questionnaires)⁴. In contrast to the study conducted in UK and Ireland, in Germany anaphylaxis as an AEFI was also reported to occur in preschool children and infants with the youngest subject being just 2 months whereby the risk of anaphylaxis following administration of vaccines used in standard immunization programs for infants appears to be low. Our finding is, however, consistent with results from the US² where 4 out of the 5 cases identified were below 2 years of age and Australia where 2 infants were reported to have suffered from anaphylaxis following concomitant receipt of hexavalent, pneumococcal and rotavirus vaccines⁵.

For monovalent measles and monovalent rubella vaccines, incidence rates of a higher magnitude were estimated (Tab 5). These calculations were, however, based on one single case each which could be subject to bias by indication or to misinterpretation and therefore have to be interpreted with caution. In contrast, only one BCCD level 4 case of anaphylaxis was reported following receipt of measles, mumps, and rubella (MMR) and no cases were reported following receipt of measles, mumps, rubella and varicella (MMRV) vaccines after administration of 924,314 and 2,072,157 doses, respectively. The incidence rates for measles and rubella strains containing vaccines reported in the literature varied considerably a fact that may also be ascribed to bias by indication or misinterpretation: 18.9 cases per 100,000 doses³ based on 1–2 cases reported and 12.0 cases per 100,000 doses⁴ based on 2 cases reported for monovalent measles vaccine;

22.4 cases per 100,000 doses ³ for monovalent rubella vaccine based on 2–3 cases reported; 1 case per 100,000 doses ²¹ based on 30 cases reported, 1.25 per 100,000 doses ⁵ based on 6 cases reported, and 5.14 per 1,000,000 doses ⁶ based on 3 cases reported for MMR vaccines; 19.8 per 1,000,000 doses ⁶ based on 2 cases reported for MMRV vaccines.

The observational period included the 2009 H1N1 pandemic mass vaccination campaign that was initiated in Germany on 26 October 2009. In our study, AS03 adjuvanted A/H1N1 pandemic influenza vaccine (Pandemrix®, GlaxoSmithKline, Rixensart, Belgium) was the vaccine with the highest absolute and relative proportion among all vaccines administered prior to anaphylactic reactions (n=8; 30.8%), although the vaccination coverage in Germany was low [< 14 years 7.8% (95% CI: 6.1–10.0); 14 – 17 years 4.0% (95% CI: 2.6–6.4)] ¹⁶. In this study, the incidence for anaphylaxis following administration of the AS03 adjuvanted A/H1N1 pandemic influenza vaccine was higher as compared to the world-wide passive reporting rate published by the manufacturer GlaxoSmithKline in 2011 ²² which was 1.8 case of anaphylaxis as an AEFI fulfilling the criteria of BCCD level 1–3 per 1,000,000 doses administered to all age groups. In line with our study, Rouleau et al. ²³ also using the BCCD found an incidence of anaphylaxis following administration of another AS03 adjuvanted A/H1N1 split influenza vaccine (Arepanrix®, GlaxoSmithKline, Mississauga, Ontario/Canada) of 13 cases per 1,000,000 doses administered for patients of all ages in Quebec, Canada.

On the one hand, different from seasonal influenza vaccines which are particularly recommended for pediatric patients suffering from chronic diseases like asthma who may have a higher frequency of underlying allergic conditions as well as hyperreactivity of

skin and mucosal structures the H1N1 pandemic influenza vaccine was recommended for all children and adolescents irrespective of underlying conditions (mass vaccination campaign). On the other hand, it has to be considered that Pandemrix was a new vaccine which was controversially discussed in the media (reactogenicity, innovative adjuvant). It is known that new products on the market may provoke increased reporting of adverse events; this has been called "Weber effect" ²⁴.

Interestingly, in half of the cases, anaphylaxis occurred after administration of the first dose, a fact that supports the notion that vaccine-associated anaphylaxis may not necessarily be due to sensitization after repeated vaccination or an IgE-mediated allergy. Instead, it may be induced by histamine release through other mechanisms ²⁵. However, a vaccine does not only contain the antigen but numerous other components like antibiotics or solvents. So, even after the first dose an allergic reaction may occur if the child was previously sensitized to a constituent of the vaccine (e.g. the antibiotic that was used in the manufacturing process).

In this study, no proven vaccine-associated cases of anaphylaxis with fatal outcome were identified. Bohlke et al. ² did not identify any case of anaphylaxis that resulted in death after administration of over 7.6 million doses. Also in the studies conducted in UK and Ireland ⁴, Australia ⁵ and the US ⁶, no fatal cases were reported. Of note, catecholamines were administered only sparsely in our study although guidelines recommend catecholamines as first-line treatment ²⁶. Thus, we speculate this may be because of fear of side effects that may occur especially when given in overdose.

Limitations

Detailed information was not available for all spontaneous case reports. Paucity of information may lead to an underestimation of the annual frequency of anaphylaxis as an AEFI. Therefore, we used a prospective active surveillance system as a second data source. It is reassuring that our estimates are in line with data from the UK and Ireland. Our estimate is limited to hospitalized cases of anaphylaxis since ESPED exclusively collaborates with children hospitals. Excluding the patients who were exclusively treated in an outpatient setting may also lead to an underestimation of the annual frequency of anaphylaxis following immunization.

Fulfilling the BCCD for anaphylaxis as an AEFI which was developed for immunization settings⁶ is irrespective of causality and reflects per se only a temporal but not a causal association. Furthermore, the BCCD does not only include anaphylactic (IgE mediated), but also anaphylactoid (non IgE mediated) reactions and maybe also non-allergic events. In consequence, capture of case reports in this study is characterized by a high sensitivity. To conclude, this study confirms that anaphylaxis following immunization is a very rare event. Nevertheless, pediatricians should always be prepared to face and manage such a potentially life-threatening adverse event in their own practice.

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Figure legend:

Figure 1. Flow chart ESPED reports. BCCD Brighton Collaboration Case Definition

Figure 2. Flow Chart PEI reports. SMQ Standardized MedDRA Queries; BCCD Brighton Collaboration Case Definition

SDC legend:

SDC 1. Symptoms of anaphylactic reaction. Absolute and relative frequencies, 95% CI^a
(n=22)

SDC 2. Treatment of anaphylactic reaction, absolute and relative frequency (based on the number of patients)

Tab 1 Characteristic features of ESPED and PEI reports, absolute and relative frequency*

Charac- teristic feature	Cases reported exclusively to ESPED (n=3)		Cases reported exclusively to PEI (n=13)		Cases reported both to ESPED and PEI (n=6)		Cases reported Total (n=22)	
	Median	Range	Median	Range	Median	Range	Median	Range
Age	2 yrs.	14 mo. – 13 yrs.	7 yrs.	2 mo. – 15 yrs.	12 yrs.	4 mo. – 17 yrs.	7 yrs.	2 mo. – 17 yrs.
Gender	n	%	n	%	n	%	n	%
Male	2	66.7	8	61.5	3	50.0	13	59.1
Female	1	33.3	5	38.5	3	50.0	9	40.9
Year	n	%	n	%	n	%	n	%
2008	1	33.3	3	23.1	3	50.0	7	31.8
2009	1	33.3	10	76.9	2	33.3	13	59.1
2010	1	33.3	0	0.0	1	16.7	2	9.1
Reported pre- existing allergy	n	%	n	%	n	%	n	%
Yes	0	0.0	2	15.4	2	33.3	4	18.2
No	3	100.0	5	38.5	3	50.0	11	50.0

n .a.	0	0.0	6	46.2	1	16.7	7	31.8
Preexisting medical condition	n	%	n	%	n	%	n	%
Yes	1	33.3	3	23.1	2	33.3	6	27.3
No	2	66.7	5	38.5	2	33.3	9	40.9
n. a.	0	0.0	5	38.5	2	33.3	7	31.8
Comedica- tion	n	%	n	%	n	%	n	%
Yes	1	33.3	1	7.7	3	50.0	5	22.7
No	2	66.7	2	15.4	3	50.0	7	31.8
n. a.	0	0.0	10	76.9	0	0.0	10	45.5
Therapy	n	%	n	%	n	%	n	%
Yes	2	66.7	11	84.6	6	100.0	19	86.4
No	1	33.3	0	0.0	0	0.0	1	4.5
n. a.	0	0.0	2	15.4	0	0.0	2	9.1
Outcome	n	%	n	%	n	%	n	%
Recovered	3	100.0	12	92.3	6	100.0	21	95.5
Death	0	0.0	0	0.0	0	0.0	0	0.0
n. a.	0	0.0	1	7.7	0	0.0	1	4.5
ESPED Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland; PEI Paul-Ehrlich-Institut; n number; mo. months; yrs. years; n. a. not available; BCCD Brighton Collaboration Case Definition * based on the number of patients.								

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**Tab 2 Vaccines reported to be administered prior to the anaphylactic reaction,
absolute and relative frequency**

Vaccine	n ¹	% ²
Seasonal influenza vaccine		
Influenza vaccine, split virion, inactivated without preservative	1	3.8
Pandemic influenza vaccine		
AS03 adjuvanted A/H1N1 pandemic influenza vaccine	8	30.8
Human papilloma virus (HPV) vaccine		
2-valent [Types 16, 18] recombinant, AS04 adjuvanted human HPV vaccine	1	3.8
4-valent [Types 6, 11, 16, 18] recombinant HPV vaccine	2	7.7
Tick borne encephalitis (TBE) vaccine		
Inactivated TBE vaccine (strain K23)	1	3.8
TBE vaccine unspec.	1	3.8
Measles vaccine		
Monovalent measles vaccine	1	3.8
Rubella vaccine		
Monovalent rubella vaccine	1	3.8
Pneumococcal vaccine		

7-valent pneumococcal conjugate vaccine (diphtheria CRM197 protein ³)	3	11.5
10-valent pneumococcal conjugate vaccine (protein D ⁴)	1	3.8
Rotavirus vaccine		
Monovalent rotavirus vaccine	1	3.8
5-valent rotavirus vaccine	1	3.8
Meningococcal type C vaccine		
Meningococcal group C conjugate vaccine (tetanus toxoid carrier protein)	1	3.8
Combined vaccines		
Combined diphtheria-tetanus-acellular pertussis (DTPa), hepatitis B, poliovirus and <i>Haemophilus influenzae</i> type b vaccine	3	11.5
Total	26	100.0
n number; n. a. not available; ¹due to concomitant administration of vaccines the number of vaccines reported to be administered exceeds the number of patients; ² based on the number of vaccines reported to be administered; ³CRM197 is a non-toxic mutant of diphtheria toxin having a single amino acid substitution of glutamic acid for glycine; ⁴Protein D is a highly conserved surface protein from Non-Typeable <i>Haemophilus influenzae</i> (NTHi).		

Tab. 3 Incidence of anaphylaxis following administration of specific vaccines^a

Vaccine	n doses administered ^{1, 2}	n cases of anaphylaxis reported BCCD level 1–3 [BCCD level 1–4] ^a	n cases of anaphylaxis estimated by capture–recapture methods ³ (point estimate and 95% CI)	Incidence of anaphylaxis ^b (point estimate and 95% CI)
Pandemic influenza vaccine	928,500	8 [10]	11.0 (8.5–26.2) [12.1 (10.2–19.5)]	11.8 (9.1–28.2) [14.0 (10.7–33.4)]
Human papilloma virus (HPV) vaccine	1,406,289	3 [3]	3.13 (3.10–4.4) [3.13 (3.10–4.4)]	2.23 (2.21–3.1) [2.23 (2.21–3.1)]
Tick borne encephalitis (TBE) vaccine	3,125,546	2 [3]	2.2 (2.1–3.7) [3.13 (3.10–4.4)]	0.69 (0.67–1.2) [1.0 (0.99–1.4)]
Monovalent measles vaccine	9,404	1 [1]	1.2 (1.1–3.3) [1.2 (1.1–3.3)]	127.6 (117.5–350.6) [127.6 (117.5–350.6)]
Monovalent	25,225	1	1.2 (1.1–3.3)	47.6 (43.8–130.7)

rubella vaccine		[1]	[1.2 (1.1–3.3)]	[47.6 (43.8–130.7)]
Measles mumps rubella vaccine	924,314	- [1]	- [1.2 (1.1–3.3)]	- [1.3 (1.2–3.6)]
Pneumococcal vaccine	4,827,653	4 [6]	4.2 (4.1–6.1) [7.0 (6.1–13.8)]	0.9 (0.8–1.3) [1.4 (1.3–2.9)]
Meningococcal type C vaccine	3,167,851	1 [1]	1.2 (1.1–3.3) [1.2 (1.1–3.3)]	0.4 (0.3–1.0) [0.4 (0.3–1.0)]
Combined diphtheria-tetanus-acellular pertussis (DTPa), hepatitis B, poliovirus and Haemophilus influenzae	4,828,737	3 [3]	3.13 (3.10–4.4) [3.13 (3.10–4.4)]	0.65 (0.64–0.9) [0.65 (0.64–0.9)]

type b vaccine				
¹ Methods to calculate exposure estimates are described in the text; ² seasonal influenza and rotavirus vaccines were not included because denominator data was not available; ³ methods to calculate capture-recapture estimates are described in the text; n number; BCCD – Brighton Collaboration Case Definition; n. a. not available; ^a estimates for BCCD level 1–4 which were calculated within the scope of sensitivity analyses are given in brackets, ^b per 1,000,000 doses administered.				

Fig. 1 Flow chart ESPED reports. BCCD Brighton Collaboration Case Definition

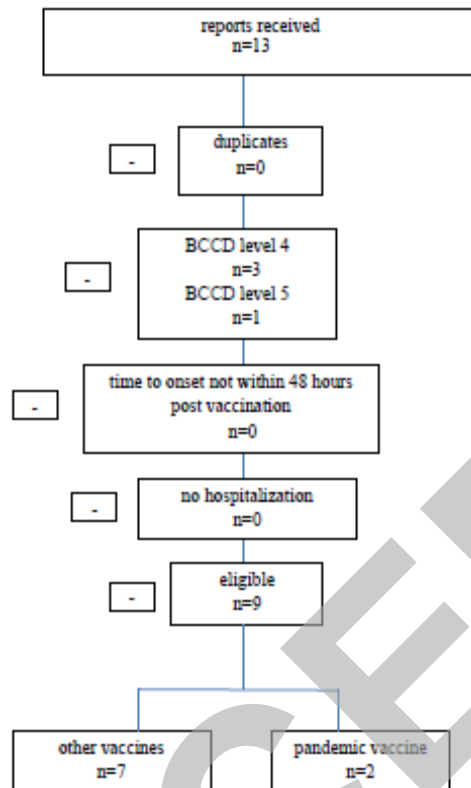
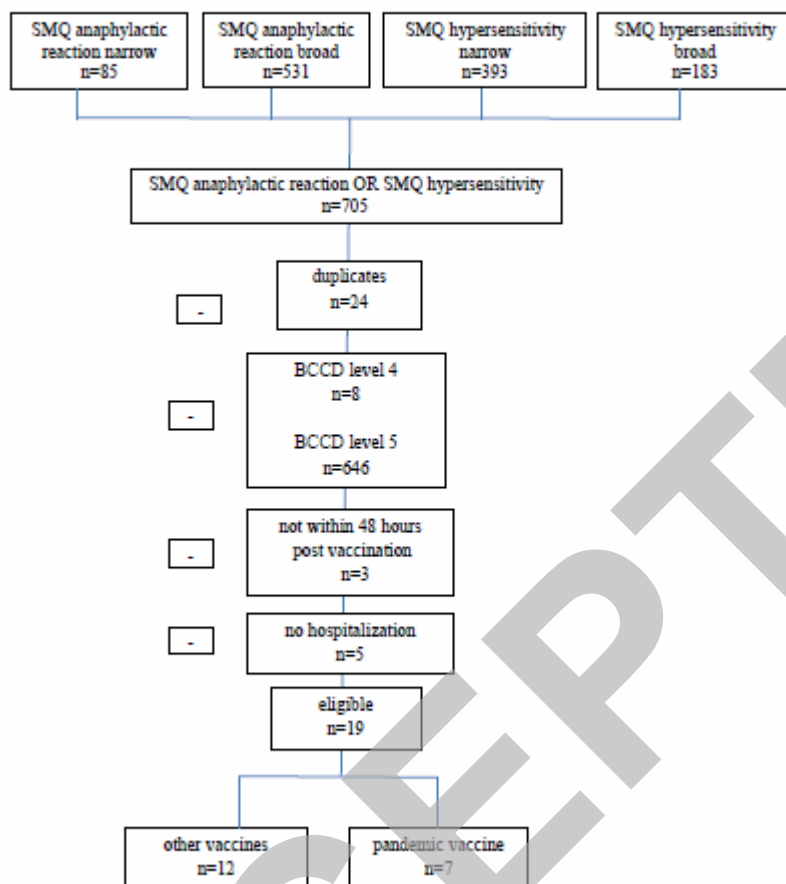


Fig. 2 Flow Chart PEI reports. SMQ Standardized MedDRA Queries; BCCD Brighton Collaboration Case Definition



SDC 1. Symptoms of anaphylactic reaction. Absolute and relative frequencies, 95 % CI^a (n=22)

Symptom	n	%	95 % CI ^a	Symptom	n	%	95 % CI ^a
Dermatologic							
Major				Minor			
• Generalized urticaria (hives) or generalized erythema	10	45.5	24.4–67.8	• Generalized pruritus without skin rash	1	4.6	0.1–22.8
• Angioedema, localized or generalized	9	40.9	20.7–63.7	• Generalized prickle sensation	1	4.6	0.1–22.8
• Generalized pruritus with skin rash	4	18.2	5.2–40.3	• Localized injection site urticaria	3	13.6	2.9–34.9
				• Red and itchy eyes	3	13.6	2.9–34.9
Cardiovascular							
Major				Minor			
• Measured hypotension	8	36.4	17.2–59.3				
• Clinical diagnosis of uncompensated	0	0.0	0.0–15.4	• Reduced peripheral	0	0.0	0.0–15.4

shock, indicated by the combination of at least 3 of the following:				circulation as indicated by the combination of at least 2 of:			
• Tachycardia	9	40.9	20.7–63.7	• Tachycardia	0	0.0	0.0–15.4
• Capillary refill time >3 s	0	0.0	0.0–15.4	• A capillary refill time of >3 s without hypotension	0	0.0	0.0–15.4
• Reduced central pulse volume	0	0.0	0.0–15.4				
• Decreased level of consciousness or loss of consciousness	8	36.4	17.2–59.3	• A decreased level of consciousness	0	0.0	0.0–15.4
Respiratory							
Major				Minor			

• Bilateral wheeze (bronchospasm)	3	13.6	2.9–34.9	• Persistent dry cough	4	18.2	5.2–40.3
• Stridor	3	13.6	2.9–34.9	• Hoarse voice	2	9.1	1.1–29.2
• Upper airway swelling (lip, tongue, throat, uvula, or larynx)	3	13.6	2.9–34.9	• Difficulty breathing without wheeze or stridor	10	45.5	24.4–67.8
• Respiratory distress—2 or more of the following:	0	0.0	0.0–15.4	• Sensation of throat closure	4	18.2	5.2–40.3
• Tachypnoea	4	18.2	5.2–40.3	• Sneezing, rhinorrhea	2	9.1	1.1–29.2
• Increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.)	0	0.0	0.0–15.4				
• Recession	0	0.0	0.0–15.4				
• Cyanosis	1	4.6	0.1–22.8				
• Grunting	0	0.0	0.0–15.4				

Gastrointestinal							
				Minor			
				• Diarrhoea	0	0.0	0.0–15.4
				• Abdominal pain	5	22.7	7.8–45.4
				• Nausea	9	40.9	20.7–63.7
				• Vomiting	7	31.8	13.9–54.9
Laboratory							
				Minor			
				• Mast cell tryptase elevation > upper normal limit	0	0.0	0.0–15.4
^a Clopper-Pearson Exact confidence limits.							

SD 2. Treatment of anaphylactic reaction, absolute and relative frequency (based on the number of patients)

	Route of administration						
Treatment	i.m.	i.v.	oral	rectal	inhal.	n.a.	any
Catecholamines	1 (4.5%)	1 (4.5%)			0 (0.0%)	1 (4.5%)	3 (13.6%)
Antihistamines		7 (31.8%)	3 (13.6%)			1 (4.5%)	11 (50.0%)
Corticosteroids		9 (40.9%)	1 (4.5%)	6 (27.3%)		1 (4.5%)	15 (68.2%)
Beta-2 sympathomimetics		0 (0%)			1 (4.5%)		1 (4.5%)

Fluids		9 (40.9%)					9 (40.9%)
Oxygen					6 (27.3%)		6 (27.3%)
i.m. intramuscular; i.v. intravenous; inhal. inhalation; n.a. not available.							