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Spontaneous reports of vasculitis as an adverse event following immunization: A descriptive analysis across three international databases

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ABSTRACT

Background: Vasculitides have been reported as adverse events following immunization (AEFI) following various vaccines. We describe reports of vasculitis to three international spontaneous reporting systems.
Methods: All spontaneous reports of vasculitis following immunization between January 2003 and June 2014 were retrieved from Eudravigilance (EV), the Vaccine Adverse Event Reporting System (VAERS), and VigiBase®. A Standard MedDRA Query (SMQ) for vasculitis was used and vaccine types were categorized using the Anatomical Therapeutic Chemical classification system. We performed a descriptive analysis by source, sex, age, country, time to onset, vaccine, and type of vasculitis.
Results: We retrieved 1797 reports of vasculitis in EV, 1171 in VAERS, and 2606 in VigiBase®. Vasculitis was predominantly reported in children aged 1–17 years, and less frequently in the elderly (>65 years). The generic term "vasculitis" was the most frequently reported AEFI in this category across the three databases (range 21.9% to 27.5% of all reported vasculitis for vaccines). For the more specific terms, Henoch–Schoenlein Purpura (HSP) was most frequently reported, (19.1% on average), followed by Kawasaki disease (KD) (16.1% on average) and polymyalgia rheumatica (PMR) (9.2% on average). Less frequently reported subtypes were cutaneous vasculitis (CuV), vasculitis of the central nervous system

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(CNS-V), and Behcet's syndrome (BS). HSP, PMR and CuV were more frequently reported with influenza vaccines: on average in 29.3% for HSP reports, 61.5% for PMR reports and in 39.2% for CuV reports. KD was reported with pneumococcal vaccines in 32.0% of KD reports and with rotavirus vaccines in more than 20% of KD reports. BS was most frequently reported after hepatitis and HPV vaccines and CNS-V after HPV vaccines.

Conclusion: Similar reporting patterns of vasculitides were observed in different databases. Implementation of standardized case definitions for specific vasculitides could improve overall data quality and comparability of reports.

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1. Introduction

Vasculitides are a heterogeneous group of disorders characterized by inflammation of blood vessels leading to tissue or end-organ injury [1]. The tissues and organs involved, the etiology, the type of vessels affected, and consequently, the clinical manifestations and prognosis can be very different [2]. Vasculitides affect both adults and children but often with varying epidemiology and clinical features [3]. Some vasculitis subtypes, such as Kawasaki disease (KD), occur almost exclusively in children, whereas others (e.g., temporal arteritis) occur almost exclusively in adults. Moreover, other vasculitides, such as polyarteritis and granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis), have different aetiological, clinical, and prognostic characteristics in children compared to adults and the elderly [4].

Vasculitides have been reported as adverse events following immunization (AEFIs) with several types of vaccines and according to some vaccine summaries of product characteristics, they are considered expected adverse reactions [5]. Vasculitides may be serious and require early diagnosis in order to start appropriate treatment. The etiology may be difficult to establish as the same type of vasculitis can have different causes, and the same agent can induce different types of vasculitis [6].

An important criterion guiding the causality assessment of each single event is the temporal relationship between the vaccine and the event, which for drug and vaccine induced vasculitis is deemed to be in the range of one to six weeks [7,8]. Heterogeneity in clinical features, epidemiology, and lack of internationally accepted clinical diagnostic criteria for each subtype make data comparison across different studies challenging.

Several attempts have been made to propose definitions and classifications of vasculitis. The two main proposals were the classification criteria of the American College of Rheumatology in 1990 and the criteria used since 1994 by a panel of experts at the Chapel Hill Consensus Conference to standardize the definitions of subtypes of vasculitis [9–11]. However, both are primarily classification systems with limited diagnostic criteria for each subtype. Additional tools incorporating new knowledge of diagnostic testing and pathogenesis of the disease were included in the European Medicines Agency algorithm for classification of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and Polyarteritis Nodosa, and the European League against Rheumatism/Pediatric Rheumatology European Society (EULAR/PReS) criteria for childhood vasculitis [12–15]. Nevertheless, standardized and internationally accepted case definitions to establish the level of diagnostic certainty for vasculitis or different subtypes as AEFI are lacking.

To fill this gap, the Brighton Collaboration formed a working group to develop standardized case definitions for vasculitides as AEFI [16]. The Brighton Collaboration's method to develop a standardized case definition includes a systematic search of available evidence in the literature [17]. For vasculitis, this was complemented by an analysis of vasculitis reports in spontaneous reporting systems to guide prioritization of case definition development. In this paper, we present the methods and findings of vasculitides reported as AEFI to three large spontaneous reporting systems.

2. Methods

All reports of vasculitis following vaccine(s) administration spontaneously reported to Eudravigilance (EV), the Vaccine Adverse Event Reporting System (VAERS), and VigiBase®, between January 2003 and June 2014 were retrieved [18–21].

All adverse events are coded according to the standardized medical terminology developed by the International Conference of Harmonization (MedDRA dictionary) [22]. The vaccine types are categorized using the Anatomical Therapeutic Chemical (ATC) classification system (for classification details, please see Table S1) [23].

The databases were searched using the terminology of MedDRA Dictionary version 17.0. The adverse events were expressed according to the Preferred term (PT), and the data were retrieved through the Standard MedDRA Query (SMQ) Vasculitis (code 20000174) [24,25]. The SMQ vasculitis was available as "narrow" and "broad" searches. We employed the more specific narrow approach (i.e., to identify events highly likely to have a condition of interest). This search method was applied consistently across the three databases (see Annex 1 in the supplementary information for the list of PT included in the SMQ narrow).

The following variables were available from the retrieved ICSRs: age, sex, vaccine type (grouped according to the Anatomic Therapeutic Classification, i.e. ATC code), type of vasculitis (i.e. PT), AEFI onset and outcome. The criteria adopted to select vasculitis subtypes for in-depth analysis were based on frequency and severity of each subtype. All analyses were performed separately on data from each of the three databases to allow for comparison. A single event may include more than one PT (related to vasculitis) and/or more than one vaccine. Thus, the number of adverse events could differ from the number of distinct ICSRs. Similarly, this data structure implied that an adverse event reported with more than one vaccine was counted once for each.

The events of vasculitis were analyzed as available in the databases without further adjudication; no exclusion criteria were adopted. Causality assessments were beyond the scope of this work. Neither the data sources nor the merely descriptive analyses allow for any inference on a causal relationship for any vaccine-event pair. We used Microsoft Excel to analyze the data.

3. Results

We retrieved 1797 reports of vasculitis in EV (corresponding to 1997 AEFI), 1171 reports in VAERS (corresponding to 1275 AEFI), and 2606 reports in VigiBase® (corresponding to 2783 AEFI), (see Table 1). More than one PT (included in the vasculitides SMQ narrow) occurred in 8.6% of the ICSRs. Overall, the reporting pattern within the different databases was similar: The distribution of vasculitis events by sex showed a slight female predominance (54.3%). The highest proportion of vasculitis reports across the three databases was in children aged 1–17 years (ranging from 30.7%

Table 1
Spontaneous reports of vasculitis following vaccination retrieved in EV, VAERS and VigiBase® by sex, age group, country, outcome and time to onset.

	EV		VAERS		VigiBase®	
No. of Vasculitis cases (ICSR)	1797		1171		2606	
No. of ADRs reported	1997		1275		2783	
Characteristics	*N*	%	*N*	%	*N*	%
Sex						
Male	777	43.2	489	41.7	1129	43.3
Female	961	53.5	632	54.0	1444	55.4
Unknown	59	3.3	50	4.3	33	1.3
Age groups						
0–12 months	336	18.7	209	17.8	477	18.3
1–17 years	572	31.8	404	34.5	799	30.7
18–65 years	443	24.7	318	27.2	763	29.3
65+ years	304	16.9	153	13.1	434	16.7
Unknown	142	7.9	87	7.6	133	5.1
Geographic region*						
Americas (for EV/VigiBase®)/USA (for VAERS)	395	19.8	449	38.3	1459	52.4
Eastern Mediterranean	5	0.2			4	0.1
Europe	1372	68.8			1125	40.4
South East Asia	5	0.2	636	54.3	2	0.1
Western Pacific	215	10.8			189	6.8
Africa	5	0.2			4	0.2
Unknown			86	7.3		
Outcome**						
Fatal	22	1.2	18	1.5	8	0.3
Not recovered/not resolved	343	18.8	337	28.9	282	10.8
Recovering/resolving/resolved/resolved with sequelae	954	52.3	393	33.6	1225	46.9
Unknown/missing/notspecified/notconverted/null	506	27.7	423	36.1	1099	42.0
Time to onset*						
0–10 days	845	40.9	575	49.1	1397	48.9
11–30 days	229	11.1	157	13.4	394	13.8
30+ days	159	7.7	134	11.4	275	9.6
Missing	834	40.3	305	26.0	790	27.7

EV: Eudravigilance; VAERS: Vaccine Adverse Event Reporting System.
* For EV and VigiBase® data refer to reactions (one reaction can be counted more than once if more than one drug has been reported with different Time to Onset), while for VAERS they refer to ICSR.
** A case can be counted in more than one category (on average this occurred in less than 1% of the ICSR).

in VigiBase® to 34.5% in VAERS). Overall, the 50.6% of vasculitis reports were in children aged 0–17 years of age. Vasculitis appears to be less frequently reported in the elderly (15.5% on average). While the majority of vasculitis events in EV occurred in Europe (68.8%), only 38.3% of VAERS vasculitis reports came from the US. In VigiBase®, more than 90% of the reports came from Europe or the Americas. Information on the outcome of vasculitis was unavailable in more than one third of events. This missing information differed between the databases, ranging from 27.7% for EV to 42.0% for VigiBase® (Table 1). Among the patients with recorded outcome, 44.3% recovered, and 1% had a fatal outcome (Table 1). Time to onset was missing in 26.0% in VAERS, 27.7% in Vigibase and 40.3% in EV. Restricting the analysis to events where this information was reported, limited to VigiBase® database, more than 50% of events reported occurred in the first 4 days and 67.5% occurred in the first 10 days in the three databases.

The frequency of the different terms (each describing a specific medical concept) included in the SMQ narrow vasculitis is shown in Fig. 1. The generic PT "vasculitis" was the most frequently reported adverse event (21.9% in EV, 27.3% in VAERS, and 27.5% in VigiBase®). The most frequently reported specific PTs across the three databases were Henoch–Schoenlein Purpura (HSP) (19.1%), followed by Kawasaki Disease (KD) (16.1%,), and polymyalgia rheumatica (PMR) (9.2%). Less frequently reported subtypes of vasculitis (i.e. <1% in at least one database) were: (i) cutaneous vasculitis (CuV); (ii) vasculitis cerebral (CNS-V); (iii) Behcet's syndrome (BS); (iv) allergic granulomatosis angiitis; and (v) arteritis.

Vasculitides were more frequently reported in association with influenza vaccines than with any other vaccines (25.7%; 1248/3484 in EV, 378/1900 in VAERS, 824/3836 in VigiBase®), followed by hepatitis vaccines (11.3%; 269/3484 in EV, 237/1900 in VAERS, 522/3836 in VigiBase®) and pneumococcal vaccines (10.9%, i.e. 304/3484, 255/1900, 412/3836 in VigiBase®); different patterns existed across the three databases (Fig. 2). Rotavirus, varicella zoster and meningococcal vaccines were reported in fewer than 5% of ICSRs available for analysis.

Stratification by age group showed a high consistency across the three databases for each vasculitis subtype (Fig. 3). KD was reported mainly in children less than one year of age (62.9% of the events; 189/316 in EV, 146/239 in VAERS, 260/383 in VigiBase®), HSP was reported more frequently in children aged 1–17 years (73.3% of the events; 271/374 in EV, 201/266 in VAERS, 355/494 in VigiBase®), BS was most frequent in adults 18–65 years of age (68.4% of the events, 8/13 in EV, 14/19 in VAERS, 14/20 in VigiBase®) or in the elderly (>65 years of age, PMR 55.4% of the events, on average, i.e. 93/186 in EV, 68/116 in VAERS and 145/252 in VigiBase®), respectively.

Stratifying vaccine types in the reports by age groups showed that rotavirus vaccines were almost entirely reported in ICSRs concerning children below 1 year of age (Fig. S1); meningococcal, pneumococcal, measles, and combinations of bacterial and viral vaccines mainly emerged in reports of the entire pediatric population (0 to 17 years). These findings reflect current practice of administering those vaccines to their target populations. Human papillomavirus (HPV) vaccines, which were targeted to adolescent girls, were mainly recorded in reports for children aged 1 to 17 years (64.3% of the events on average). Influenza vaccines were most frequently reported as suspected vaccines in reports for adults and the elderly.

Stratification by vaccine types for the selected vasculitides showed that PMR, CuV, and HSP were most frequently reported with influenza vaccines (on average 61.5%, 39.2%, and 29.3%, respectively) (Fig. 4). KD was reported most commonly following pneumococcal and rotavirus vaccines (in more than 20% of KD

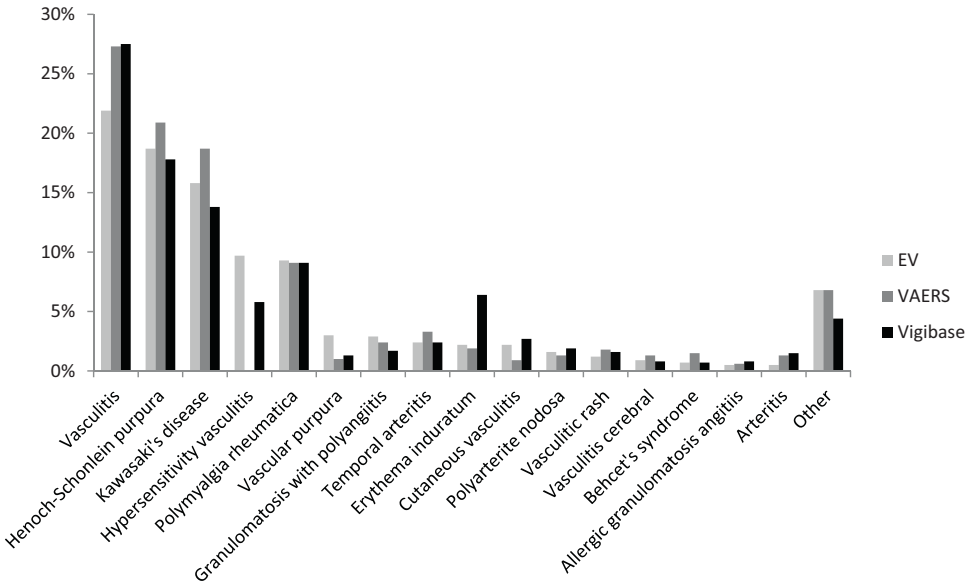

Fig. 1. *Frequency of vasculitis subtype reports in EV, VAERS and VigiBase® from January 2003 to June 2014. All PTs with a frequency <0.5% in Vigibase were categorized as "Other".* EV: Eudravigilance; VAERS: Vaccine Adverse Event Reporting System.

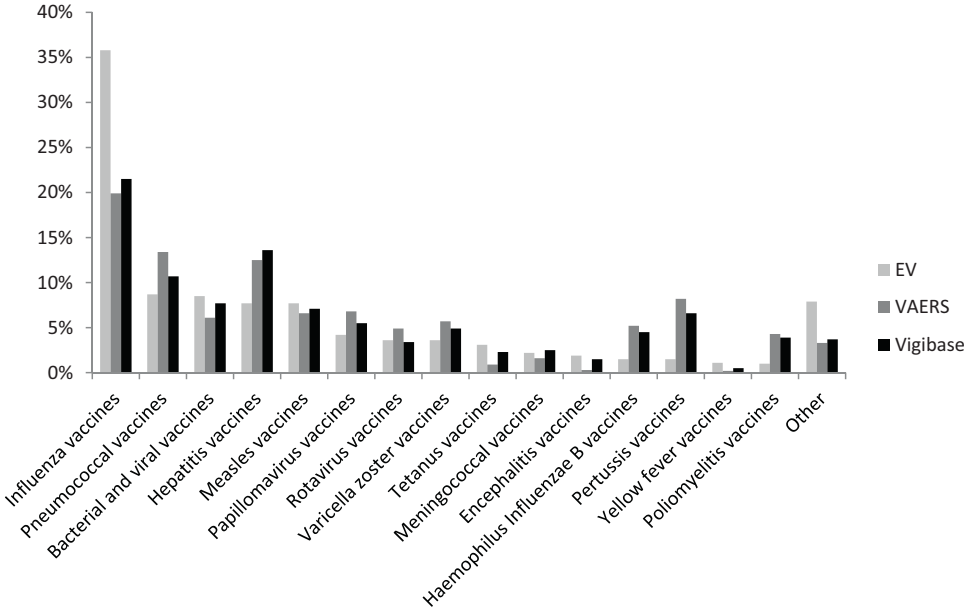

Fig. 2. *Frequency of vasculitis reports by vaccine types in EV, VAERS and VigiBase® from January 2003 to June 2014. Details on vaccine types included in "other" are reported in table S1 under supporting information.* EV: Eudravigilance; VAERS: Vaccine Adverse Event Reporting System.

events) and BS following hepatitis and HPV vaccines (on average 34.6% and 32.6%, respectively). Of the CNS-V reports, almost 40% were in association with HPV vaccines (ranging from 20.7% in EV to 44.4% in VAERS).

On stratification of vaccine types by vasculitis subtype, we found that HSP was more frequently reported with meningococcal, measles and HPV vaccines, while KD were more often reported with pneumococcal and combined bacterial and viral vaccines (Fig. S2). For rotavirus vaccine, overall 91.5% of the vasculitides reported were of the KD type.

As for the overall vasculitis group, analysis of the vasculitis subtype stratified by time to onset showed that the majority of AEFIs occurred within 10 days after vaccination across all subtypes (Fig. 5). However, for BS and CNS-V lack of information on the time to onset was high (almost 50% on average for both, with a higher peak in EV); moreover, among ICSRs with timing information, BS and CNS-V more frequently had a delayed onset after vaccination. Restricting the analysis to events where the onset is reported, the percentage of events with onset >30 days is 27.7% and 36.1% for BS and for CNS-V, respectively, compared to other vasculitis subtypes (e.g. 8.8% for HSP or 19.6% for PMR).

Considering time to onset for each vaccine (only using VigiBase® data), hepatitis, rotavirus and HPV vaccines showed a greater time to onset as compared to other vaccines (Fig. S3).

Finally, seasonality analysis was attempted on VigiBase® data and is presented in the supporting information (Fig. S4).

4. Discussion

The aim of this study was to describe vasculitis AEFI reports from three major databases; to the best of our knowledge this is the first

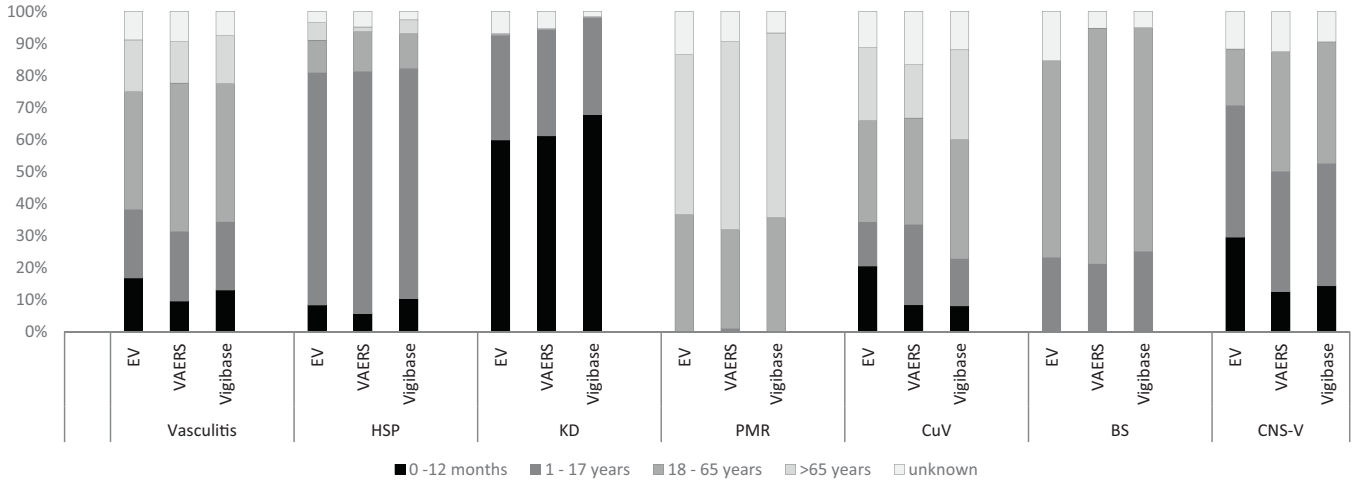

Fig. 3. Reports of selected vasculitis subtypes stratified by age group across the three databases. HSP: Henoch–Schonlein purpura; KD: Kawasaki disease; PMR: polymyalgia rheumatica; CuV: Cutaneous vasculitis; BS: Behcet's syndrome; CNS-V: Vasculitis cerebral; EV: Eudravigilance; VAERS: Vaccine Adverse Event Reporting System.

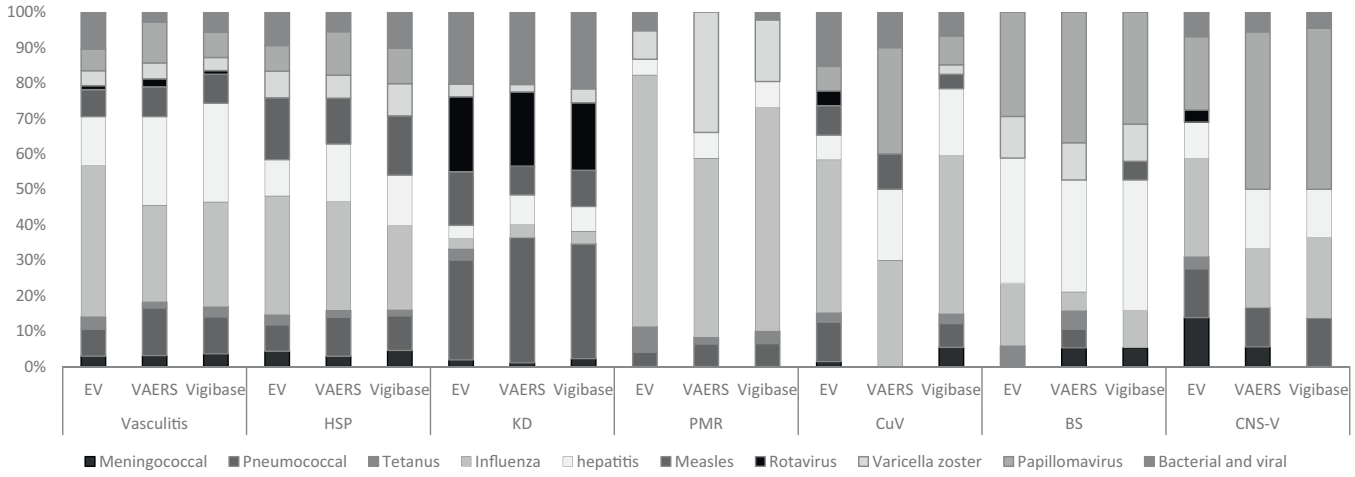

Fig. 4. *Reports of selected vasculitis subtypes stratified by vaccine type across the three databases*. HSP: Henoch–Schonlein Purpura; KD: Kawasaki disease; PMR: polymyalgia rheumatica; CuV: Cutaneous vasculitis; BS: Behcet's syndrome; CNS-V: Vasculitis cerebral; EV: Eudravigilance; VAERS: Vaccine Adverse Event Reporting System.

attempt to compare current reporting practices on a specific AEFI through the analysis of three databases.

This descriptive study, based on more than 2600 spontaneous reports of vasculitis, is the largest conducted to date and draws on three large databases of spontaneous reports (EV, VAERS and VigiBase®). Overall, the study findings show high consistency across the three databases. Vasculitides appear to be more frequently reported in the pediatric population, among females, and

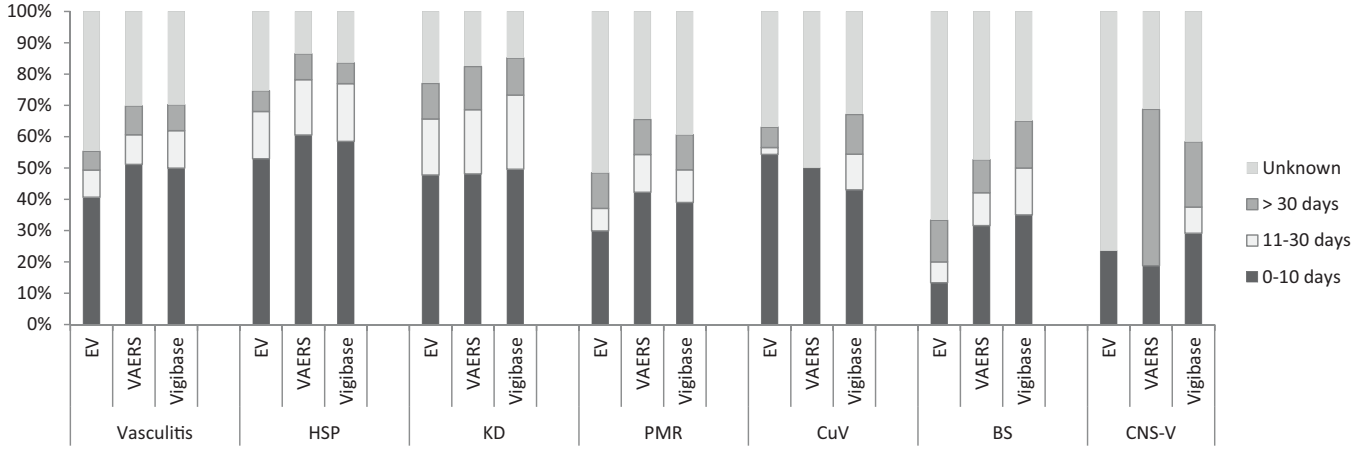

Fig. 5. *Reports of selected vasculitis subtypes stratified by time to onset across the three databases*. HSP: Henoch–Schonlein purpura; KD: Kawasaki disease; PMR: polymyalgia rheumatica; CuV: Cutaneous vasculitis; BS: Behcet's syndrome; CNS-V: Vasculitis cerebral; EV: Eudravigilance; VAERS: Vaccine Adverse Event Reporting System

with a time to onset within 10 days from vaccination. The higher reporting in the pediatric population could be related to the greater number of vaccines given in childhood compared to adults. The fact that the generic term vasculitis was the most frequently reported AEFI within the scope of our queries across the three databases indicates an opportunity for improving data quality. This may be supported by classifications and definitions differentiating vasculitis subtypes. Reports for which specific subtypes of vasculitis were reported, HSP and KD were the most commonly reported vasculitides. With regards to the vaccines in the reports, influenza vaccines were the most frequently reported vaccines in association with vasculitis.

Available published evidence primarily consists of event-reports of specific vasculitis subtypes following specific vaccines. Our study provides age specific data on the frequency of spontaneous reports of all types of vasculitis and after all marketed vaccines. Any assessment of risk would require formal hypothesis testing studies. However, six retrospective/observational studies have been conducted to investigate a potential relationship between specific vaccines and single vasculitis subtypes. KD has been studied in association with general vaccination and with rotavirus vaccination; neither study confirmed an increased risk [8,26]. Two studies investigated a potential association between influenza vaccination and granulomatosis with polyangiitis or ANCA-associated vasculitis and neither detected an increased risk [27,28].

Comparison between the three spontaneous reporting databases showed very similar reporting trends across different databases. This consistency could be interpreted as a result of the harmonization policies in the field of pharmacovigilance. However, overlap of reports between the reporting systems should also be considered, as reports to EV and VAERS may be included in VigiBase®. Completeness of the reported data was generally acceptable, although for ADR outcome and time to onset missing data exceeded 30% of the events.

This study has several strengths. First, it was based on spontaneous reports coming from the general population exposed to vaccines without pre-defined exclusion/inclusion criteria. Second, the use of a standard and validated tool (i.e. the SMQ vasculitis narrow) to search specific events within all three databases increased the comparability between databases. Third, given the pharmacovigilance setting, this study highlighted rarer vasculitis subtypes such as BS or CNS-V, which were reported at a very low frequency and are usually not seen in trials or prospective studies. Fourth, the consistency of data analyzed across different databases can be considered as a strength since it increased the robustness of the results.

In general, our study suffers from unavoidable limitations of all spontaneous reporting systems, i.e. likely incomplete and variable event ascertainment and lack of denominators. Since spontaneous reports come from very different countries with distinct demographic factors, national immunization programs, and types of vaccines, we cannot usefully estimate the number of administered vaccines or vaccinated subjects for specific vaccines. Some additional limitations are: (i) different immunization programs as well as different diagnostic practices in specific geographical areas may affect the patterns of spontaneous reports; (ii) the diagnosis reported in the spontaneous reports was not further validated; (iii) vasculitides were analyzed without considering the presence or absence of a causal relationship with the administered vaccines; (iv) the effect of the concomitant administration of different vaccines (and the received doses) on the onset of vasculitides, and underlying diseases were not considered in this study, representing a confounding factor to be further evaluated through specific studies, as age that represents an important confounder for the finding that outcomes are predominantly in the pediatric population. Another important limitation is that we were not able to investigate the severity of the vasculitis subtypes including the complications of the diseases and the recurrences. Further, comparison between databases would be much improved if a common data model was available for all databases allowing for integrated analysis and evaluation of reporting overlap.

5. Conclusions

This study confirmed the usefulness of comparative analyses between different spontaneous reporting databases and showed similar reporting patterns of vasculitides across different databases. Analysis of spontaneous reporting databases by disease group may provide a useful overview of the spectrum of reported events and associated vaccines. Implementation of standardized case definitions for specific vasculitides could improve overall data quality and comparability of reports.

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Disclaimer

The findings, opinions, and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant’s organization (e.g., government, university, or corporation). Specifically, the information does not represent the opinion of the World Health Organization or regulatory institutions. Data retrieved came from the VigiBase®, Eudravigilance and VAERS databases and are not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse event.

Conflict of interest statement

Patrizia Felicetti, Francesco Trotta, Caterina Bonetto, Carmela Santuccio, Yolanda Brauchli Pernus, David Burgner, Rebecca Chandler, Robert D. M. Hadden, Sonali Kochhar, Merita Kucuku, Giuseppe Monaco, Novilia Sjafri Bachtiar, Amina Tebaa, Karina Top, Frederick Varricchio, Giovanna Zanoni, Saša Živkovic, Jan Bonhoeffer have no conflict of interest to disclose. Giampiero Girolomoni has been principal investigator in clinical trials sponsored by many pharmaceutical/cosmetic industries. Robert P. Wise is a full time employee of MedImmune/AstraZeneca, the manufacturer of a licensed live attenuated influenza vaccine and another licensed biological product, Synagis. In addition, he retired in 2011 from a long career at the FDA’s Center for Biologics Evaluation and Research, where he was heavily involved in safety surveillance for many licensed vaccines. Linny Phuong previously worked as a Medical Information Specialist with GlaxoSmithKline (Jun 2004–Dec 2007). She is no longer working at GSK, there is no financial relationship and/or other relationships or activities that influence this work. Seza Ozen received consultation fees and/or speaker’s honoraria from Novartis, SOBI and Roche. But nothing directly relevant to this article. Barbara Pahud served on advisory board for Pfizer and has been an investigator in vaccine clinical trials for GlaxoSmithKline.

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Appendix A. Supplementary data

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.09.027.

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