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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 (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.



## 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).



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