

Vasculitis as an adverse event following immunization – Systematic literature review[☆]



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ABSTRACT

Background: Several types of vasculitis have been observed and reported in temporal association with the administration of various vaccines. A systematic review of current evidence is lacking.

Objective: This systematic literature review aimed to assess available evidence and current reporting practice of vasculitides as adverse events following immunization (AEFI).

Methods: We reviewed the literature from 1st January 1994 to 30th June 2014. This review comprises randomized controlled trials, observational studies, case series, case reports, reviews and comments regardless of vaccine and target population.

Results: The initial search resulted in the identification of 6656 articles. Of these, 157 articles were assessed for eligibility and 75 studies were considered for analysis, including 6 retrospective/observational studies, 2 randomized controlled trials, 7 reviews, 11 case series, 46 case reports and 3 comments. Most of the larger, higher quality studies found no causal association between vaccination and subsequent development of vasculitis, including several studies on Kawasaki disease and Henoch-Schönlein purpura (IgA vasculitis). Smaller case series reported a few cases of vasculitis following BCG and vaccines against influenza and hepatitis. Only 24% of the articles reported using a case definition of vasculitis.

[☆] 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).

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¹ See Appendix A for additional members of the Working Group.

Conclusions: Existing literature does not allow establishing a causative link between vaccination and vasculitides. Further investigations were strengthened by the use of standardized case definitions and methods for data collection, analysis and presentation to improve data comparability and interpretation of vasculitis cases following immunization.

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1. Background

1.1. Why this review?

Vasculitides are a group of related disorders characterized by inflammation of blood vessels leading to tissue or end-organ injury [1] with diverse and only partially understood etiology and with a wide spectrum of clinical manifestations and prognosis [2]. The 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides was the most recent attempt to conceptualize vasculitis and the spectrum of clinical manifestations [3]. With a specific focus on the pediatric population, the Paediatric Rheumatology European Society (EULAR/PReS) [4] endorsed consensus criteria for the classification of childhood vasculitides; these were later revised and validated as the Ankara 2008 criteria [5]. Both are among the most valuable contributions to improving a shared understanding and harmonized approach to vasculitis research.

Although vasculitis research is evolving rapidly and new evidence is improving the ability to discern and better describe distinct forms of vasculitis, up-to-date epidemiological data reflecting these developments are limited. Overall, vasculitis in children is rare. The annual incidence of new cases of vasculitis in children is estimated to be 53.3/100,000 subjects [6]. However, incidence rates of vasculitis are age, location and type specific. The most frequent pediatric manifestations are Henoch-Schönlein purpura (HSP) (also called IgA vasculitis according to the new nomenclature) (10–20/100,000) and Kawasaki Disease (KD) (1–19/100,000), but these rates vary by country, with highest KD incidence rates reported in Japan [6,7]. In adults, the most common subtype is cutaneous small vessel vasculitis (or hypersensitivity vasculitis). There are significant geographic and ethnic differences in epidemiology of various types of vasculitis, as illustrated by the common occurrence of microscopic polyangiitis (MPA) in Asian regions, and predominance of granulomatosis with polyangiitis (GPA) in northern Europe and North America [8]. Comparatively, Takayasu's arteritis (TAK) is more common in Japan, and giant cell arteritis (GCA) is more common in Europe and North America. The annual incidence of GCA is up to 66 per 100,000 in a cohort aged 70–79 years, compared to peak incidence of 65 per 1,000,000 for antineutrophil cytoplasmic antibody-associated vasculitis (AAV) in a cohort aged 65–74 years [8]. Additionally, there are also age differences with higher incidence of MPA and GCA after the age of 65 years. Similar geographic and ethnic differences were also reported for systemic diseases associated with vasculitides, including systemic lupus erythematosus (SLE) and sarcoidosis [9]. Epidemiology of vasculitides also depends on environmental triggers, including infections. A successful hepatitis B (HBV) vaccination campaign in France was followed by a drop in incidence of polyarteritis nodosa (PAN) [10]. A broad range of etiologic agents have been linked with vasculitides such as infectious micro-organisms, connective tissue disease, malignancies, different drugs, and toxins, but others remain unknown. Vasculitides may be triggered by an infectious agent or may be a complication of primary autoimmune dysregulation and/or immunosuppressive therapy [11], among other disorders. Various forms of vasculitis have also been observed and reported as adverse events following immunization (AEFI) after various vaccines. KD, HSP and “vasculitis” in general are listed as

adverse events in the Summary of Product Characteristics (SPC) of several vaccines [12]. During the 2009 influenza H1N1 pandemic, they were monitored as “adverse events of special interest” by regulatory authorities [13].

The aim of this systematic literature review was to assess the existing evidence of vasculitides as AEFI and to determine the need for standardized case definitions for specific vasculitides as AEFI.

2. Methods

The Brighton Collaboration *Vasculitis Working Group* was created in May 2014. Following the standard Brighton Collaboration Process [14] a systematic literature review was conducted in PubMed, EMBASE, and we also searched in Opengrey.eu and in Web of science (Conference Proceedings Citation Index). The literature search included the following Medical Subject Headings (MESH) terms and free text terms: vaccination, immunization and related truncations (e.g. vaccin*, immun*), vasculitis and its subtypes based on the Chapel Hill Consensus nomenclature and related truncations (e.g. vasculit*, arterit*, kawasaki*). The complete search strategy is available as additional online material ([Appendix 1, see Supplementary material](#)). The search included articles between 1st January 1994 and 30th June 2014 in any language and was limited to human studies. Search results were imported into Zotero references manager and de-duplicated. The articles were screened for eligibility based on titles and abstracts (CB). Eligible articles were clinical trials, observational studies, case series, case reports, reviews and comments of vasculitis as AEFI regardless of vaccine, study setting or target population. Full texts of eligible studies were retrieved, and unavailable studies discarded. Uncertainty during the screening process with regard to inclusion/exclusion of studies was resolved by consensus with a second reviewer (CS) or arbitrated by a third (FT). The rationale for study exclusion was recorded as part of the screening process. Data from all publications meeting the inclusion criteria were abstracted into a structured data collection form encompassing the various variables (e.g. type of publication, title, association, type of vasculitis, skin biopsy for histological evaluation/confirmation).

3. Results

An overview of the study flow is presented in [Fig. 1](#). The search in PubMed and EMBASE resulted in the identification of 1572 and 5084 articles, respectively (overall sample 6656). The search in Opengrey.eu and Web of Science did not deliver any additional reference. A total of 5639 records remained after removing duplicates. We then excluded 5240 articles that did not relate to vasculitis or vasculitis following immunization. Full text articles were retrieved for the 399 remaining publications with potentially relevant material for detailed review. An additional 242 articles were excluded as they referred to vasculitis case definitions as such, vasculitis treatment, genetic aspects, pathogenesis or pathophysiology, animal research, surgical procedures, general epidemiology, vaccine effectiveness in patients with vasculitis, reactivation of vaccination injection site reaction, or vasculitis not associated with vaccination. In total, 75 studies were included for analysis, including 6 retrospective/observational studies, 2 randomized controlled trials, 7

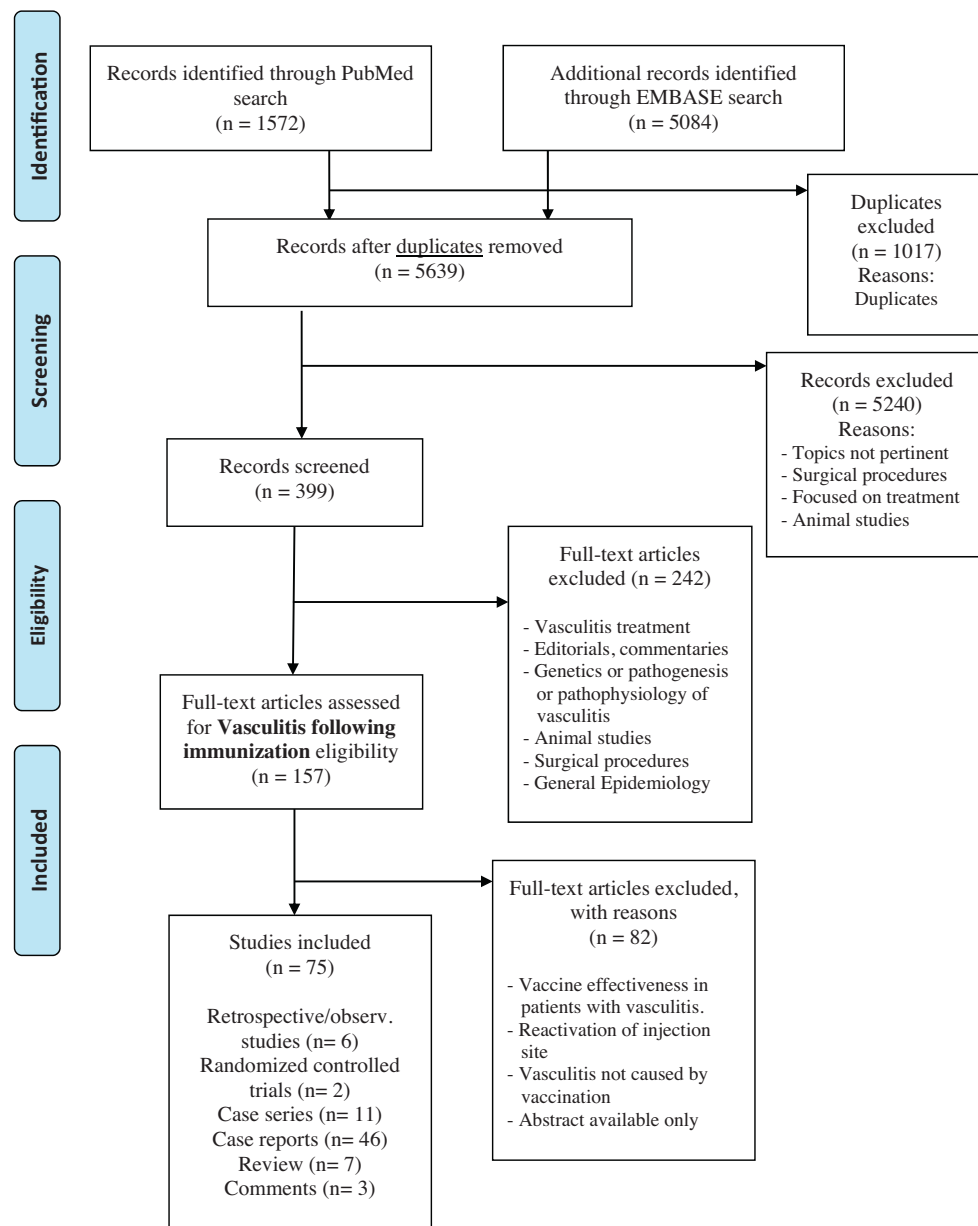


Fig. 1. Study flow chart.

reviews, 11 case series, 46 case reports and 3 comments. Details of selected literature are provided as supplementary online material in Table S1.

Over the last decades various vasculitides (Fig. 2) have been reported in association with a variety of vaccines (Fig. 3). Eight clinical studies reported vasculitides following immunization: six retrospective/observational studies [15–20] and two randomized controlled clinical trials [21,22]. Stassen et al. [15] studied 230 consecutive patients with AAV in their retrospective study. They observed no increase in relapses of AAV after vaccination against influenza. The authors considered vaccination against influenza as safe in patients with AAV with respect to increasing the rate of relapses. Goodman et al. [17] estimated the incidence rate of HSP after meningococcal polysaccharide vaccine in a US Vaccine Safety Datalink cohort 16 to 20 years of age. No cases of HSP were seen in the 42 days after 49,027 doses administered. The background incidence rate was 4.16/100,000 person-years. Exposure of these cases to other vaccines was not analyzed. The authors argued that

these data do not provide evidence of a causative association in this population.

The prospective study by Oberle et al. [20] searched for all spontaneously reported KD cases in association with rotavirus vaccination (i.e. RotaTeq® or Rotarix®) from 2001 to 2010. A total of four KD cases after vaccination with RotaTeq® and zero cases after vaccination with Rotarix® were identified. The four KD cases after vaccination with RotaTeq® revealed no clustering regarding age, gender and time to onset of the AEFI. Although both the proportional reporting ratio (3.1 [95% CI 1.1–9.1; *p*-value: 0.0311]) and the reporting odds ratio (3.1 [95% CI 1.1–9.2]) showed an increased number of case reports in association with rotavirus vaccination compared with other vaccinations, a causal association was denied by the authors, mainly due to a biological mechanism being unknown. Abrams et al. [19] investigated KD rates in 1,721,186 children aged 0–6 years between 1996 and 2006 in the Vaccine Safety Datalink. The author's conclusion was that there was no evidence that vaccination increased the risk of KD, but instead

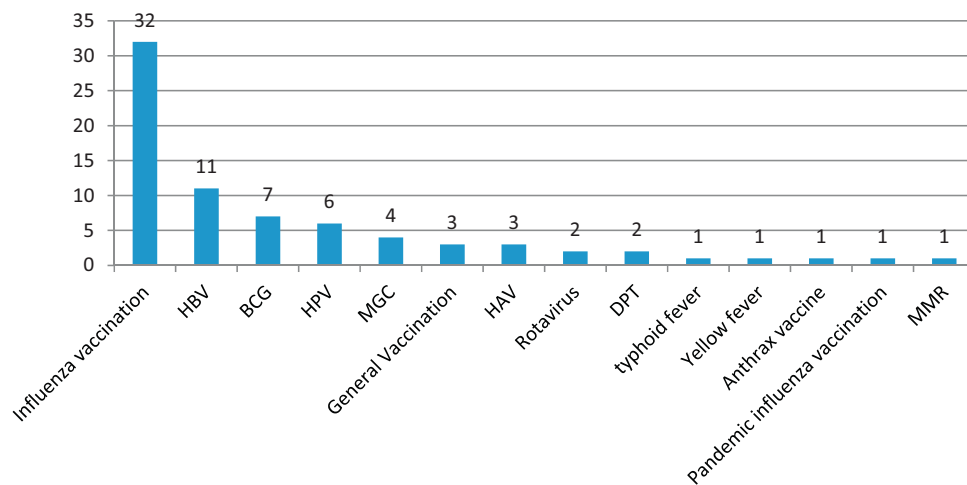


Fig. 2. Number of published articles on vasculitis–vaccine association by vaccine type.

BCG: Bacille Calmette–Guerin; DPT: diphtheria, pertussis and tetanus vaccination; HAV: hepatitis A vaccination; HBV: hepatitis B vaccination; HPV: human papillomavirus vaccination; MGC: meningococcal vaccination; MMR: measles, mumps, and rubella vaccination.

that it may be associated with a transient reduction in incidence of KD. The study by Sexton et al. [18] conducted in New Zealand investigated the risk of new onset of HSP within 15, 30 or 60 days following meningococcal B vaccination and did not find an increased incidence of this disease.

The two randomized controlled trials did not demonstrate an association between immunization and the respective vasculitis subtype. Holvast et al. [21] investigated the immunogenicity of influenza vaccination in patients with GPA in quiescent phase (49 vaccinated, 23 non-vaccinated patients) and the risk of relapse of the disease. However, the study was not aimed to detect a difference in the rate of relapse between groups. Seo et al. [22] performed a study in Korea enrolling 83 infants: 54 with complete KD and 29 with incomplete KD. The purpose of this study was to test whether the inflammation at the BCG inoculation site (BCGitis) can be a useful diagnostic feature of KD as also discussed by Lai et al. [16] in a retrospective study from Taiwan. All subjects were infants at the time of admission. Authors concluded that clinical, laboratory, and echocardiographic variables of patients with incomplete KD and BCGitis, did not differ from those of patients with the complete presentation. The authors applied the American Heart Association algorithm [23] for diagnosing incomplete KD. This study was

limited by the sample size and possibly underestimated z scores of coronary artery diameters, because z scores in controls were lower than zero [22].

Seven reviews were taken into account for this literature review:

- Hua et al. [24] made reference to the prelicensure clinical trials of the live oral pentavalent rotavirus vaccine RotaTeq®; in which 6 KD cases were identified: 5 among 36,150 vaccine recipients and 1 among 35,536 placebo recipients, with a crude relative risk (RR) of 4.9 (95% CI 0.6–239.1). All 5 cases after RotaTeq® occurred within 30 days of vaccination. Although not statistically significant, this prompted a revision of the RotaTeq® labeling with KD added to the Serious Adverse Events section. Analysis of post-marketing data in the Vaccine Adverse Events Reporting System (VAERS) by Hua et al. [24] did not suggest an elevated risk of KD for RotaTeq® or other US-licensed vaccines. The authors concluded that KD can occur in a temporal relationship with vaccination, but a causal association has not been established.
- “Systemic polyarteritis nodosa following hepatitis B vaccination” by de Carvalho et al. [25] in 2008. The authors concluded that vaccination may be the triggering factor for vasculitis in individuals with a genetic predisposition.

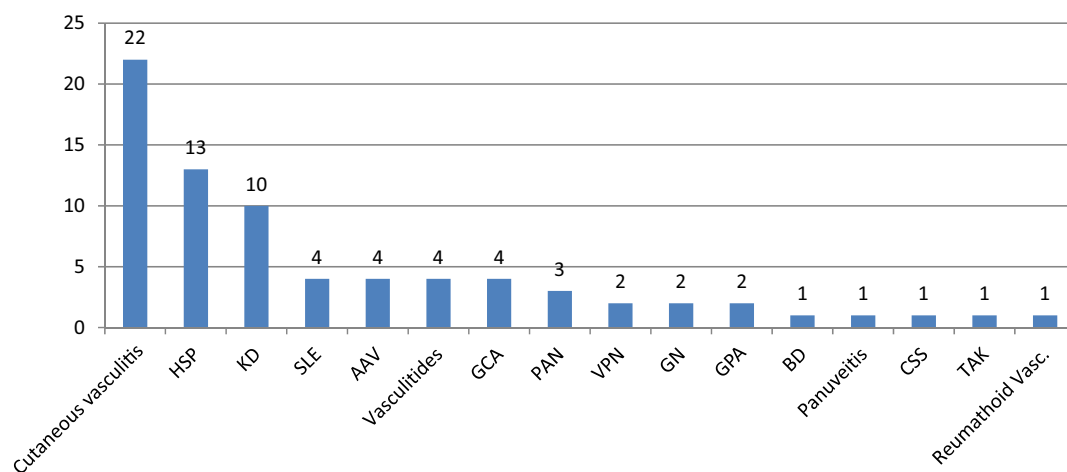


Fig. 3. Number of published articles on vasculitis–vaccine association by vasculitis type.

AAV: ANCA-associated vasculitis; BD: Behcet disease; CSS: Churg Strauss syndrome; CV: cutaneous vasculitis; GCA: giant cell arteritis; GN: glomerulonephritis; HSP (IgA vasculitis); Henoch–Schönlein purpura; KD: Kawasaki disease; PAN: polyarteritis nodosa; SLE: systemic lupus erythematosus; TAK: Takayasu arteritis; VPN: vasculitic peripheral neuropathy; GPA: granulomatosis with polyangiitis.

- “Giant cell arteritis and polymyalgia rheumatica after influenza vaccination: report of 10 cases and review of the literature” by Soriano et al. [26] in 2012. The authors suggested strict observation for 2–6 months following administration of influenza vaccination to subjects at higher risk of developing GCA/polymyalgia rheumatica (such as females at a susceptible age).
- “Hypersensitivity and vaccines: an update” by Barbaud et al. [27] also summarized a total of 24 cases of vasculitis after influenza vaccination, including one case after influenza A H1N1, published in the literature.
- “Skin complications of Bacillus Calmette-Guerin immunization” by Bellet and Prose [28]. In this review authors focused on the cutaneous complications of BCG vaccination. They concluded that it is important for health care providers to recognize the routinely anticipated cutaneous findings of the vaccination, in addition to complications relating to the injection for all infants living in tuberculosis endemic areas.
- “Influenza vaccination and skin disease-coincidence or causal association?” A review by Hehn et al. [29] focused on influenza vaccination and subsequent skin diseases in subjects from 5 to 92 years old. In a second part, the paper also reports on 29 cases from the German spontaneous reporting system. The authors concluded that vasculitis has been documented to be associated with influenza vaccination.
- “A multicomponent serogroup B meningococcal vaccine is licensed for use in Europe: what do we know, and what are we yet to learn?” a review by Martin and Snape [30] summarized the vaccine composition, clinical trials and suggested schedules of this vaccine, with specific attention to immunogenicity, reactogenicity, safety, potential coverage and optimal implementation of this vaccine. The authors concluded that a relationship of KD to vaccination has not been established and is complicated by the known tendency for geographical and temporal clustering of KD.

Of 11 case series, 4 referred to HPV vaccination [31–34], 3 to HBV vaccination [35–37], 3 to influenza vaccination [38–40] and 1 to vaccination in general [41]. The series related to HPV vaccination mainly reported on a possible association between onset of SLE and the vaccine. Gatto et al. [31] collected the medical history of six women (age range between 13 and 32 years) who presented with SLE or SLE-like disease following HPV immunization. In the reported cases, several common features were observed, such as personal or familial susceptibility to autoimmunity or adverse response to a prior dose of the vaccine, both of which may be associated with a higher risk of postvaccination autoimmunity. The authors concluded that a temporal association between immunization with HPV vaccine and the appearance of a spectrum of SLE-like conditions is reported and, in addition, a personal or familial medical history of autoimmunity should be considered a risk factor for such adverse events. The case series by Soldevilla et al. [33,34] showed the difficulty of establishing a direct causal relationship between HPV and SLE. The complex relationship between genetic susceptibility and infection, as already investigated by Gatto et al. [31], has been intensively investigated to search for possible etiologies of the evolution and/or exacerbation of an existing autoimmune disease, particularly SLE. In these cases a common factor seemed to be the history of HPV vaccination administered 2–4 months prior to the current SLE episode. Melo Gomes et al. [32] reported two cases of 13- and 15-year old girls developing HSP after HPV vaccination. They noted a close temporal relationship between the administration of the bivalent HPV vaccine and the development of vasculitis. However, although the authors concluded that HPV vaccine could have been a triggering factor for HSP, they could not infer causality from this rare association.

Le Hello et al. [35] reported two cases of cutaneous vasculitis and one of cerebral vasculitis after HBV vaccination and suggested that the chronology of the events and the exclusion of other identifiable etiologies or historical factors were indicative of vaccine-induced vasculitis; Mathieu et al. reported two cases of cryoglobulinemia occurring after recombinant HBV vaccine administration [36]. Zaas et al. [37] described two women who developed large artery vasculitis shortly after receiving recombinant HBV vaccination. One patient developed TAK, and the other developed a vasculitis involving subclavian and renal arteries. Both developed renal failure. The authors concluded that it was not possible to determine whether the large artery vasculitis evident in their patients was caused by the vaccination or was simply temporally associated [37].

Birck et al. [38] and Duggal et al. [39] described 6 cases of new onset or relapsing AAV temporally associated with influenza vaccination. They noted that previous studies conducted in patients with pre-existing AAV did not find an increased risk of clinical exacerbations of vasculitis after influenza vaccination [15,21], and concluded that the temporal association of AAV to influenza vaccination suggested that the vaccine might serve as a trigger for development of AAV in predisposed individuals [38,39]. Tavadia et al. [40] described four cases of leukocytoclastic vasculitis following influenza vaccination. However, they could not prove a causative link. Begier et al. [41] in 2004 reviewed PAN reports in VAERS and published literature submitted from 1990 through 2001. The authors concluded that current adverse event reports do not support a causal link between vaccination and PAN.

Published single case reports comprise a variety of vaccines, vasculitides and associations. The authors of 43 case reports (93%) considered that a link between vasculitis and vaccination was possible or likely. The hypothesis is that the mechanism may involve immune complex deposition in the blood vessel wall. Such a link was suspected based on the timing of vasculitis and the absence of evidence of other underlying risk factors [42].

A total of 24 of the case reports referred to influenza vaccination (53.3%) and 8 of those to patients over 65 years of age. These case reports suggested that seasonal influenza vaccination might trigger vasculitis, involving the skin and nerves in some patients [43] as previously reported. Eight of those case reports (33%) referred to cutaneous vasculitis and four to HSP. In two cases, authors did not hypothesize a link between the onset of vasculitis and influenza vaccination [44,45]. These two case reports concern cutaneous vasculitis in two adult women, without histological confirmation.

A total of 8 of 46 single case reports referred to HAV and HBV vaccination. Among them the most commonly reported vasculitides were small vessel cutaneous vasculitis [46,47] and HSP [48,49]. Only Drucker et al. [47] rejected a causal association of lymphocytic vasculitis in a 26-year-old female following HBV vaccination. Five of those 8 reports included a skin biopsy which confirmed the diagnosis.

The other case reports referred to BCG vaccination ($n=4$), HPV, meningococcal and DPT vaccination ($n=2$ per vaccine), anthrax, MMR, typhoid and yellow fever vaccination ($n=1$ for each). The most commonly reported vasculitides were cutaneous vasculitis (33%), HSP (24%) and KD (19%). The authors of all these 22 reports considered an association between the event and vaccination possible. In 11 reports the authors reported that a skin biopsy for evaluation or confirmation was performed.

For this literature review we also considered 3 published comments. Park and Shin [48] commented on the case report by Jariwala et al. [49] suggesting a possible mechanism of immunopathogenesis for HSP after HAV vaccination. Soriano and Manna [50] commented on the article published by Wada et al. [51] mentioning their review titled “Giant cell arteritis and polymyalgia rheumatica after influenza vaccination: report of 10 cases and review of the literature” [26]. The editorial by Zafriir et al. [11] commented on the

Table 1
Table of case definitions used in publications ($n = 18$).

| Author | Year | Study type | Title | Vaccine type | Type of vasculitis | Case definition used |
|--------------------------------------------------|------|-----------------------------|------------------------------------------------------------------------------------------------------------------------------|-----------------------------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kawasaki disease | | | | | | |
| Oka et al. | 2012 | Case report | Kawasaki disease after diphtheria–pertussis–tetanus (DPT) | DPT | KD | KD was diagnosed because he satisfied 5 of the 6 criteria for KD (not specified). |
| Ortigado et al. | 2010 | Case report | Kawasaki disease and H1N1 influenza A virus: a case report | Influenza vaccination | KD | The diagnosis of incomplete KD was made. With classic clinical criteria of KD (not specified). |
| Oberle et al. | 2010 | Observational study | Vaccination against gastroenteritis caused by rotavirus: association with Kawasaki disease? | Rotavirus vaccination | KD | [1] Morens DM, O'Brien RJ. Kawasaki disease in the United States. <i>J Infect Dis</i> 1978;137:91–3. [2] Centers of Disease Control and Prevention Kawasaki syndrome. Centers of Disease Control and Prevention. http://www.cdc.gov/kawasaki/ [accessed 21.04.15]. |
| Seo et al. | 2012 | Randomized controlled trial | Diagnosis of incomplete Kawasaki disease in infants based on an inflammation at the Bacille Calmette–Guérin inoculation site | BCG | KD | [3] Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. <i>Circulation</i> 2004;110:2747–71. [4] Ayusawa M, Sonobe T, Uemura S, Ogawa S, Nakamura Y, Kiyosawa N, et al. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). <i>Pediatr Int</i> 2005;47:232–4. |
| Lai CC et al. | 2013 | Retrospective study | Reaction at the Bacillus Calmette–Guérin inoculation site in patients with Kawasaki disease | BCG | KD | [3] Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. <i>Circulation</i> 2004;110:2747–71. [5] Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. <i>Arerugi</i> 1967;16:178–222. [6] Research Committee on Kawasaki Disease. Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease Japanese Ministry of Health and Welfare 1984. |
| Hua et al. | 2009 | Review | Kawasaki disease after vaccination: reports to the vaccine adverse event reporting system 1990–2007 | Rotavirus vaccination | KD | [2] Centers of Disease Control and Prevention Kawasaki syndrome. Centers of Disease Control and Prevention. http://www.cdc.gov/kawasaki/ [accessed 21.04.15]. [7] American Academy of Pediatrics. Kawasaki disease. In: Pickering LK, Baker CJ, Long SS, et al., editors. <i>Red Book: 2006 report of the committee on infectious diseases</i> . Elk Grove Village, IL: American Academy of Pediatrics; 2006. |
| Henoch–Schönlein purpura (IgA vasculitis) | | | | | | |
| Courtney et al. | 2001 | Case report | Henoch–Schönlein purpura following meningitis C vaccination | Meningitis C vaccination | HSP (IgA vasculitis) | [8] Mills JA, Michel BA, Bloch DA, Calabrese LH, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Henoch–Schönlein purpura. <i>Arthritis Rheum</i> 1990;33:1114–21. |
| Jariwala et al. | 2011 | Case report | Henoch–Schönlein purpura after hepatitis A vaccination | HAV | HSP (IgA vasculitis) | [9] Jennette JC, Falk RJ. Small-vessel vasculitis. <i>New Engl J Med</i> 1997;337:1512–23. [10] Ozen S, Ruperto N, Dillon MJ, Bagga A, Barron K, Davin JC, et al. EULAR/PreS endorsed consensus criteria for the classification of childhood vasculitides. <i>Ann Rheum Dis</i> 2006;65:936–41. |
| Sexton et al. | 2009 | Observational study | Henoch–Schönlein purpura and meningococcal B vaccination | Meningococcal B vaccination | HSP (IgA vasculitis) | [8] Mills JA, Michel BA, Bloch DA, Calabrese LH, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Henoch–Schönlein purpura. <i>Arthritis Rheum</i> 1990;33:1114–21. |

Table 1 (Continued)

| Author | Year | Study type | Title | Vaccine type | Type of vasculitis | Case definition used |
|-----------------------------------------|------|---------------------|------------------------------------------------------------------------------------------------------------------------------|---------------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Goodman et al. | 2010 | Retrospective study | Henoch-Schönlein purpura and polysaccharide meningococcal vaccine | Meningococcal vaccination | HSP (IgA vasculitis) | [8] Mills JA, Michel BA, Bloch DA, Calabrese LH, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura. <i>Arthritis Rheum</i> 1990;33:1114–21. |
| Melo Gomes et al. | 2013 | Case series | Vasculitis following HPV immunization | HPV | HSP (IgA vasculitis) | [11] Ozen S, Pistorio A, Iusan SM, Bakaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PReS criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. <i>Ann Rheum Dis</i> 2010;69:798–806. [12] Sunderkotter C, Sindrilaru A. Clinical classification of vasculitis. <i>Eur J Dermatol</i> 2006;16:114–24. |
| Giant cell arteritis | | | | | | |
| Perez et al. | 2000 | Case report | Giant cell arteritis after influenza vaccination | Influenza vaccination | GCA | [13] Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. <i>Arthritis and rheumatism</i> . 1990;33:1122–8. |
| Wada et al. | 2011 | Case report | Giant cell arteritis with polymyalgia rheumatica associated with influenza vaccination | Influenza vaccination | GCA | [13] Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. <i>Arthritis Rheum</i> 1990;33:1122–8. |
| Soriano et al. | 2012 | Comment | Giant cell arteritis and polymyalgia rheumatica after influenza vaccination: comparing different experiences | Influenza vaccination | GCA | [14] Bird HA, Esselinckx W, Dixon AS, Mowat AG, Wood PH. An evaluation of criteria for polymyalgia rheumatica. <i>Ann Rheum Dis</i> 1979;38(October (5)):434–9. |
| Soriano et al. | 2012 | Review | Giant cell arteritis and polymyalgia rheumatica after influenza vaccination: report of 10 cases and review of the literature | Influenza vaccination | GCA | [13] Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. <i>Arthritis Rheum</i> 1990;33:1122–8. [15] Healey LA. Long-term follow-up of polymyalgia rheumatica: evidence for synovitis. <i>Semin Arthritis Rheum</i> 1984;13:322–8. |
| Granulomatosis with polyangiitis | | | | | | |
| Gil et al. | 2011 | Case report | Systemic vasculitis: a dual diagnosis? | HBV | GPA | [13] Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. <i>Arthritis Rheum</i> 1990;33:1122–8. [15] Healey LA. Long-term follow-up of polymyalgia rheumatica: evidence for synovitis. <i>Semin Arthritis Rheum</i> 1984;13:322–8. |
| Behcet's disease | | | | | | |
| Molloy et al. | 2004 | Case report | An unusual case of Behcet's syndrome: triggered by typhoid vaccination? | Typhoid fever vaccination | BD | [16] Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. <i>Arthritis Rheum</i> 1990;33:1101–7. [17] Lightfoot Jr RW, Michel BA, Bloch DA, Hunder GG, Zvaifler NJ, McShane DJ, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. <i>Arthritis Rheum</i> 1990;33:1088–93. |
| Polyarteritis nodosa | | | | | | |
| Ventura et al. | 2009 | Case report | Cutaneous polyarteritis nodosa in a child following hepatitis B vaccination | HBV | PAN | [18] Lee ES, Bang D, Lee S. Dermatologic manifestation of Behcet's disease. <i>Yonsei Med J</i> 1997;38:380–9. [19] Dillon MJ, Ozen S. A new international classification of childhood vasculitis. <i>Pediatr Nephrol (Berlin, Germany)</i> 2006;21:1219–22. [12] Sunderkotter C, Sindrilaru A. Clinical classification of vasculitis. <i>Eur J Dermatol</i> 2006;16:114–24. |

DPT: diphtheria, pertussis, tetanus vaccination, BCG: Bacillus-Calmette-Guérin vaccination, HAV: hepatitis A vaccination, HPV: human papillomavirus vaccination, HBV: hepatitis B vaccination.
 KD: kawasaki disease; HSP (IgA vasculitis): Henoch Schoenlein purpura; GCA: giant cell arteritis; GPA: granulomatosis with polyangiitis; BD: bechet disease; PAN: polyarteritis nodosa.

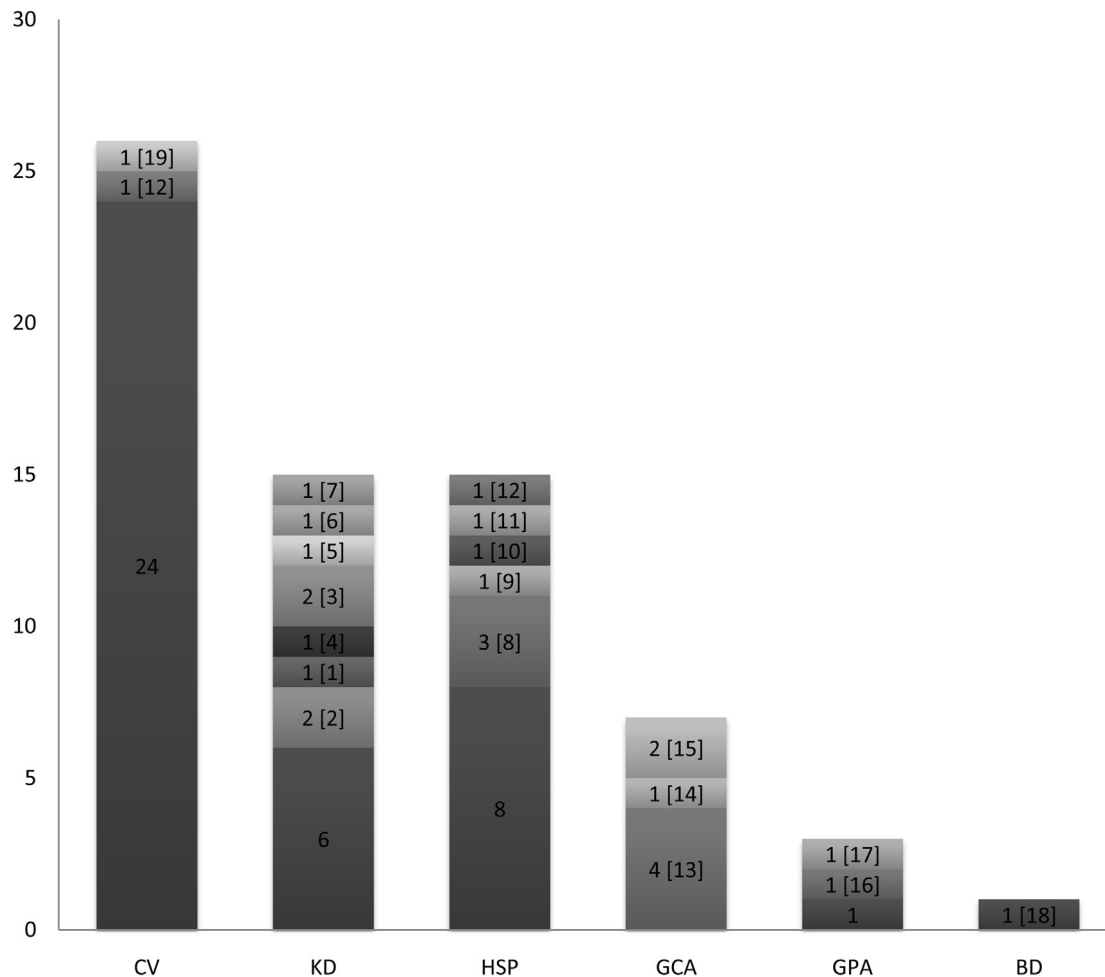


Fig. 4. Case definitions used in the articles by vasculitis type.

BD: Behcet disease; CV: cutaneous vasculitis GCA: giant cell arteritis; HSP (IgA vasculitis): Henoch-Schönlein purpura; KD: Kawasaki disease; GPA: granulomatosis with polyangiitis; the reference in brackets refers to Table 1.

Bar sections without reference define articles without case definitions.

post-influenza vaccination vasculitides based on cited articles (e.g. [38,52]). The authors concluded that the accumulation of so many reports and the classic temporal association suggested the possibility of a causal association between influenza vaccine and vasculitis. They suggested that this did not necessarily mean that the vaccine is the single initiator of the autoimmune process but rather that it might serve as a trigger for presentation of an overt disease or exacerbation of a nonsymptomatic one [11].

Only 24% (18/75) of the articles reported using a case definition: 2 observational studies, 2 retrospective studies, 1 randomized controlled trial, 2 reviews, 1 case series, 9 case reports and 1 comment. Fig. 4 shows the heterogeneity of case definitions used in evaluating and reporting vasculitis as AEFI. To make the information more accessible, all described data are summarized in Table 1. Sexton et al. [18] and Goodman et al. [17] referred to The American College of Rheumatology (ACR) 1990 criteria for the classification of HSP [53] while the criteria cited by Oberle et al. [20] were the CDC definition [54] for KD in the United States [55]. Lai et al. [16] cited the first diagnostic criteria for KD by Kawasaki [56] and the Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in KD [57]. The randomized controlled trial used the diagnostic criteria from Ayusawa et al. [58] and from Newburger et al. [23] published by the American Heart Association. The two reviews by Hua et al. [24] and Soriano et al. [26] cited the CDC definition [54], The ACR 1990 criteria for the classification of GCA [59] and the criteria from Report of

the Committee on Infectious Diseases published by the American Academy of Pediatrics. Melo Gomes et al. [32] and Jariwala et al. [49] adopted the EULAR/PreS endorsed consensus criteria for the classification of childhood vasculitides [4]. In the two reported articles of KD [60,61] the diagnosis was obtained according to diagnostic criteria but it was not specified what diagnostic criteria were used. For the diagnosis of Behcet disease, Molloy et al. [62] in 2004 used the criteria from Lee et al. [63]. Ventura et al. [64] for the diagnosis of PAN adopted the criteria by Dillon and Ozen from the new international classification of childhood vasculitis [65] and the clinical classification of vasculitis from Sunderkotter and Sindrilaru [66], also used by Melo Gomes et al. [32].

In 44 of 75 reviewed articles (59%) a biopsy was performed for histological evaluation and/or confirmation.

4. Discussion

The literature review showed numerous reports of vasculitides following vaccination with a limited number of controlled studies. Standard diagnostic criteria for vasculitis are limited and rarely applied as shown in Fig. 4 and Table 1; therefore, it is not possible to draw any conclusion on causality based on current data. Whether vaccination is considered to be a possible risk factor for inducing or promoting any clinical manifestation of vasculitis is still an issue of debate [11].

This review revealed that the vaccine most often reported to precede vasculitis is influenza vaccine. This is particularly in elderly, which could be explained by the elderly representing a target population for influenza vaccination. Furthermore, it is noted that, in spite of the large numbers of spontaneous reports as well as published case reports and case series suggesting an association between vaccination and vasculitides, the few observational and clinical trials investigating relationships between various vaccines and vasculitis subtypes failed to confirm such an association. Overall, the retrieved articles showed that the current diagnostic practice is based on clinical signs and symptoms, medical history and examination, while efforts toward elucidating potential etiologies were limited.

However, there is increasing evidence establishing various types of infections as potential triggers or causes of different types of vasculitis. A potential link is best established for HBV and HCV infections leading to PAN and cryoglobulinemic vasculitis [67]. It has been estimated that 34% of patients with PAN and 35% of patients with cryoglobulinemic vasculitis are HBV and HCV positive, respectively [10]. In France, a successful campaign of vaccination against HBV was followed by a decrease in the incidence of PAN [10]. In children, a seasonal peak of HSP has been observed in autumn–winter, often after an upper respiratory tract infection. Sometimes several members of the same family may be affected, suggesting a correlation with a transmissible infectious process serving as a trigger. Associations with a wide array of pathogens, including bacteria, viruses and parasites have been proposed [68]. Furthermore, emerging evidence has hypothesized a possible role of infections in KD as well [69]. Therefore, the potential of vaccination-induced vasculitis should be considered in the context of decreased risk of infection-induced vasculitis. It is worth highlighting that the new Chapel Hill 2012 criteria now classify HBV associated PAN as a “vasculitis with probable etiology” [70]. Drug associated vasculitis can also be well classified in this category. The new Chapel Hill 2012 criteria also provide updated disease concept descriptions for vasculitides.

Standard criteria for diagnosis of vasculitis are limited as often different terms are used to report the same clinical manifestation, and the terms used can be at times synonymous but at other times may refer to a specific form of vasculitis, or to a general condition without any specifications, i.e. primary or secondary to another disease. It is acknowledged that validated classification criteria are available for HSP, PAN, GPA and TAK. These Ankara 2008 criteria have been developed by the revision of the previous 2006 criteria and was endorsed by EULAR, PRIS and PRINTO [5].

However, there is room for further standardization of terminology and specification of standardized definitions of the disease. As shown in Table 1, various concept definitions were used in the studies for different vasculitis types. Although an in-depth analysis of the differences between the various case definitions for each vasculitis type was not done so far, the variability suggests that standardization would strengthen the available evidence. With vasculitides being relatively rare, large sample sizes and optimal data comparability within and across studies are preconditions for meaningful epidemiologic assessments of incidence rates and risks associated with immunization. This highlights the importance of a shared understanding, standardized terminology and case definitions for vasculitis subtypes. The Brighton Collaboration Vasculitis Working Group will propose standard case definitions following the published standard process [71].

5. Conclusions

Existing literature does not allow establishing a causative link between vaccination and vasculitides. Further investigations would

be strengthened by development of standardized case definitions and methods for data collection, analysis and presentation to improve comparability and interpretation of vasculitis cases following immunization(s).

Conflict of interests

Caterina Bonetto, Francesco Trotta, Patrizia Felicetti, Carmela Santuccio, Graciela S. Alarcon, Novilia Sjafrin Bachtar, Yolanda Brauchli Pernus, Rebecca Chandler, Robert D.M. Hadden, Merita Kucuku, Karina Top, Frederick Varricchio, Giovanna Zanoni, Saša Živković, Jan Bonhoeffer have no conflict of interests to disclose. Giampiero Girolomoni has been principal investigator in clinical trials sponsored by many pharmaceutical/cosmetic industries. Nothing directly relevant to this article. Seza Ozen, received consultation fees and/or speaker's honoraria from Novartis, SOBI and Roche. Nothing directly relevant to this article. 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. Barbara Pahud served on advisory board for Pfizer and has been an investigator in vaccine clinical trials for GlaxoSmithKline.

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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.2015.09.026>.

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