



CEPI | Brighton Collaboration

Case Definition Companion Guide for Single Organ Cutaneous Vasculitis (SOCV)

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Description of the deliverable	This deliverable collates into a single document SPEAC resources (ICD9/10-CM, MedDRA & SNOMEDCT codes, background rates, risk factors, guidance (real time investigation, data collection, analysis and presentation) and tools (data abstraction & interpretation form, tabular summary of key case definition criteria and algorithms for level of certainty determination) for Single Organ Cutaneous Vasculitis (SOCV). This guide can be used by stakeholders to assess the occurrence of SOCV in several settings including as an adverse event following immunization.		
Key words	Single Organ Cutaneous Vasculitis, SOCV, Brighton case definition, risk factors, background rates, ICD-9-CM, ICD-10-CM, MedDRA, SNOMEDCT, case definition level of certainty.		

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DEFINITIONS & ACRONYMS

A/C	Acute / Convalescent
AEFI	Adverse event following immunization
AESI	Adverse event of special interest
AFib	Atrial fibrillation
Ag	Antigen
AHEI	Acute hemorrhagic edema of infancy
ALT	Alanine transaminase
ANA	Anti-nuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibodies
Anti-CCP	Anti-citrullinated peptides antibodies
Anti-ds DNA	Anti-double stranded DNA
ASOT	Anti-streptolysin O titer
AST	Aspartate transferase
AZ	AstraZeneca
BC	Brighton Collaboration
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CD	Case definition
CEPI	Coalition for Epidemic Preparedness and Innovation
CHF	Congestive heart failure
CIM	Classification Internationale des Maladies
CLD	Chronic liver disease
CM	Clinical Modification (Relates to numbered versions of ICD codes)
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CSVV	Cutaneous small vessel vasculitis
CV	Cutaneous vasculitis
CUI	Concept unique identifier
DOI	Digital object identifier
DM	Diabetes mellitus
DT	Digital transformation
EBV	Epstein Barr virus
ENA	Extractable nuclear antigen
F	Female
GERD	Gastro-esophageal reflux disease
GP	General practitioner
GPA	Granulomatosis with polyangiitis (previous name Wegener granulomatosis)
HHV6	Human herpesvirus type 6
HHV7	Human herpesvirus type 7
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
HSP	Henoch-Schönlein purpura
HT	Hypertension

HUV	Hypocomplementemic urticarial vasculitis
HV	Hypersensitivity vasculitis
HypoT4	
Hypothyroidism	
HZ	Herpes Zoster
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
IL12B	Interleukin 12, subunit beta
IL12RB1	Interleukin 12 receptor beta 1 subunit
Inact	inactivated
IOM	Institute of Medicine (now known as National Academy of Medicine)
ITP	Immune thrombocytopenia
LCV	Leukocytoclastic vasculitis
M	Male
MedDRA	Medical Dictionary for Regulatory Activities
MenB	Meningococcal group B
MMR	Measles mumps rubella combination vaccine
NOS	Not otherwise stated
NS	Not stated
NUV	Normocomplementemic urticarial vasculitis
PAN	Polyarteritis nodosa
PCR	Polymerase chain reaction
PCV	Polycythemia vera
PPV23	23-valent pneumococcal polysaccharide vaccine
RF	Rheumatoid factor
rVSV	Recombinant vesiculostomatitis virus
SARS-2-CoV	Severe acute respiratory syndrome type 2 coronavirus
SCTSPA	Spanish version of SNOMED codes
SLE	Systemic lupus erythematosus
SNOMEDCT	Systematized Nomenclature of Medicine-Clinical Terms
SOCV	Single Organ Cutaneous Vasculitis
Sp	Species
SPEAC	Safety Platform for Emergency vACcines
TIV	Trivalent inactivated influenza vaccine
TNF	Tumor necrosis factor
UK	United Kingdom
UMLS	Unified Medical Language System
USA	United States of America
UV	Urticarial vasculitis
VZV	Varicella Zoster Virus
UMLS	Unified Medical Language System

1. Background

CEPI has contracted with the Brighton Collaboration (BC), through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key aspect of this harmonization has been creation of lists of potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI prioritized epidemic diseases. Having identified relevant AESI, SPEAC then works to ensure tools and resources are available to facilitate a standard approach to global vaccine safety research and pharmacovigilance activities.

The AESI resources include tabulation of relevant medical codes as well as background incidence data and risk factors. The tools include new case definitions (CD) if there were no published Brighton Collaboration case definition (BC CD) exists, case report forms for standard data collection that would support meeting the case definition levels of certainty and algorithms for assessing level of certainty based on available evidence for each case.

Initially these resources and tools were developed as separate documents but starting in 2020 they were pulled together into a single 'Companion Guide' for each published Brighton Collaboration Case Definition. All Companion Guides are available on the [Brighton Collaboration website](#). In addition, since the summer of 2022, all SPEAC Companion Guides are published on the [SPEAC community](#) of Zenodo, a public open-access repository of research. This enables all Companion Guides to have a citable digital object identifier (DOI).

The focus of this document is to provide a Companion Guide for the Single Organ Cutaneous Vasculitis Case Definition.¹

2. Objective of this deliverable

To collate SPEAC & BC tools and resources that have been developed for Single Organ Cutaneous Vasculitis (SOCV) in a manner that is harmonized with all Companion Guides.

3. Methods

The methods used are briefly described in Appendix 6 of this Guide along with links to source documents which have more detailed methodology. In addition, any new methodology, relevant to the content of this Guide, is also provided in appendix 6.

4. Results

As noted in Appendix 6.2 and 6.3 two literature searches were conducted for background incidence and risk factors, one of which focused on epidemiology and incidence and the other on vaccines / immunization. As there was some overlap in content between the two searches the results have been combined.

A total of 114 articles were found in the two searches. 52 were removed based on title/abstract, including the SOCV Brighton CD publication, 1 duplicated article, 1 non-English article, 2 focused on therapy, and 47 because the focus was systemic vasculitis or some disease other than SOCV.

The full text of the remaining 62 articles were reviewed and 18 excluded for the following reasons: 8 were case reports of cutaneous vasculitis with no prior vaccination; 3 were case reports of cutaneous vasculitis following vaccination but with clear systemic involvement and thus not SOCV; 1 was a case report of cutaneous vasculitis following vaccination with no skin biopsy; 1 was a report of a genetic association with systemic vasculitis; and 5 were general articles on cutaneous vasculitis with nothing new relative to the ones selected to include in the guide.

The remaining 44 articles are all included in this guide: 14 informed the general risk factors and 30 case reports of skin biopsy-confirmed small vessel cutaneous vasculitis which followed vaccination.

An additional 43 articles were found by hand search of citations in the full text review of articles found in the literature search including 7 on general risk factors, 32 eligible case reports of cutaneous vasculitis following vaccination and 4 with original background incidence data.

The outputs are provided as separate appendices to simplify printing as needed. These are provided for SOCV as shown below:

1. Diagnostic Codes for: ICD-9CM, ICD-10CM, MedDRA and SNOMEDCT ²⁻⁶
2. Background Rates ⁷⁻¹⁰
3. Risk Factors ¹¹⁻⁹⁷
4. Case Definition key caveats for diagnosis, data analysis and presentation
5. Data Abstraction and Interpretation Form with algorithms for assessing level of diagnostic certainty and a glossary of relevant terms.
6. Summary of methods. It also provides links, as appropriate, to the original deliverable documents with more detailed methodology.

As noted in Appendix 3, the only evidence regarding potential vaccine association with SOCV was from case reports which cannot confirm causality. Despite that, the cases are presented since they serve as a source of mechanistic evidence for possible causality.^{32, 35} A total of 62 reports of 67 cases were found that met the SOCV criteria for skin rash morphology along with a skin biopsy showing small vessel cutaneous vasculitis. Most case reports (60/67) also did one or more lab tests to rule out systemic involvement although there was not a uniform approach to the specific tests done. Details of each case report are provided in Table 3.2 including country, sex, age, underlying comorbidities, vaccine, time from vaccination to onset, skin biopsy pattern, types of tests done to rule out systemic disease and time to resolution.

In summary, the case reports were from 22 different countries including: 18 (26.9%) North American (16 USA, 2 Canada); 30 (44.8%) European (8 Italy, 5 Spain, 4 France, 3 Slovenia, 3 Turkey, 2 Croatia and 1 each from Portugal, UK, Ireland, Switzerland and Germany); 10 (14.9%) Asian (5 India, 2 Thailand, 1 each from Taiwan, S Korea and Japan), 4 (6.0%) Middle Eastern (3 Iran, 1 Saudi Arabia), 2 (3.0%) African (both Egypt), 2 (3.0%) South American (both Brazil) and 1 (1.5%) Australian.

There were 31 (46.2%) male cases, 34 (50.7%) females and 2 unknown sex. Median (range) age of the cases was 52 (1-91) years. Comorbidities were present in 22 (32.8%) cases, not present in 37 (55.2%) and not mentioned in 8 (11.9%).

Cutaneous vasculitis was the first episode for 66 (98.5%) and a recurrence for 1 (1.5%) case. A biopsy showed leukocytoclastic vasculitis in 48 (71.6%) cases, lymphocytic vasculitis in 9 (13.4%), urticarial vasculitis in 5 (7.5%) and other

patterns in 5 (7.5%) including 2 immune complex vasculitis and 1 each of small vessel vasculitis, allergic vasculitis and necrotizing vasculitis.

Vaccines involved included: 44 (65.7%) COVID-19 vaccines of which 18 (40.9%) were mRNA platforms (12 Pfizer, 5 Moderna, 1 not stated), 18 (40.9%) adenovirus platforms (15 ChAdOx1, 3 Ad26COV) and 8 (11.9%) inactivated vaccines (4 COVAXIN, 1 Sinopharm, 1 CoronaVac and 2 not specified); and 23 other vaccines including 9 (13.4%) influenza vaccines given alone (4 seasonal, 3 2009 pandemic H1N1, 2 not stated), 3 (4.5%) smallpox (ICAM 2000), 3 (4.5%) MMR, 1 given concomitantly with VZV; 2 (3.0%) 23-valent pneumococcal polysaccharide vaccine (1 given alone and 1 with seasonal influenza which had been given in the 10 previous years with no ill effect); and 1 (1.5%) for each of the following vaccines: Meningococcal B, Herpes Zoster, Anthrax, Ebola (rVZV platform), Hepatitis A and Hepatitis B. The median (range) days from vaccination to onset of SCOV was 7.7 (0.14-42) days. The time from onset to resolution was ≤ 2 weeks for 24 (35.8%) cases, 3 weeks to ≤ 1 month for 12 (17.9%) cases, >1 month to ≤ 3 months for 9 (13.4%), >3 months for 1 (1.5%) case and not stated for 21 (31.3%) cases.

5. Recommendations & discussion

This guide brings together many resources and tools related to SOCV including ICD-9/10-CM, MedDRA and SNOMEDCT codes for data entry or database searching, background rates, risk factors and guidance for real time investigation. It also provides tools for collecting and interpreting clinical data to apply the BC SOCV case definition and determine the level of diagnostic certainty.

SPEAC recommends that the tools be used to assign level of diagnostic certainty for all identified AEFI with features of SOCV. This standard, harmonized approach will facilitate signal detection and assessment as well as the capacity to combine data across trials for meta-analyses.

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ANNEXES

Annex 1

ICD-9-CM, ICD-10-CM, MedDRA and SNOMEDCT Codes for Single Organ Cutaneous Vasculitis

1.1 Single Organ Cutaneous Vasculitis Diagnostic Codes: ICD-9/10-CM, MedDRA and SNOMEDCT.

All codes, concepts and terms in the table below were generated by Codemapper.²⁻⁶ See appendix 6 for more detail regarding methods of obtaining the codes.

TABLE 1.1 NARROW SEARCH TERMS FOR Single Organ Cutaneous Vasculitis By definition, skin can be the only organ involved to meet any level of the SOCV case definition. All the concepts in the table below specify cutaneous vasculitis, however, it is still possible that cases retrieved by some of these codes could involve more than just skin. That said, there are several that clearly indicate disease limited to the skin – these are boldfaced in the table.

UMLS CUI & Concept Name		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0151436	Vasculitis, Leukocytoclastic, Cutaneous	Allergic vasculitis	10001736		D69.0	
		Allergic cutaneous angiitis	10001710			
		Cutaneous leukocytoclastic angiitis				718217000
		Hypersensitivity angiitis	10020752	446.2	M31.0	60555002 195350001
		Hypersensitivity angiitis, unspecified	10020753	446.20		
		Hypersensitivity angiitis NOS				195352009
		Hypersensitivity vasculitis	10020764			
		Vasculitis allergic	10047118			
C0262988	Vasculitis of the skin	Cutaneous vasculitis	10011686			
		Skin vasculitides	10040948			
		Skin vasculitis NOS	10040949			
		Vasculitis limited to skin, unspecified			L95.9	
		[X]Vasculitis limited to skin, unspecified				201305007 201430009
		Vasculitis of the skin				53312001
C0477527	Other vasculitis limited to the skin	Other Vasculitis of the skin			L95.8	
		[X]Other vasculitis limited to skin				201424009
C0477529	Other specified disorders of skin and subcutaneous tissue	Other specified disorders of skin and subcutaneous tissue			L98.8	
		[X]Other specified disorders of the skin and subcutaneous tissues				201426006
C0494887	Vasculitis limited to skin, not elsewhere classified	Vasculitis limited to skin, not elsewhere classified			L95	

C0162819	Skin Diseases, Vascular	Skin vascular abnormalities	10047043			
		Vascular disorders of skin	10047072	709.1		
		Vascular disorders of skin NOS				201306008 267820009
		Vascular disease of the skin				11263005
		Vascular skin disorder	10062171			
		Vascular skin condition NOS	10047109			

TABLE 1.2 BROAD SEARCH TERMS FOR Single Organ Cutaneous Vasculitis. It should be noted that the presence of any organ involvement beyond the skin will render the case a level 5 – Not a case. By definition skin can be the only organ involved to meet any level of the SOCV case definition.

UMLS CUI & Concept Name		Diagnostic Coding System Term and Codes				
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C0042384	Vasculitis	Angiitis	10002369			266325003
		Vasculitis	10047115			195375002 31996006 393589007
		Vasculitis NOS	10047128			718217000
		Vasculitides	10047112			

Annex 2

Single Organ Cutaneous Vasculitis Background Rates

2.1 Single Organ Cutaneous Vasculitis Background Rates

TABLE 2.1. Single Organ Cutaneous Vasculitis BACKGROUND RATES BY GEOGRAPHIC REGION

Note: none of the studies listed below used the BC SOCV case definition. That said, 3 studies ⁷⁻⁹ only included biopsy confirmed cutaneous vasculitis which is required to meet level 1 or 2 of the case definition. Further, 2 studies ^{8,9} specifically excluded any cases with involvement beyond the skin and thus can be considered to meet LOC 1 or 2 of the case definition. The USA study⁷, did not exclude systemic disease but did provide information that 54% were single organ cutaneous vasculitides. However, there was no age breakdown, so it isn't possible to determine age-specific incidence for SOCV. The European ACCESS study¹⁰ identified cases with medical codes and cases were not validated against the SOCV or any other case definition.

Country	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)			
			All	Males	Females	
AFRICA						
No data found						
AMERICAs						
USA ⁷ (Minnesota) Population based study; all LCV cases were confirmed by skin biopsy; 54% (45 cases) had SOCV; the remainder had evidence of systemic involvement but no breakdown by age was provided	1996- 2010	0-19	1.2 [0.5-2.6] (7)	0.3[0.0-1.9] (1)	2.2 [0.8-4.8] (6)	
		20-29	3.4 [1.6-6.5] (9)	4.7[1.7-10-2] (6)	2.2 [0.5-6.5] (3)	
		30-39	2.3 [0.9-4.8] (7)	2.0[0.4-5.8] (3)	2.7 [0.7-6.9] (4)	
		40-49	6.8 [4.1-10.5] (20)	6.8[3.3-12.6] (10)	6.7 [3.2-12.3] (10)	
		50-59	7.3 [4.3-11.7] (17)	6.2[2.5-12.7] (7)	8.4 [4.0-15.4] (10)	
		60-69	9.7 [5.3-16.3] (14)	10.2[4.1-21.0] (7)	9.3 [3.7-19.2] (7)	
		≥70	6.2 [3.0-11.5] (10)	10.9[4.4-22.5] (7)	3.1 [0.6-9.1] (3)	
			All ages	4.5 [3.5-5.4] (84)	4.8 [3.3-6.2] (41)	4.4 [3.1-5.7] (43)
	1996- 2000	All ages	3.7 [2.1-5.3] (21)	3.2 [0.9-5.6] (8)	4.4 [2.0-6.8] (13)	
	2001- 2005	All ages	4.6 [2.9-6.3] (29)	5.4 [2.7-8.1] (16)	4.0 [1.8-6.1] (13)	
	2006- 2010	All ages	5.0 [3.3-6.7] (34)	5.3 [2.8-7.9] (17)	4.8 [2.5-7.0] (17)	
ASIA						
No data found						
AUSTRALIA/OCEANIA						
No data found						
MIDDLE EAST						
No data found						
EUROPE						
Spain ⁸ (retrospective single hospital study; All cases with biopsy proven cutaneous vasculitis; excluded cases with systemic involvement as well as HSP)		1988- 1997	>20	3.0 [2.2-3.7] (63)	3.8 [2.6-5.1]	2.2 [1.3-3.1]
UK ⁹ (single center study; all cases biopsy proven Leukocytoclastic Anaiitis based on Chapel Hill		1990- 1994	>16 years	1.54 [1.06-2.18] (32)	0.6 [0.22-1.31] (6)	2.42 [1.58-3.55] (26)

Consensus Conference definition; skin disease only – no systemic disease)

European ACCESS cohort study¹⁰ European study of background incidence based on a distributed data network of 10 healthcare databases from 7 European countries. Medical codes were used to identify SOCV in the database from each participating centre (for codes see following publication: Engelen, R., Willame, C., Martín-Pérez, M., García-Poza, P., Souverein, P., Belbachir, L., Durán, C., & Sturkenboom, M. (2021). ACCESS-Background rate of adverse events-definition –Single Organ Cutaneous Vasculitis (1.0). Zenodo. <https://doi.org/10.5281/zenodo.5234977>). Validation of cases via medical record review was not done. The study population varied from region to region as shown in the 5 rows below. The database name, data source and coding system used is shown for each country below the table.

Italy ^A , Spain ^{B+C} , UK ^D	2017-2020	All ages GP based population	8.16 [5.09-11.23]		
The Netherlands ^E		All ages Inpatient only	1.50 [0.99-2.01]		
Italy ^F		All ages Inpatient + Emergency room	8.04 [6.28-7.29]		
Spain ^{G+H}		All ages GP + In/Out-patients	14.58 [2.47-26.68]		
Denmark ^I , France ^J		All ages In/Outpatient	11.16 [4.74-17.59]		

^A PEDIANET; National Italian pediatricians' medical records (population 0.2 million); ICD-9-CM

^B BIFAP; GP medical records; ICD-9-CM / ICD-10-CM / SCTSPA

^C SIDIAP; Catalonia, Spain (population 6.2 million); Record linkage; ICD-10-CM

^D CPRD; sub-national sample (population 4.7 million); GP medical records; Read code

^E PHARMO; sub-national sample (population 9.2 million); Record linkage; ICD-9-CM

^F ARS; Tuscany, Italy (population 3.0 million); Record linkage; ICD-9-CM

^G FISABIO; Valencia, Spain (population 5.8 million); Record linkage; ICD-9-CM / ICD-10

^H BIFAP; 8 regions of Spain, not including Valencia or Catalonia (population 10.3 million); GP medical records; ICD-9-CM / ICD-10 / SCTSPA (Spanish version of SNOMED)

^I Danish national registries (population 5.9 million); record linkage; ICD-10

^J SNDS; French national insurance claims (population 7.5 million); CIM-10

Annex 3

Risk Factors for Single Organ Cutaneous Vasculitis

3.1 Risk Factors for Single Organ Cutaneous Vasculitis¹¹⁻⁹⁷

There are many possible causes of cutaneous vasculitis. An adequate skin biopsy is essential for diagnosis but may not always be obtained. The table below provides risk factors for cutaneous vasculitis some of which could lead to SOCV (malignancy, infection, drugs) and some of which rule out SOCV because they involve more systems than the skin alone (autoimmune diseases, connective tissue disorders). All are included in the table since they may be indistinguishable at the time of presentation, may all result in a histopathologic picture of cutaneous leukocytoclastic vasculitis on biopsy and help to guide investigation so that a diagnosis of SOCV can be met or ruled out.

In an extensive review¹¹, Carlson et al presented pooled data from 30 studies with 2,161 cases of cutaneous vasculitis with a frequency distribution (mean % and range) for the many contributing factors or associated diseases. These are listed below. Note that 1 through 4 are potentially compatible with SOCV whereas 5 through 8 would rule it out since other systems would be involved. The table provides more detail for known associations for 2-4 and 6-8 in the categories listed below.

- 1. 39.0% (3-72%) idiopathic vasculitis (no identified cause)
- 2. 22.5% (0-62%) possible infectious cause
- 3. 20.1% (0-69%) possible drug-related cause
- 4. 4.3% (0-16%) malignancy
- 5. 10.1% (0-88%) Henoch-Schönlein purpura (IgA vasculitis)
- 6. 4.4% (0-13%) primary systemic vasculitis
- 7. 11.7% (0-44%) connective tissue disease
- 8. 2% (0-15%) other systemic disorders

TABLE 3.1 Cutaneous Vasculitis RISK FACTORS

The entries in the table are based on evidence presented in the SOCV published case definition¹ and several general reviews of cutaneous vasculitis¹¹⁻¹⁵ or acute hemorrhagic edema of infancy^{16, 17}. In addition, evidence informing specific risk factors¹⁸⁻⁹⁷ are cited within the table.

Age	Acute hemorrhagic edema of infancy (AHEI) is a rare form of SOCV found primarily in 4 months to two-year-old children. It is also known as Finkelstein-Seidlmayer vasculitis after two of the first physicians to report on the disease in 1938 and 1939. The typical features are rapid onset of raised annular or nummular erythematous eruptions accompanied by inflammatory non-pitting edema of the skin, primarily in the face and ears but may also involve hands and feet. Despite the dramatic appearance of the rash and edema affected children are usually in no acute distress, remaining otherwise well appearing and playful. Biopsy of the rash reveals leukocytoclastic vasculitis (LCV). Complications are rare but have been reported (intussusception, renal involvement, arthritis, testicular torsion; notably such cases would not meet the definition of SOCV given systemic involvement). Like other forms of SOCV, associations with preceding infection and drugs including vaccine have been made but not causally proven.
Genetics	Inherited deficiency in IL12B or IL12RB1. ¹⁸ This manifests as an increased susceptibility to mycobacterial disease and infections by <i>Salmonella sp</i> , and may present with early onset immunodeficiency. The increased risk of LCV is a late manifestation. It isn't clear if the LCV is secondary to the genetic defect or recurrent mycobacterial or <i>Salmonella sp</i> infection.
Comorbidity	Malignancy especially hemoproliferative disorders but also solid organ tumors ¹⁹ such as intestinal adenocarcinoma or lung cancer. Systemic disorders including: <ul style="list-style-type: none">• Henoch-Schönlein purpura (IgA vasculitis)

	<ul style="list-style-type: none"> • Primary systemic vasculitis: Wegener granulomatosis, Polyarteritis nodosa, Churg-Strauss syndrome, Giant cell arteritis, Microscopic polyangiitis • Connective tissue disease: Systemic lupus erythematosus, Rheumatoid arthritis, Sjögren syndrome • Other systemic disorders: Behçet disease, Sarcoidosis, Inflammatory bowel disease, Cryoglobulinemic vasculitis
Infection	<p>Both acute and chronic infections, by a multitude of microbial pathogens, have been noted to precede SOCV. The pathogenesis is not clear, but a search for possible infection would be relevant when assessing SOCV as an AEFI. The following pathogens have been implicated:</p> <p>Viral: CMV, EBV, Hantavirus, Hepatitis A/B/C, HHV6, HHV7, HIV, HSV, Parvovirus B19, SARS-2-CoV²⁰⁻²³, Enterovirus²⁴, Rotavirus²⁵</p> <p>Bacterial: <i>Neisseria sp.</i>, <i>S. aureus</i>, <i>Streptococcus sp.</i>, <i>Syphilis</i>, <i>Mycobacteria sp.</i>, <i>Rickettsial sp.</i>, <i>Chlamydiae sp.</i>, <i>Mycoplasma pneumoniae</i>^{26, 27}</p> <p>Fungal: chronic fungal infections</p> <p>Protozoal: Malaria, helminthic infections</p>
Medication	<p>It is beyond the scope of the guide to provide primary evidence for all possible medications or toxins associated with leukocytoclastic vasculitis. The drugs listed here are from reviews of cutaneous vasculitis^{11, 13, 14, 29} and reports of drug-associated cutaneous vasculitis^{30, 31}</p> <p>Analgesics: aminosalicic acid, phenylbutazone</p> <p>Antimicrobial drugs: acyclovir, cephalosporins, chloramphenicol, clindamycin, doxycycline, erythromycin, isoniazid, levamisole, penicillin, quinine, quinolones, rifampicin, streptomycin, sulfonamides, trimethoprim-sulfamethoxazole, vancomycin</p> <p>Cardiovascular drugs: amiodarone, beta-blockers, captopril, diltiazem, furosemide, heparin, hydralazine, metformin, spironolactone, thiazides, warfarin</p> <p>Rheumatologic drugs: allopurinol, azathioprine, colchicine, cyclophosphamide, gold, methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, rituximab, secukinumab, TNF inhibitors</p> <p>Anticonvulsants: carbamazepine, phenytoin, valproic acid</p> <p>Selective serotonin reuptake inhibitors: amitriptyline, trazodone</p> <p>Cancer chemotherapy: fluoruracil, granulocyte colony stimulating factor (GCSF), leucovorin, oxaliplatin, tamoxifen,</p> <p>Other: insulin, interferons, leukotriene inhibitors (montelukast), nicotine patches, oral contraceptives, phenothiazine, potassium iodide, propylthiouracil, streptokinase</p>
Chemicals, Toxins, environmental agents	<p>As with drugs, it is beyond the scope of the guide to find original evidence for all risk factors in this category, and thus what is listed below is from a detailed review of cutaneous vasculitis¹¹:</p> <p>Insecticide, petroleum products, particulate silica (quartz, granite, sandstone, grain dust), solvents, drug abuse (cocaine), radiocontrast media, arthropod bites, coral ulcers,</p>
Vaccine	<p>There is no evidence to date for a causal association between vaccines and SOCV. The IOM, in their 2011 review of vaccines used for routine immunization in the U.S.³² noted some mechanistic evidence for both influenza and hepatitis B vaccines and vasculitis based on vasculitis occurring with each of the wild type diseases as well as very limited case reports – 1 from VAERS (review committee obtained report from the FDA) which had temporal evidence of leukocytoclastic vasculitis occurring twice in the same individual after influenza vaccine – i.e., evidence for rechallenge; and 3 published case reports post hepatitis B vaccine.</p> <p>Two systematic literature searches^{33, 34} reviewed the evidence for association between vaccines routinely administered in the USA and a multitude of AESIs. No evidence for causal association was found for vasculitis. However, SOCV was not specified in either review.</p>

	<p>The National Academies of Sciences, Engineering, and Medicine did a systematic review of all COVID-19 vaccines used in the USA for evidence of association with several neurologic, hematologic, cardiovascular and gynecologic AESIs.³⁵ Vasculitis, and in particular SOCV was not covered.</p> <p>The only other published evidence linking cutaneous vasculitis to vaccination is found in published case reports, especially following COVID-19 vaccines.³⁶⁻⁹⁷ These are summarized in Table 3.2 below. None of these provide evidence of causality, however, they do provide a picture of the pattern of events in terms of age and timing. Cases were included in the table only if there was biopsy proven cutaneous vasculitis and no evidence of involvement of any other body systems other than the skin.</p>
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TABLE 2.2. Case reports of SOCV following vaccination. To be included in the table there had to be small vessel cutaneous vasculitis demonstrated on skin biopsy. Case reports with evidence of involvement beyond the skin were excluded from the table.

Abbreviations used in Table: Throughout: NS = Not Stated; Sex: F = Female; M = Male; Comorbidity: AFib = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart failure; CLD = chronic liver disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; GERD = gastro-esophageal reflux disease; HT = hypertension; HypoT4 = hypothyroid; IBD = Inflammatory bowel disease; ITP = immune thrombocytopenia; PCV = polycythemia vera; Vaccine: AZ = AstraZeneca; HZ = Herpes Zoster; Inact = inactivated; J&J = Johnson and Johnson; MMR = measles, mumps, rubella vaccine; Men B = meningococcal group B; PPV23 = pneumococcal polysaccharide 23 valent vaccine; rVZV = recombinant vesiculostomatitis virus vaccine platform; TIV = trivalent inactivated influenza; VZV = Varicella Zoster virus vaccine; Skin biopsy diagnoses: AV = allergic vasculitis; ICV = immune complex vasculitis; LCV = leukocytoclastic vasculitis; LV = lymphocytic vasculitis; NV = necrotizing vasculitis; SVV = small vessel vasculitis; UV = urticarial vasculitis; Investigations: Chem = ≥ 1 of: CBC, liver and urine function tests, urinalysis, ESR, CRP; Inf = ≥ 1 test for infectious causes (e.g., COVID-19, Coxsackie virus, CMV, EBV, Hepatitis B/C, HIV, HHV6, HHV7, Parvovirus B19, ASOT, Lyme disease, syphilis) AID = ≥ 1 test for autoimmune disease (e.g., RF, ANA, ANCA, anti-dsDNA, ENA, anti-cardiolipin antibodies, lupus anticoagulant, cryoglobulins); Cancer = ≥ 1 imaging examination for cancer.

Author	Country	Sex	Age (yrs)	Comorbidity	Vaccine	Dose	Days to rash onset	Biopsy	De Novo or Recurrence	Investigations	Time to resolution
COVID-19 Vaccines											
Abdelmaksoud ³⁶	Egypt	M	48	NS	mRNA ^{Pfizer}	2	4	LCV	De novo	NS	3 weeks
Cohen ³⁷	USA	F	46	Psoriasis, arthritis, IBD	mRNA ^{Pfizer}	2	2	LCV	Recurrence	Chem+Inf	2 weeks
Larson ³⁸	USA	F	83	None	mRNA ^{Pfizer}	2	5	LCV	De novo	Chem + AID	NS
Dicks ³⁹	USA	M	65	HT, DM	mRNA ^{Pfizer}	3	2	LCV	De novo	NS	8 weeks
Colia ⁴⁰	Italy	F	22	None	mRNA ^{Pfizer}	2	7	LCV	De novo	Chem + AID	3 weeks
Erlar ⁴¹	Germany	F	42	Obese, HT	mRNA ^{Pfizer}	1	4	LCV	De novo	Chem + AID + Inf	1 week
Altun ⁴²	Turkey	M	38	None	mRNA ^{Pfizer}	1	4	LCV	De novo	Chem + AID	2 weeks
Zagorec ⁴³	Croatia	F	68	HT, depression	mRNA ^{Pfizer}	2	6	NV	De novo	Chem + AID + Inf	2 months
Gomez ⁴⁴	USA	M	81	Afib, HT, HypoT4	mRNA ^{Pfizer}	3	10	LCV	De Novo	Chem + AID + Inf	3weeks
Vassallo ⁴⁵	Italy	F	51	None	mRNA ^{Pfizer}	1	0.25	LCV	De Novo	Inf	2 weeks
Nakashima ⁴⁶	Japan	F	52	NS	mRNA ^{Pfizer}	3	4	UV	De Novo	Chem	NS
Carillo-Garcia ⁴⁷	Spain	F	91	DM, HT, dementia	mRNA ^{Pfizer}	2	4	LCV	De Novo	Chem + AID + Cancer	≤ 1 month

Bostan ⁴⁸	Turkey	F	57	Epilepsy;	mRNA ^{NS}	1	1	LCV	De novo	Chem + AID	1 week
Avallone ⁴⁹	Italy	M	16	None	mRNA ^{Moderna}	3	3	LV	De Novo	NS	NS
Gazquez-Aguilera ⁵⁰	Spain	M	52	None	mRNA ^{Moderna}	2	12	AV	De Novo	Chem + AID	NS
Nazzaro ⁵¹	Italy	F	27	None	mRNA ^{Moderna}	1	10	UV	De Novo	Chem	2 months
Casale ⁵²	USA	M	80	Prior ITP	mRNA ^{Moderna}	1	3	LCV	De Novo	NS	NS
Hocevar ⁵³	Slovenia	NS	20s	None	mRNA ^{Moderna}	NS	8	ICV	De Novo	NS	NS
		NS	60s	None	ChAdOx1 ^{AZ}	NS	9	ICV	De Novo	NS	NS
Fritzen ⁵⁴	Brazil	F	60	CLD, DM, HypoT4, PCV	ChAdOx1 ^{AZ}	2	8	LCV	De Novo	Chem	2 weeks
Criado ⁵⁵	Brazil	F	61	HT	ChAdOx1 ^{AZ}	1	5	LCV	De Novo	Chem + AID + Inf	NS
Ungari ⁵⁶	Italy	M	64	None	ChAdOx1 ^{AZ}	2	3	LV	De Novo	Chem + AID	2 weeks
Khajavirad ⁵⁷	Iran	F	77	HT	ChAdOx1 ^{AZ}	1	2	LV	De Novo	Chem + AID + Inf	7 days
Jin ⁵⁸	S Korea	F	68	None	ChAdOx1 ^{AZ}	1	2	LCV	De Novo	Chem + AID	3 weeks
Cavalli ⁵⁹	Italy	F	53	None	ChAdOx1 ^{AZ}	1	6	LCV	De Novo	Chem + AID + Inf	2 weeks
Liang ⁶⁰	Australia	F	62	NS	ChAdOx1 ^{AZ}	1	7	LCV	De Novo	Chem + AID	3 weeks
Guzman-Perez ⁶¹	Spain	F	57	HT, hypoT4	ChAdOx1 ^{AZ}	1	1-5	LCV	De Novo	Chem + AID + Inf	≤ 2 weeks
Shahrigharahkoshan ⁶²	Canada	F	77	None	ChAdOx1 ^{AZ}	1	10	LCV	De Novo	Chem	5 weeks
Baraldi ⁶³	Italy	F	78	None	ChAdOx1 ^{AZ}	1	7	UV	De Novo	Chem + AID	NS
Fiorillo ⁶⁴	Italy	F	71	HT, fibrocystic mastopathy	ChAdOx1 ^{AZ}	2	4	LCV	De Novo	Chem + AID	2 weeks
Sandhu ⁶⁵	India	F	55	None	ChAdOx1 ^{AZ}	1	5	LCV	De Novo	Chem + AID + Inf	2 weeks
		M	48	HT	ChAdOx1 ^{AZ}	2	2	LCV	De Novo	Chem + AID + Inf	NS
Pournazari ⁷⁴	Iran	M	41	None	ChAdOx1 ^{AZ}	2 ^{1st dose was Sinopharm}	14	LCV	De Novo	AID	NS
Dordevic Betetto ⁶⁶	Slovenia	M	30	None	Ad26COV ^{Janssen/J&J}	1	17	LCV	De Novo	Chem + AID + Inf	Several weeks
Ball-Burack ⁶⁷	USA	M	22	None	Ad26COV ^{Janssen/J&J}	NS	10	LCV	De Novo	Chem + AID	NS

Berry ⁶⁸	USA	M	65	HT, hyperlipidemia	Ad26COV ^{Janssen/J&J}	1	7	LCV	De Novo	Chem + AID + Inf	NS
Kharkar ⁶⁹	India	F	31	None	Inact ^{COVAXIN}	2	4	SVV	De Novo	Chem + AID + Inf	2 weeks
Kar ⁷⁰	India	F	46	None	Inact ^{COVAXIN}	1	5	LCV	De Novo	Chem + Inf	15 days
Dash ⁷¹	India	M	27	NS	Inact ^{CoronaVac}	2	7	UV	De Novo	Chem	1 week
Bencharattanaphakhi ⁷²	Thailand	F	23	None	Inact ^{COVAXIN}	1	1.5	LCV	De Novo	Chem + AID + Inf	4 weeks
		F	26	None	Inact ^{COVAXIN}	1	0.14	LCV	De Novo	Chem + AID + Inf	4 weeks
Shakoei ⁷³	Iran	M	45	None	Inact ^{Sinopharm}	1	2	LCV	De Novo	Chem	NS
Azzazi ⁷⁵	Egypt	F	57	None	Inact ^{NS}	2	5	LCV	De Novo	Chem + AID + Inf	6 weeks
Bostan ⁷⁶	Turkey	M	33	None	Inact ^{NS}	1	3	LCV	De Novo	Chem + AID	NS
Vaccines Other than COVID-19											
Cao ⁷⁷	Canada	M	60	Idiopathic pulmonary fibrosis	Influenza ^{TIV}	NS	5	LCV	De Novo	Chem + AID + Inf	10 days
Chen ⁷⁸	USA	M	88	HT, CHF, GERD, Pulmonary fibrosis	Influenza ^{TIV}	NS	14	LCV	De Novo	None	≤12 days
Walker ⁷⁹	UK	F	64	NS	Influenza ^{TIV}	NS	10	LCV	De Novo	‘Vasculitis screen’	3 months
Hu ⁸⁰	Taiwan	F	54	None	Influenza ^{Vaxigrip}	NS	4	LV	De Novo	Chem + AID	2 weeks
Monjazeb ⁸¹	USA	F	89	HT, DM	Influenza ^{NS}	NS	11	LCV	De Novo	Chem	3 weeks
Barbarroja-Escudero ⁸²	Spain	M	86	HT, DM, sleep apnea	Influenza ^{NS}	NS	7	LCV	De Novo	Chem + AID + Inf	3 weeks
Liu ⁸³	Taiwan	F	17	None	Influenza ^{H1N1}	NS	3	LCV	De Novo	Chem + AID	2 weeks
Hughes ⁸⁴	France	F	21	None	Influenza ^{H1N1}	NS	9	UV	De Novo	Chem + AID + Inf	2 weeks
Ferreira ⁸⁵	Portugal	M	2	NS	Influenza ^{H1N1}	NS	14	LCV	De Novo AHEI	Chem + Inf	2 weeks
Abdalla ⁸⁶	Ireland	M	76	HT, AFib, COPD, Smoker	PPV23, Influenza ^{TIV}	1 9	3	LV	De Novo	Chem + AID + Inf	NS

Fox ⁸⁷	USA	M	57	CAD	PPV23	NS	14	LCV	De Novo	AID + Inf	>3months
Babic ⁸⁸	Croatia	M	1.14	None	MMR	NS	14	LCV	De Novo AHEI	Chem + AID + Inf	NS
Binamer ¹⁶	Saudi Arabia	M	2	NS	MMR	NS	14	LCV	De Novo AHEI	Chem + Inf	1 month
Blasini ⁸⁹	USA	M	1	None	MMR, VZV	1 for each	21	LCV	De Novo AHEI	Chem	NS
Velasco-Tamariz ⁹⁰	Spain	F	6	None	MenB ^{Bexsero}	1	7	LCV	De Novo	Chem + AID + Inf	2 weeks
Puram ⁹¹	USA	M	60	HT, Obese, Sleep apnea	HZ ^{Merck}	NS	42	LCV	De Novo	Chem + AID + Inf	NS
Muniz ⁹²	USA	M	53	None	Anthrax ^{AVA}	4	11	LCV	De Novo	Chem + AID	NS
Beachkofsky ⁹³	USA	M	25	None	Vaccinia ^{ACAM2000}	NS	10	LV	De Novo	Skin lesions from all 3 were negative for Vaccinia by PCR. No other tests noted.	53 days
		M	19	None	Vaccinia ^{ACAM2000}	NS	15	LV	De Novo		32 days
		M	26	None	Vaccinia ^{ACAM2000}	NS	13	LV	De Novo		11 days
Huttner ⁹⁴	Switzerland	F	48	NS	Ebola ^{rVZV-ZEBOV}	1	12	LV	De Novo	Chem + Inf	10 days
Bani-Sadr ⁹⁵	France	M	24	None	Hepatitis A ^{Havrix}	1	9	LCV	De Novo	Chem + AID + Inf	6 days
LeHello ⁹⁶	France	F	16	None	Hepatitis B GenHevac B	NS	20	LCV	De Novo	Chem + AID + Inf	NS

Annex 4

Single Organ Cutaneous Vasculitis Case Definition: Key Caveats for Diagnosis, Data Analysis and Presentation

4.1. Single Organ Cutaneous Vasculitis (SOCV) Case Definition¹ Key Caveats for Diagnosis, Data Analysis and Presentation

4.1.1 Key elements of Case Definition (CD)

- CD is aligned with the 2012 Chapel Hill Consensus Conference on vasculitis nomenclature, in particular, single organ vasculitis (SOV).⁹⁷ The BC CD Working Group used SOCV to refer to involvement of skin alone.
- There are 3 levels of diagnostic certainty (LOC) that meet the case definition. Levels 1 and 2, but not Level 3, require a skin biopsy. LOC 1 requires all three classic histopathologic features of cutaneous leukocytoclastic vasculitis:
 - leukocytoclasia (perivascular inflammatory cells infiltrates dominated by neutrophils with fragmented nuclei). In lymphocytic small vessel vasculitis lymphocytes may dominate. Eosinophils may also be present.
 - RBC extravasation
 - fibrinoid necrosis or degeneration of the dermal postcapillary venules (other small vessel walls may be affected).
 - Direct immunofluorescence is not required, but if done may show a predominance of IgM, IgG and C3.
 LOC 2 requires only the first 2 features.

- LOC 1, 2 and 3 all require rash morphology that has at least 1 of the following:
 - Hemorrhagic papules
 - Urticarial lesions lasting > 24 hours, leaving bruising or hyperpigmentation
 - Purpuric targetoid plaques on face, ears and extremities plus edema plus low-grade fever (typical of Acute Hemorrhagic Edema of Infancy, AHEI).

At the outset, the rash may consist of red-to-pink macules and papules which progress to the more classic palpable purpura and non-blanching petechiae. Other morphologies (necrosis, ulcers, petechiae, hemorrhagic bullae or pustules) may be present but are not required to meet the SOCV CD. Typically, the rash is predominant below the waist in gravity-dependent areas or areas of constriction by clothing.¹⁴

- LOC 1, 2 and 3 also all require that vasculitic involvement of other organs be ruled out. LOC 5 (Not a case of SOCV) is reached if there is evidence of involvement of any organs other than skin. If testing is not done or results are not available, the case is considered to be LOC 4 (fails to meet any other LOC).
- SOCV may be accompanied by symptoms such as low grade fever, mild arthralgia or malaise. Symptoms such as those listed in Table 4.1 should prompt a search for evidence of systemic vasculitis such as may occur in:
 - Systemic lupus erythematosus (SLE)
 - Rheumatoid arthritis
 - Behcet's disease
 - Sjogren syndrome
 - Polyarteritis nodosa
 - Henoch Schonlein Purpura (HSP)
 - Sarcoidosis
 - Mixed connective tissue disease
 - Scleroderma
 - Dermatomyositis
 - Relapsing polychondritis
 - ANCA associated vasculitis (but important to note that up to 60% of patients with only skin involvement may be + for ANCA¹²)
 - Cryoglobulinemic vasculitis

- Hypocomplementemic urticarial vasculitis
- The temporal course of cutaneous vasculitis may be a clue to the underlying cause¹²
 - Typically SOCV following exposures such as infection, drugs and possibly vaccine (causality not established) is a single self-limited episode that usually resolves in ≤6 months
 - In HSP and other systemic vasculitides there is often relapsing disease with symptom-free periods
 - A chronic, unremitting course should suggest cryoglobulinemia or malignancy

4.1.2 Recommendations for real time assessment

- Description of skin rash including location, morphology and associated symptoms
- Description of any concurrent signs, symptoms, known diseases, medications
- Histopathology establishes the diagnosis of small vessel cutaneous vasculitis. The ideal timing of the skin biopsy is within 48 hours of the onset of the lesion where the biopsy will be taken.
- Other testing (see Table 4.1) is done to:
 - rule in or out systemic disorders that may also cause small vessel cutaneous vasculitis (see Table 4.1 below)
 - look for specific etiologies of SOCV such as infection (see Table 3.1 Infectious risk factors for a guide to the types of infection that may cause SOCV. Testing should be based on locally prevalent infections as well as clinical correlation.)
- Course of rash and condition at follow-up, in particular any residual lesions (e.g., scars, hyper- or hypopigmentation).

TABLE 4.1 Clinical and laboratory clues to systemic involvement in vasculitic processes^{1, 11-14}

Diseases involving:	Clinical Symptoms/Signs	Tests (evidence of systemic involvement)
Blood	Pallor, spontaneous bleeding from sites other than skin	CBC (normochromic, normocytic anemia; thrombocytopenia)
Kidneys	Hypertension	Urinalysis (proteinuria, hematuria) Serum creatinine, BUN (levels increased) 24-hour urine collection (decreased urine output)
Lungs	Dyspnea, persistent cough, wheeze, hemoptysis, pleuritic chest pain	CXR (patchy or diffuse infiltrates, pleural effusion)
Gut	Vomiting, oral mucosal lesions, GI bleeding	Stool for occult blood (positive)
Liver	Jaundice	Liver enzymes – ALT+AST (elevated) Bilirubin (increased)
Musculoskeletal	Arthritis, muscle weakness	
Brain or peripheral nerves	Altered level of consciousness, focal neurologic signs, mononeuritis	
Mucous membranes / eyes	Oral or genital ulcers, retinal exudates or hemorrhages, uveitis, episcleritis, proptosis, conjunctivitis	
Autoimmunity	Any of the above	Markers of autoimmunity (ANA, anti-ds-DNA, ANCA, RF, anti-citrullinated peptides antibodies, cryoglobulins, anticardiolipin antibody, lupus anticoagulant, reduced serum complement factors: C3, C4, C1q, CH50)

Other	Unexplained weight loss, night sweats, photosensitivity, dry eyes or mouth	
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4.1.3 Data Collection Guidelines

4.1.4 Data Analysis Guidelines

- Classify reported events in one of five categories:
 - Level 1 Single Organ Cutaneous Vasculitis
 - Level 2 Single Organ Cutaneous Vasculitis
 - Level 3 Single Organ Cutaneous Vasculitis
 - Level 4: reported event of Single Organ Cutaneous Vasculitis but insufficient evidence to meet any level of the respective case definition
 - Level 5: Not a case of Single Organ Cutaneous Vasculitis

4.1.5 For immunized cases meeting the SOCV CD at Levels 1, 2 or 3 classify the time to onset following vaccination as follows:

- ≤ 24 hours
- 2 – 3 days
- 4 – 7 days
- 8 – 14 days
- 14 – 21 days
- > 21 days (with 7 day increments thereafter up to < 3months)
- 3 – 12 months (with 1-month increments)

Annex 5

Single Organ Cutaneous Vasculitis Data Abstraction and Interpretation Forms with Algorithms for Assessing Level of Diagnostic Certainty and Glossary of Terms

5.1. Single Organ Cutaneous Vasculitis Data Abstraction and Interpretation Form with algorithms for assessing level of diagnostic certainty

The form is organized in a series of Steps presented as tables.

- **Step 1** guides the collection of data needed to meet the case definition criteria for Generalized Convulsive Seizure. Depending on the specific criterion, data are collected using two formats:
 - i. as mutually exclusive answers of YES, NO or UNKNOWN to a series of questions
 - ii. as a checklist of specific things that were noted to be present (i.e. YES) like signs or symptoms, or lab test results.

Relatively simple criteria used in the case definition may be defined directly in step 1. Others may require formulae to define – as done in Step 2.

- **Step 2** uses some or all of the data entered in Step 1 to assign values (YES, NO or UNKNOWN) to selected case definition criteria, as necessary.
- **Step 3** is a small tabular summary of the assigned value (YES, NO or UNKNOWN) for each criterion in the case definition.
- **Step 4** provides a tabular algorithm to assign the Level of certainty that meets the case definition (Level 1, 2 or 3) or that does not meet the case definition (Levels 4 and 5).
- A Pictorial algorithm is presented that presents, in a single page, all the relevant criteria needed to meet the case definition and a flow diagram that shows the path to each level of diagnostic certainty depending on the criterion values.
- A Glossary of Terms is also included. Any terms defined in the glossary are **yellow highlighted** in the Step 1 data form.

Digital Transformation: For the digital version, when available, the Automated Brighton Classification (ABC) Tool requires users to enter data into the online form for Step 1 only and an LOC will be provided (based on the information in Steps 2-4 which operate in the background of the Tool) along with a summary of the data entered. In addition, the pictorial algorithm will be provided so users can see how the LOC was derived based on data entered. In contrast, for the analog version, as here in the Companion Guide, users must complete all 4 steps in order to reach the LOC.

The data abstraction form (analog or digital versions) can be used in several settings:

- **Epidemiologic research:** As a case report form for data abstraction from a hospital/other institutional chart as part of epidemiologic studies or hypothesis testing studies for causal association between vaccine (s) and SOCV.
- **Real world evidence studies:** Guide data collection for case validation (all or a subset) in studies where electronic health data were used for case identification based on selected medical codes (ICD9/10, SNOMEDCT, MedDRA).
- **Clinical vaccine trials:** Serve as a supplement to a clinical trial case report form that does not capture information specific to SOCV; i.e., when SOCV is not part of solicited safety information in the clinical trial. In such settings it may also serve as a guide for the type of data to be collected and investigations to be done should SOCV occur as an unsolicited adverse event.
- **Pharmacovigilance:** Most AEFI report forms, including the CIOMS form, allow for free text to describe an adverse event but are not set up to collect specific information that would facilitate applying a standard Brighton case definition. In the event of a possible safety signal involving SOCV, the abstraction form could be used to gather the information needed to assess individual cases to see if they meet the Brighton case definition. In the absence of a

signal, where SOCV is considered an AESI (such as in the COVID-19 pandemic campaign), the data abstraction form can be used to guide selection of critical criteria needed to meet the case definition, that could then be added to a special AEFI report form for use in a mass campaign setting.

TABLE 5.1 Single Organ Cutaneous Vasculitis KEY CASE DEFINITION CRITERIA AND LIKELY SOURCES OF RELEVANT INFORMATION. Space is also provided to record the actual sources of information.

Criterion	Criterion category	Likely sources of information	Actual sources of Information
A	Characteristic skin lesions	<ul style="list-style-type: none">History and physical examination from clinic visit(s) or emergency room or hospital admissionSpecialist consultation notes (dermatology, immunology, infectious disease)	
B	Skin lesion histopathology	<ul style="list-style-type: none">Autopsy or skin biopsy histopathology reportDermatology or immunology consultation notes	
X	Other system(s) involvement due to vasculitis or infection	<ul style="list-style-type: none">Laboratory tests for kidney, liver, blood function testsChest x-raySerology for hepatitis B and C, EBV, Parvovirus B19 or other viruses; ASOT;Blood test for ANA, ANCA, rheumatoid factor, anti-CCP antibodies, cryoglobulins, complement factors, other tests for autoimmune diseaseSpecialist consultations notes: hematology, nephrology, respirology, gastroenterology, cardiology, rheumatology,, neurology, immunology	

Step 1. Complete the case data entry form choosing the most appropriate answer as defined below:

- 'YES' means there was written or verbal evidence that the criterion was present.
- 'NO' means there was written or verbal evidence that the criterion was not present.
- 'UNKNOWN' means there was uncertainty in interpreting whether the criterion was present or absent, OR nothing was documented about the criterion.

Terms with a glossary definition

Criterion	Question	Possible Answers		
A – Characteristic skin lesions.				
A <i>Note: only 1, 2 and 3 are relevant to reaching a level of certainty. The WG noted that the lesions listed in 4-10 may be present. They are not required to be answered but may be helpful in reviewing the case.</i>	*1. Hemorrhagic papules	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	*2. Erythematous edematous urticaria-like lesions lasting ≥24 hours and on disappearance leaving bruising or hyperpigmentation	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	*3. Purpuric rash on face, ears and extremities accompanied by edema and fever (≥38.0 °C)	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	4. Urticaria-like lesions other than those described in 2 above	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	5. Necrotic skin lesions	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	6. Skin ulcer(s)	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	7. Petechiae	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	8. Hemorrhagic bullae	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	9. Pustules	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	10. Purpuric rash without accompanying edema or fever	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
B – Histopathology of skin lesions				
B0.1	Was a sample of skin tissue obtained for histopathology within 48 hours of lesion onset? If YES, answer B 1-7 below.	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
B	1. Perivascular Inflammatory cells infiltrate dominated by neutrophils with fragmented nuclei (leukocytoclasia)	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	2. Red blood cell (erythrocyte) extravasation or haemorrhage into the dermis.	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	3. Fibrinoid necrosis or degeneration of the dermal postcapillary venules	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	4. Perivascular Inflammatory cells infiltrate predominantly lymphocytes	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	5. Perivascular Inflammatory cells infiltrate predominantly eosinophils	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	6. Thrombotic obliteration of affected vessels	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	7. Direct immunofluorescence shows a predominance of IgM and IgG and C3	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN

X. Evidence of other vasculitic organ system involvement or infections that target more systems than skin				
X	1. Blood: ≥1 of thrombocytopenia or normochromic normocytic anemia	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	2. Kidneys: ≥1 of proteinuria, haematuria, increased serum creatinine, hypertension	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	3. Lungs: ≥1 of dyspnea, cough, hemoptysis, patchy or diffuse alveolar infiltrates on CXR	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	4. Gut: ≥1 of abdominal pain, vomiting, gastrointestinal bleeding	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	5. Liver: ≥1 of elevated liver enzymes (AST, ALT) or bilirubin	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	6. Serosal involvement: ≥1 of: pericardial effusion or pleural effusion seen by ultrasound or CXR	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	7. Joints: if arthritis present, synovial aspirate done and confirms synovitis	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	8. Neurologic system (brain or peripheral nervous system) involvement: ≥1 central neurologic deficit or peripheral neurologic deficit	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	9. Positive blood test for ANA	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	10. Positive blood test for ANCA	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	11. Positive blood test for rheumatoid factor	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	12. Positive blood test for anti-CCP antibodies	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	13. Positive blood test for cryoglobulins	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	14. Reduction in serum complement factors (C3, C4, C1q)	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	15. Positive Hepatitis C serology	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	16. Positive Hepatitis B serology	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	17. Positive EBV serology	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	18. Positive Parvovirus B19 serology	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN
	19. Positive ASOT	<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> UNKNOWN

Step 2. Based on clinical data entered in Step 1, assign a value to CD criteria A1, B1, B2 and X1 using the rules in Criterion Options columns

CRITERION					CRITERION VALUE: compare data entered in step 1 table to formulae in the YES, NO and UNKNOWN columns to determine FINAL VALUE for each criterion		
CLINICAL CATEGORY	Name	FINAL VALUE (Circle / Highlight)			Criterion = YES (Y) IF:	Criterion = NO (N) IF:	Criterion = UNKNOWN (U) IF:
Clinical features of small vessel vasculitis required for all levels of certainty	A1	Y	N	U	A(1 or 2 or 3) = YES	A(1 and 2 and 3) = NO	A(1 and 2 and 3) = NO or UNKNOWN*
Histopathology findings	B1	Y	N	U	B(1 and 2 and 3) = YES	B(1 or 2 or 3) = NO	B(1 and 2 and 3) = YES or UNKNOWN**
	B2	Y	N	U	B(1 and 2) = YES	B(1 or 2) = NO	B(1 and 2) = YES or UNKNOWN**
Exclusion of other vasculitic organ system involvement	X1	Y	N	U	≥1 of X(1-19) = YES	All of X(1-19) = NO	All of X (1-19) = NO or UNKNOWN*

* choose UNKNOWN if there is a combination of NO and Unknown (e.g. if A(1) = NO and A(2 and 3) = Unknown, then A1 = Unknown)

** choose UNKNOWN if there is a combination of YES and Unknown (e.g. if B(1) = YES and B(2 and 3) = Unknown, then B1 = Unknown)

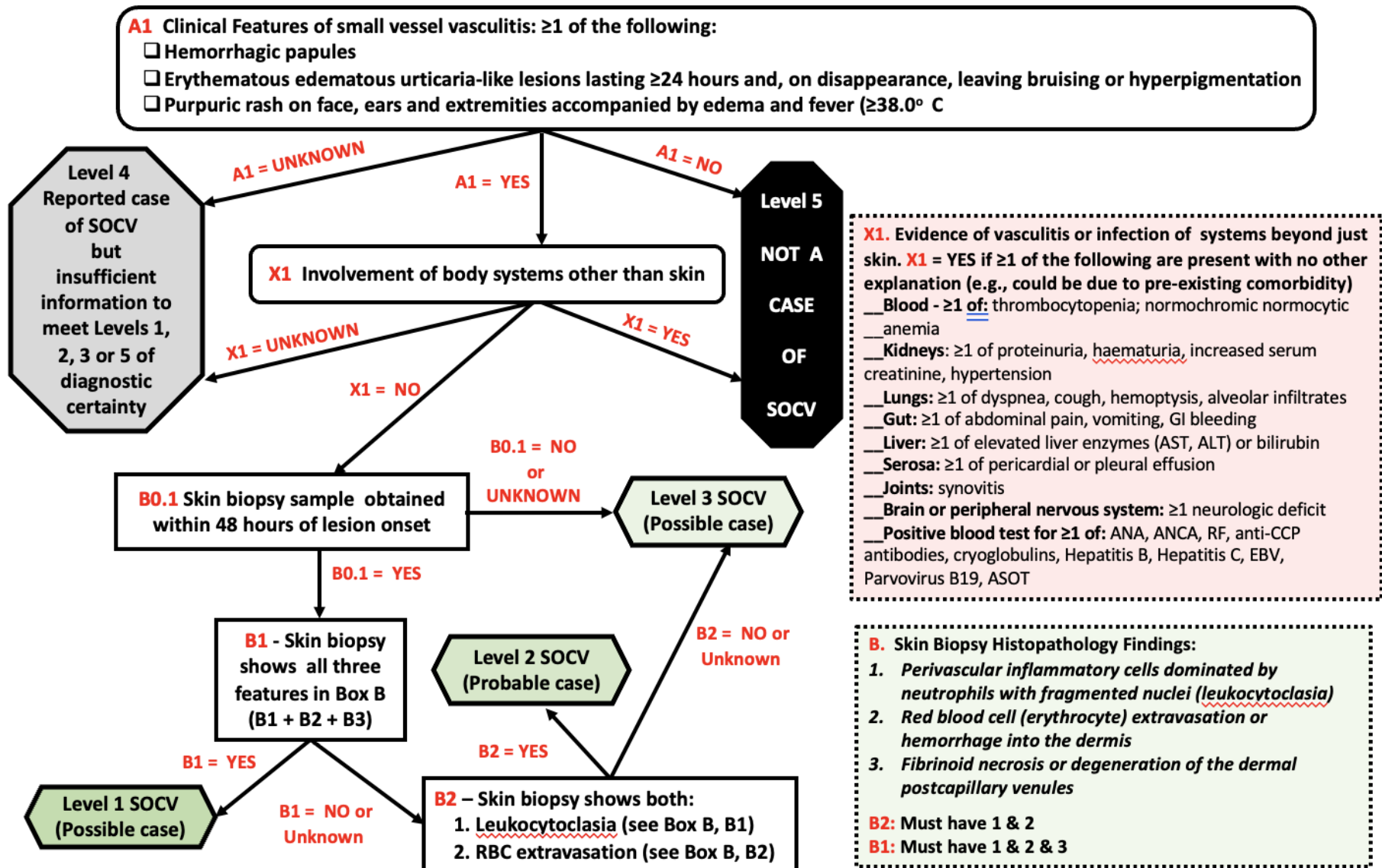
Step 3. Record the final value for Criteria (B0.1) from the step 1 table and for criteria (A1, B1, B2 and X1) from the Step 2 table. Y = YES, N = NO, U = UNKNOWN

Criterion	A1	B0.1	B1	B2	X1
Final Value					

Step 4. Use the final values of all criteria recorded in the Step 3 Table above to determine the level of certainty based on the formulae below for Single Organ Cutaneous Vasculitis. Start with Level 1 (criteria **A1, B1, X1**). If Level 1 not met, then move to Level 2 (criteria **A1, B2, X1**) and, if not met, try Level 3(**A1, B0.1, X1**). If none of Levels 1, 2 or 3 met, try Level 5 (criteria **A1, X1**). If Levels 1, 2, 3 and 5 not met, then assign Level 4.

Level of Certainty	AESI
Level 1	(A1 AND B1 = YES) AND (X1 = NO)
Level 2	(A1 AND B2 = YES) AND (X1 = NO)
Level 3	(A1 = YES) AND (B0.1 AND X1 = NO)
Level 4	Unable to meet any level of certainty
Level 5	(A1 = NO) OR (X1 = YES)

FIGURE 1. Pictorial algorithm for determining SINGLE ORGAN CUTANEOUS VASCULITIS (SOCV) level of diagnostic certainty



GLOSSARY OF TERMS RELEVANT TO Single Organ Cutaneous Vasculitis The table lists, in alphabetical order all terms relevant to the criteria needed to meet the case definition along with a brief definition for each.

Term	Definition
Alveolar infiltrate	Abnormal appearance on chest-xray or other imaging due to fluid in the alveoli (could be blood, pus or other fluid)
Anemia	Deficiency of red blood cells in the blood. Abnormally low hemoglobin
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibodies
Anti-CCP	Antibodies to cyclic citrullinated peptides. Antibodies found in most Rheumatoid arthritis patients.
Arthritis	Inflammation of one or many joints
ASOT	Anti-streptolysin-O Titer
AST	Aspartate Aminotransferase (liver enzyme)
ALT	Alanine transaminase (liver enzyme)
Central neurologic deficit	Neurologic abnormality that results from a pathologic process or injury of a part of the brain or spinal cord.
Complement factors	Proteins that make up the complement system
Cryoglobulins	Atypical proteins in the blood which can block blood flow causing inflammation of blood vessels and damage to body organs (skin, joints, nerves, kidney, liver etc).
CXR	Chest X-Ray
Dermis	Layer of skin that lies beneath the epidermis
Dyspnea	Shortness of breath
EBV serology	Serologic markers indicating Epstein Barr Virus infection
Edematous	Swollen
Erythematous	Red colour
Extravasation	Leakage of blood from a blood vessel into surrounding tissue
Fibrinoid necrosis	Necrosis refers to the death of cells lining blood vessels; fibrinoid relates to the appearance in stains used for histopathology – typically the dead cells resemble fibrin (deeply red, homogenous and refractile).
Hematuria	Blood in the urine. May be visible to the eye (macroscopic) or require microscopy (microscopic hematuria) to detect
Hemoptysis	Coughing up blood
Hemorrhagic bullae	Blood-filled cavities or elevations ≥ 1 cm in diameter.
Hemorrhagic papules	Red (because of bleeding) discrete, solid elevated body usually < 0.5 cm in diameter.
Hyperpigmentation	Darkening of the skin
Inflammatory cells	Cells that play a role in the body's defense system against infection or injury; include neutrophils, eosinophils, lymphocytes, plasma cells, histiocytes

Leukocytoclasia	Debris of neutrophils or other inflammatory cells within the blood vessel walls
Necrotic	dead
Normochromic normocytic anemia	Anemia in which the red blood cells are of a normal colour and size
Pericardial effusion	Collection of fluid around the heart
Peripheral neurologic deficit	Neurologic abnormality that results from a pathologic process or injury of one or more nerves that connect the brain and spinal cord to the rest of the body
Perivascular	Tissue or space surrounding a blood vessel
Pleural effusion	Excess collection of fluid in the pleural space surrounding the lungs
Proteinuria	Protein in the urine
Purpuric rash	Purplish-red spots or blotches on the skin due to extravasation of blood into the skin or tissues under the skin
Pustules	Superficial vesicle containing cloudy or purulent fluid; Usually <0.5cm diameter
Rheumatoid Factor	Proteins made by the immune system that are often markers of autoimmune diseases
Synovial aspirate	Sample of synovial fluid usually obtained by placing a needle into a joint space.
Synovitis	Inflammation of synovial tissue which are the membranes that line most of the joints in the body
Thrombocytopenia	Reduced platelet count
Thrombotic obliteration	Blockage of a blood vessel by thrombus
Ulcer	A circumscribed loss of the epidermis or mucosa extending to the dermis
Urticaria-like	Red itchy plaques with a smooth surface. Plaques are discrete, solid, elevated skin lesions that are usually >0.5 mm in diameter.

Annex 6

Methodology: Brief Summary

6.1. Single Organ Cutaneous Vasculitis ICD-9/10-CM, MedDRA and SNOMEDCT Codes ²⁻⁶

An initial set of codes were retrieved through the Codemapper tool that was developed in the IMI-ADVANCE project. Subsequently they were reviewed and classified into narrow or broad codes by the authors.

CodeMapper² builds upon information from the Metathesaurus of the Unified Medical Language System (UMLS). The Metathesaurus is a compendium of many medical vocabularies, which have been integrated by assigning equivalent codes and terms from different source vocabularies to the same concepts. Each concept in the UMLS is identified by a CUI. A CUI is a Concept Unique Identifier for a Metathesaurus concept to which strings with the same meaning are linked. The Metathesaurus contains more than one million concepts connected to codes from 201 vocabularies. Each concept is assigned to one or more of 127 semantic types, which define broad conceptual categories like Disease or syndrome, Finding, or Substance.³ Codemapper was built on the version 2016AA of the UMLS. The automatic concept identification of CodeMapper is based on lexical information from the Metathesaurus. The lexical information of a concept consists of terms that can be used in free text to refer to that concept. We compiled a dictionary for the concepts in the semantic groups Anatomy, Chemicals & Drugs, Disorders, Genes & Molecular Sequences, Living Beings, Phenomena, Physiology, and Procedures of non-suppressible, English terms from several vocabularies including ICD-9 CM, ICD-10 CM, and MedDRA.^{4,5} A text-indexing engine Peregrine uses this dictionary to identify medical concepts in the case definition.⁶ Of note, while SPEAC focused on ICD-9/10-CM and MedDRA codes, the CodeMapper concepts shown in the table can be used to search for codes in other systems including SNOMEDCT, MeSH, ICPC-2 and Read-CTv3. In this updated version of the Companion Guide, the SNOMEDCT codes have been added.

CodeMapper has three screens.

1. The first displays the free text entered by the user – in this case the Brighton case definition. Medical concepts are automatically identified in the text and highlighted inline.
2. The second displays the mapping as a table with one row for each medical concept, and one column for each targeted vocabulary. Each cell contains the names of the codes that are used to represent the medical concept of the row in the targeted vocabulary of the column. The codes are displayed when the names are hovered over with a cursor. Several user operations are available for revising the mapping. The user can remove concepts from the mapping, search and add concepts, or retrieve more general and more specific concepts. The retrieved concepts are shown in a list and can be selected by the user for inclusion in the mapping. The user can also add or remove vocabularies that should be targeted by the mapping. After every operation, the codes are automatically updated and displayed in the table.
3. The third shows a list of all operations that have been made, for later traceability of the mapping process. When the user saves the mapping, he has to provide a summary of the modifications, which is incorporated into the mapping history. The user can download the mapping as a spreadsheet file to incorporate the codes into extraction queries. The spreadsheet file comprises the original free-text case definition, the concepts of the mapping, the codes for the targeted vocabulary, and the full history of the mapping process.

Codemapping was conducted by MS. The output of the Codemapper concepts was reviewed by a medical expert (BL) familiar with the encephalitis Brighton case definitions for all Tier 1 AESI. The concepts identified for encephalitis were considered relevant for background incidence rate determination as well as to study hypotheses related to encephalitis as a vaccine-product related reaction. Most of the terms include encephalitis and acute disseminated encephalomyelitis since encephalitis may be part of these broader categories.

For a more detailed description of methodology, see SO2-D2.3 Tier 1 AESI: ICD-9/10-CM and MedDRA Codes which is available on [Zenodo](#).

6.2. Single Organ Cutaneous Vasculitis Background Incidence

A systematic literature search to estimate the incidence of Single Organ Cutaneous Vasculitis (SOCV) in the population was conducted using the following search strategy:

Multiple synonyms were used for single organ cutaneous vasculitis as follows:

("Vasculitis, Leukocytoclastic, Cutaneous"[Mesh] OR "cutaneous vasculitis"[tiab] OR "cutaneous vasculitides"[tiab] OR "cutaneous allergic vasculitis"[tiab] OR "cutaneous allergic vasculitides"[tiab] OR "cutaneous leukocytoclastic vasculitis"[tiab] OR "cutaneous leukocytoclastic vasculitides"[tiab] OR "lymphocytic vasculitis"[tiab] OR "lymphocytic vasculitides"[tiab] OR "urticarial vasculitis"[tiab] OR "urticarial vasculitides"[tiab] OR "hypersensitivity vasculitis"[tiab] OR "hypersensitivity vasculitides"[tiab] OR "hypersensitivity angiitis"[tiab] OR "hypersensitivity angiitides"[tiab] OR "cutaneous angiitis"[tiab] OR "cutaneous angiitides"[tiab] OR "cutaneous allergic angiitis"[tiab] OR "cutaneous allergic angiitides"[tiab] OR "cutaneous leukocytoclastic angiitis"[tiab] OR "cutaneous leukocytoclastic angiitides"[tiab] OR "cutaneous small vessel vasculitis"[tiab] OR "cutaneous small vessel vasculitides"[tiab] OR "Acute hemorrhagic oedema of infancy"[tiab] OR "Acute hemorrhagic edema of infancy"[tiab] OR "Finkelstein's disease"[tiab])

These terms were searched in combination with the following: ("Incidence"[Mesh:noexp] OR "incidence"[tiab] OR "Epidemiology"[Mesh:noexp] OR "epidemiology"[tiab])

Included articles had to meet the following criteria:

1. Original research/meta-analysis
2. Population-based study (selecting the entire population or using probability-based sampling methods)
3. Reported an incidence estimate (or raw numbers that allowed the calculation of an estimate).
4. English language
5. Published between 1900 and Oct 25, 2023 when the search was run.

If multiple articles reported data from the same study population, the most comprehensive data were used. When studies reported on different data collection years or subgroups (sex, age), efforts to include all non-overlapping data were made. Age, sex, study location, sources of ascertainment, and definitions/diagnostic criteria for SOCV were extracted. SOCV incidence estimates, raw numbers, and confidence intervals (CIs) (when provided) were recorded along with any stratified results by age, sex, or year of data collection.

Articles were screened by a single medical reviewer (BL). Screened in articles were then reviewed independently by an additional reviewer (MRV) who then abstracted relevant data for inclusion in the background rate table.⁷⁻¹⁰ The [spreadsheet with all extracted background incidence data](#) is available on the Brighton Collaboration website.

6.3. Single Organ Cutaneous Vasculitis Risk Factors ^{1, 11-97}

A risk factor is “an exposure, behavior, or attribute that, if present and active, clearly alters the occurrence of a particular disease compared with an otherwise similar group of people who lack the risk factor”. According to James Last dictionary of epidemiology version 4, a risk factor is an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiologic evidence, is known to be associated with health-related condition(s) considered important to prevent. The term risk factor is rather loosely used, with any of the following meanings:

1. An attribute or exposure that is associated with an increased probability of a specified outcome, such as the occurrence of a disease. Not necessarily a causal factor. A RISK MARKER.

2. An attribute or exposure that increases the probability of occurrence of disease or another specified outcome. A DETERMINANT.
3. A determinant that can be modified by intervention, thereby reducing the probability of occurrence of disease or other specified outcomes. To avoid confusion, it may be referred to as a modifiable risk factor.

Risk factors can include infection, medication, diet, surgical or medical procedure, environmental location, stress, toxins, trauma and vaccine. Attribute includes genetic makeup, age, gender, ethnicity, social status, occupation. Behavior includes smoking, drinking, other substance abuse, sexual practices, level of physical activity. A standard tabular format, as shown in the appendices was used to summarize the key known risk factors for each AESI. Risk factors are only included if there is evidence for an association with the AESI.

The published Brighton Case definition for SOCV¹ was reviewed for evidence related to associated risk factors.

In addition, a new literature search was conducted using the strategy shown below to identify new articles published after the search end date as done for the published Brighton case definition.

The same synonym terms for SOCV as presented in 6.2 above were used for risk factors. These were combined with terms relative to vaccines as follows:

("Vaccines"[Mesh] OR "vaccine"[tiab] OR "vaccines"[tiab] OR "vaccination"[Mesh] OR "vaccination"[tiab] OR "vaccinations"[tiab] OR "vaccinate"[tiab] OR "vaccinated"[tiab] OR "immunization"[mesh] OR "immunization"[tiab] OR "immunizations"[tiab] OR "immunisation"[tiab] OR "immunisations"[tiab] OR "immunize"[tiab] OR "immunized"[tiab] OR "immunise"[tiab] OR "immunised"[tiab])

Included articles had to meet the following criteria:

1. Observational study or clinical trial or case series or case report or causality assessment or review or meta-analysis or protocol or letter to the editor (case reports only).
2. English language
3. Published between 1900 and Oct 25, 2023 when the search was run.
4. Case reports of cutaneous vasculitis following vaccination were excluded if no skin biopsy was done or if there was evidence of a systemic process involving organs other than the skin. Results of the skin biopsy had to be described and to be consistent with small vessel cutaneous vasculitis as defined in the SOCV case definition.

Articles were screened by a single medical reviewer (BL). Citations of all included articles were also searched for any relevant publications not captured by the literature search.

In addition, 4 systematic reviews of the evidence for vaccine causing several AESIs were reviewed to see if there was any discussion of cutaneous vasculitis. Three had been used for previous Companion Guides³²⁻³⁴, and the fourth was the National Academy of Medical Sciences review of events associated with COVID-19 vaccines.³⁵

6.4. Single Organ Cutaneous Vasculitis Case Definition¹ key caveats for diagnosis, data analysis and presentation

The published Brighton case definition for Single Organ Cutaneous Vasculitis¹ was reviewed and key aspects identified relevant to real time assessment of SOCV in the context of a clinical trial where it occurs as an AEFI. In addition, the guideline section of the published SOCV case definition was reviewed, and key recommendations identified for data collection, analysis and presentation specific to the adverse event reproduced or summarized.

6.5. Data Abstraction & Interpretation Form, Tabular Checklist and Algorithms for Level of Certainty Determination

The Brighton Collaboration case definition for Single Organ Cutaneous Vasculitis¹ (SOCV) was thoroughly and repeatedly reviewed by one individual (Barbara Law) to identify all clinical, laboratory and other criteria (e.g., temporal course of disease) used to define case definition level of diagnostic certainty.

A data abstraction form was developed to capture information relevant to the SOCV case definition criteria. The form uses a standard format developed to ensure harmonized approaches between paper forms (as here in the Companion Guide) and digital forms used online. The questions in the form are designed to enable one of three possible answers:

- **'YES'** means there was written or verbal evidence that the criterion was present.
- **'NO'** means there was written or verbal evidence that the criterion was absent or not present.
- **'UNKNOWN'** means there was uncertainty in interpreting whether the criterion was present or absent OR nothing was documented about the criterion

Step 1 involves completing the data abstraction form. Most of the criteria used to determine Level of diagnostic Certainty (LOC) are determined by the evidence provided in Step 1. However, for some criteria further manipulation of the data entered in Step 1 is needed to define one or more specific criteria. This is done in Step 2. A small summary table of all the final criterion values from the first two steps is done as Step 3. Step 4 involves a tabular algorithm that uses the values of the Case Definition Criteria (YES, NO or UNKNOWN) to determine the highest achievable LOC with Level 1 being the highest, most specific level (Definite Case). A one-page pictorial algorithm is created to show the stepwise pathway to each defined LOC based on the criterion values. This algorithm is designed for use as a stand-alone tool for LOC calculation since in addition to the pathway it also provides defines the data needed for each criterion.

A glossary of terms relevant to the case definition criteria was developed based initially on the published case definition. Where possible, the term definition was taken directly from the published case definition (often from the footnotes provided within each published case definition). If there was no definition in the Brighton publication, then an on-line search was done to obtain definitions based on available medical dictionaries or other on-line resources. The glossary is provided for use by data-abstractors without a medical background.