EVENT DEFINITION FORM

Event: COVID-19 & Enhanced disease
Outcome/covariate: Outcome
Version: 1
Status: final

Contributing authors

authors	Role	Date
Philippine van Wijngaarden	Medical/drafting v0.1	24/06/2020
Miriam Sturkenboom	Review & adding draft BC definition	
Leila Belbachir	Medical review	August 22, 2020
Caitlin Dodd	Addition of code list and algorithm proposal	03-09-2020
Miriam Sturkenboom	Inclusion of codes used in Final report ACCESS	23-08-2021
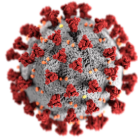
1. Event definition

Vaccine mediated disease enhancement is characterized by a vaccine that results in increased disease severity if the subject is alter infected by the natural virus.[1]

NOTE: A Brighton Collaboration definition is currently under review the text below is directly obtained from the draft document[2]. Once the guidance is published (early Sept) on the Brighton Collaboration website it will be altered
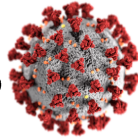
The potential for vaccination against SARS-CoV-2 to be associated with disease enhancement is of theoretical concern, given similar observations with other respiratory viruses in general and in animal models of highly pathogenic coronaviruses in particular

Given the broad spectrum of disease associated with SARS-CoV-2, clinical assessment of both systemic vaccine-associated enhanced disease (VAED), and organ specific vaccine-associated enhanced respiratory disease (VAERD) will be necessary during the pre-licensure evaluation of candidate vaccines and after the implementation of vaccination for COVID-19. The broad spectrum of disease manifestations makes it very difficult, if not impossible, to determine how severe COVID-19 infection would have been in the absence of vaccination in the individual case. Someone who might have been completely asymptomatic without prior vaccination but who develops mild respiratory symptoms because of prior vaccination could logically be considered a case of VAERD. However, this end of the spectrum of possible VAERD would have very little clinical significance at the level of the individual. At the population level however, even a small shift in the spectrum of disease towards greater severity could have major clinical and societal impact. Because more severe illness will be far easier to detect and characterize, the case definitions discussed herein will focus exclusively on more severe possible manifestations of VAED and VAERD.

There is no uniformly accepted definition of VAED or VAERD. Frequently used related terms include "vaccine-induced enhancement of infection", "vaccine-mediated enhanced disease", "disease enhancement", "immune enhancement", and "antibody dependent enhancement (ADE)". This is potentially confusing as the mechanisms for disease enhancement may vary, and data comparability across trials or surveillance systems utilizing a consistent case definition would facilitate data interpretation and promote the scientific understanding of this potential event. This is particularly important for SARS-CoV-2, given the urgent need for safe and effective vaccines for the world's population.

Vaccine-associated enhanced disease (VAED)
   a. Is an illness that occurs in persons who receive a vaccine and who are subsequently infected with the pathogen that the vaccine is meant to protect against. This definition assumes previously antigen-naïve vaccine recipients, which can be assessed by determining seronegative status prior to vaccination, when feasible. The need for documentation of sero-negativity prior to vaccination, which can be done retrospectively, is particularly relevant in Phase II-III clinical trials. In the

context of such trials, the Working Group acknowledged the difficulty in distinguishing between vaccine failure and VAED. Thus, all cases of vaccine failure should be evaluated for VAED.

b. VAED may present as severe disease or modified/unusual clinical manifestations of a known disease presentation. The illness presumably is more severe or has characteristics that distinguish it from illness that might occur in unvaccinated individuals.

c. VAED may involve one or multiple organ systems (lungs, heart/cardiovascular, liver, kidney, hematopoietic system, central nervous system, musculoskeletal system, skin (e.g. rash)

d. VAED may also present as an increased incidence of COVID-19 disease in vaccinees compared to controls or known background rates.

Vaccine-associated enhanced respiratory disease (VAERD)

a. Refers to the predominant lower respiratory tract presentation of vaccine-associated enhanced disease. The mechanisms of pathogenesis might be specific to the lower respiratory tract or part of a systemic process.

Approach for identification of cases of VAED or VAERD

Potential cases may be initially identified though the assessment of clinical characteristics alone or complemented with laboratory evaluation. In the context of vaccine clinical trials, the routine collection of adverse events (AE), serious adverse events (SAE), and adverse events of special interest (AESI) is an existing mechanism to evaluate the occurrence of illnesses and outcomes that are serious, including those that are new, require medical care, result in disability, are life threatening or result in hospitalization or death. Similarly, AE are evaluated for severity, using existing tools, such as severity grading scales and toxicity tables for clinical and laboratory outcomes that are adapted to various populations including adults, children and pregnant women. [See : DAIDS Toxicity tables https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf] The working group concurs that these methods of assessment of events occurring after vaccination are appropriate to be able to identify potential cases of VAED or VAERD.

Since this definitions was drafted, the final Brighton Collaboration definition is published[1]

2. Synonyms / lay terms for the event

- Disease enhancement
- Antibody disease enhancement
- Antibody dependent enhancement
- Disease enhancement syndrome

[1] Flor M. Munoz, Jakob P. Cramer, Cornelia L. Dekker, Matthew Z. Dudley, Barney S. Graham, Marc Gurwith, Barbara Law, Stanley Perlman, Fernando P. Polack, Jonathan M. Spergel, Eva Van Braeckel, Brian J. Ward, Arnaud M. Didierlaurent, Paul Henri Lambert
Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data Vaccine, Volume 39, Issue 22, 21 May 2021, Pages 3053-3066
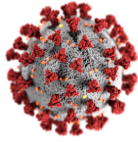
- Immunce enhancement
- Vaccination induced antibody dependent enhancement of disease
- Excacerbated illness
- Enhanced illness following immunization
- Enhanced illness following vaccination
- Vaccine induced disease enhancement
- Vaccine mediated disease enhancement

3. Laboratory tests that are specific for event

As per the draft Brighton Collaboration definition [2] there are no specific clinical diagnostic laboratory tests for this event because there are only existing animal models of COVID-19. There have been an CEPI/BC meeting about the assessment of risk of disease enhancement with COVID-19 vaccines where it discusses some potential markers [1]:

Gross pathology demonstrated swollen and enlarged lungs with moderate interstitial pneumonia. Histological studies documented an accumulation of inflammatory cells including monocytes and lymphocytes in alveolar interstitium, with thickening of alveolar walls. SARS-CoV-2 S protein was detected by IHC in alveolar macrophages and epithelia

Potential markers of safety in these animal models could include:
- The relative levels of neutralizing vs non-neutralizing antibodies
- Antibody affinity
- T-cell response profile
- Quantitative virology in the upper and lower respiratory tract
- Characterization of lung histopathology with immunohistochemistry of viral antigen and immune cell makers
- Passive transfer in NHPs of human antibodies generated during Phase 1 trials, followd by viral challenge could be considered to asses the risk of disease enhancement
- Challenge of immunized animals with a closely related heterologous CoV strains may asses the risk of enhancement during future outbreaks
- In case of disease enhancement, in-depth studies in animal models may give some indications on the mechanism of immunopathology. They can inform human trial designers on the critical immunological risk markers to be monitored in phase 1 trials
- Based on previous experience with SARS and other viral diseases, it may be useful to evaluate the risk of disease enhancement for COVID-19 vaccines (particularly those including whole virions or N protein) in an established NHP model before advanced clinical development.
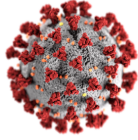
Regarding Phase 1 clinical trials:

- Level of neutralizing antibodies and determination of the relative ratio of binding to neutralizing antibodies will be important to assess the potential risk of enhanced disease. Also, detection of initial priming that includes CD8 T cells and/or a CD4 Th1 biased response is likely to mitigate the risk of disease enhancement. Determination of memory responses will be useful, particularly if SARS-CoV-2 continues to circulate.

Table: Suggested laboratory evaluation for the assessment of VAED/VAERD as per draft BC definition [2]

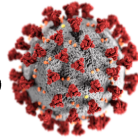| PARAMETER	LABORATORY FINDINGS SUGGESTIVE OF VAED/VAERD
Evidence inadequate or unbalanced neutralizing antibody responses	- Low or inappropriate total binding (IgG, IgM, IgA) antibody titers - Low neutralizing antibody titers - Low ratio of neutralizing to binding antibody - Low absolute affinity of IgG antibody to receptor binding domain (RBD) - Lack of acquisition or loss of affinity of IgG to RBD - Increased viral load
Evidence of inadequate or inappropriately biased cellular immune responses	- Lymphopenia or lymphocytosis - High CD4 lymphocyte subset - Low CD8 lymphocyte subset - Th2 (IL-4, IL-5, IL-13) CD4 T cell predominant response over Th1 (INFg, TNF) responses (testing in vitro stimulation with viral peptides or proteins, ELISPOT, or intracellular cytokine staining assays). - Low virus-specific cytotoxic T-cells (CTL)
Evidence of exuberant inflammatory responses	- Elevated IL-1, IL-6, IL-8 - Increased pro-inflammatory chemo/cytokines: INF-g, type 1-INF, TNF, CCL2, CCL7 - Reduced expression of type I interferons (eg. IFN-⟨, INF-b) - Elevated C-reactive protein, Ferritin, Lactate dehydrogenase (LDH), D-dimers
Evidence of immunopathology in target organs involved, by histopathology	- Present or elevated tissue eosinophils in tissue - Elevated pro-inflammatory Th2 cytokines in tissue (IL4, IL5, IL10, IL13) - C4d tissue deposition (evidence for complement activation through immune complex deposition) - C1q assessments of immune complexes in fluids - Low C3 levels as evidence complement consumption
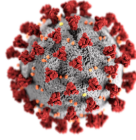
4. Diagnostic tests that are specific for event

There is no specific clinical diagnostic test for this event. The Brighton Collaboration draft definition recommends:

Table Assessment for VAED in the context of vaccine development: relevant clinical and laboratory diagnostic parameters [2].

ORGAN SYSTEM	CLINICAL PARAMETERS	LABORATORY PARAMETERS
Respiratory system	- Cough - Tachypnea - Dyspnea - Lower respiratory tract disease - Respiratory failure - Pulmonary hemorrhage - Radiographic abnormalities	- Oxygen requirement - Hypoxemia - PaO2 - PaO2/FiO2 ratio - Aa gradient
Cardiovascular system	- Tachycardia - Hypotension/ Hypertension - Acute cardiac injury - Vasculitis/ Vasculopathy - Myocarditis - Heart failure - Cardiogenic shock	- Abnormal ECG - Abnormal Echocardiogram - Troponin - B-Natriuretic Peptide (BNP)
Hematopoietic and Immune system	- Coagulopathy - Disseminated intravascular coagulation - Bleeding/ Thrombotic events	- Leukopenia, lymphopenia - Thrombocytopenia - B and T cell function assays - Altered coagulation parameters (PT, PTT, D-Dimer, INR)
Inflammatory markers	Pro-inflammatory state	- Elevated inflammatory markers (CRP, procalcitonin) - Elevated Ferritin, LDH - Elevated cytokines
Renal system	- Renal dysfunction - Acute kidney injury - Renal replacement therapy	- Decreased urine output - Serum creatinine - Glomerular filtration rate
Gastrointestinal and hepatic system	- Emesis/Diarrhea - Abdominal pain - Hematochezia/Melena - Hepatitis - Liver dysfunction - Acute liver failure	- Electrolyte abnormalities - Elevation of liver enzymes - Elevated bilirubin

Central Nervous System	• Altered mental status • Convulsions/seizures • Cranial nerve involvement • Unconsciousness	• Elevated intracranial pressure • Abnormal CSF parameters
Other	• Fatigue • Myalgia/myositis/myonecrosis • Arthralgia/arthritis • Multiorgan failure • Death	• Viral load (PCR Ct value) • Antibody titers • Histopathology

5. Drugs that are used to treat event

Immunosuppressive therapy: dexamethasone, remdesivir, anticoagulants

6. Procedures used specific for event treatment

Mechanical ventilation

7. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

Outpatient for mild severity, in-hospital for serious disease

8. Diagnosis codes or algorithms used in different papers to extract the events in Europe/USA: seek literature for papers that have studied this event, and see how they extracted/measured the event.

WHO guidance
New ICD-10 codes for COVID-19:
- U07.1 COVID-19, virus identified
- U07.2 COVID-19, virus not identified
o Clinically-epidemiologically diagnosed COVID-19
▪ Probable COVID-19 ▪ Suspected COVID-19
Details of the updates to ICD-10 are available online at:

9. Experience of participating data sources in extracting the events prior to ACCESS (to be completed by each data source, if no experience please state NA)
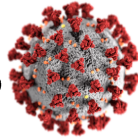
Will be completed during project
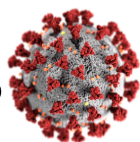
10. Proposed codes to build algorithms for case finding

COVID disease as codes, we also include specific COVID-19 testing /diagnosis registers
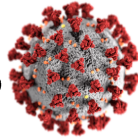
Coding system	Code	Code name	Concept	Concept name	Algorithm
ICD10CM	B34.2	Coronavirus infection, unspecified	C0206750	Coronavirus Infections	Narrow
ICD10CM	**U07.1**	**COVID-19, virus identified**			Narrow
ICD10CM	U07.2	COVID-19, virus not identified			Possible
ICD10CM	U071.1	COVID-19, forme respiratoire, virus non identifié			Possible
ICD10CM	U071.2	COVID-19, porteur de SARS-CoV-2 asymptomatique, virus identifié			Narrow
ICD10CM	U071.4	COVID-19, autres formes cliniques, virus identifié			Narrow
ICD10CM	U071.5	COVID-19, autres formes cliniques, virus non identifié			Possible
ICD9CM	078.89	Other specified diseases due to viruses	C0859831	Other specified diseases due to viruses	Possible
RCD2	1JX..00	Suspected coronavirus infection		Covid	possible
RCD2	1JX1.00	Suspected disease caused by 2019-nCoV (novel coronavirus)		Covid	possible
ICPC	R83.03	SARS-Cov-2			narrow
RCD2	**4J3R100**	**2019-nCoV (novel coronavirus) detected**		**Covid**	narrow
RCD2	65PW.00	Coronavirus contact		Covid	possible
RCD2	9N31200	Telephone consultation for suspected 2019-nCoV (novel coronavirus)		Covid	possible
RCD2	65PW100	Exposure to 2019-nCoV (novel coronavirus) infection		Covid	possible
RCD2	A795.	Coronavirus infection	C0206750	Coronavirus Infections	Narrow
RCD2	**A795.00**	**Coronavirus infection**		**Covid**	narrow
RCD2	**A795100**	**Disease caused by 2019-nCoV (novel coronavirus)**		**Covid**	narrow
RCD2	A7y00	Coronavir caus dis clas oth ch	C0348984	Coronavirus as the cause of diseases classified to other chapters	Narrow
RCD2	**A7y0000**	**Coronavirus as cause of dis classified to other chapters**		**Covid**	narrow
RCD2	AyuDC	[X]Coronavirus infection,unspc	C0206750	Coronavirus Infections	Narrow
RCD2	AyuDC00	[X]Coronavirus infection, unspecified		Covid	narrow
RCD2	**AyuKL00**	**Covid**		**Covid**	narrow
SCTSPA	88711001	coronavirus	C0206419	Genus: Coronavirus	Narrow
SCTSPA	186747009	infección por coronavirus	C0206750	Coronavirus Infections	Narrow
SCTSPA	186758000	Coronavirus como causa de enfermedades clasificadas en otros capítulos	C0348984	Coronavirus as the cause of diseases classified to other chapters	Narrow
SCTSPA	187467005	[X]infección por coronavirus, no especificada	C0206750	Coronavirus Infections	Narrow
SCTSPA	187587009	Coronavirus as the cause of diseases classified to other chapters	C0348984	Coronavirus as the cause of diseases classified to other chapters	Narrow
SCTSPA	243608008	Coronavirus	C0206419	Genus: Coronavirus	Narrow
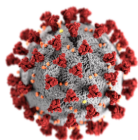
| SCTSPA	700217006	sospecha de infección por coronavirus	C3838696	Suspected coronavirus infection	Possible
SNOMEDCT_US	88711001	Coronavirus	C0206419	Genus: Coronavirus	Narrow
SNOMEDCT_US	186747009	Coronavirus infection	C0206750	Coronavirus Infections	Narrow
SNOMEDCT_US	186758000	Coronavirus as the cause of diseases classified to other chapters	C0348984	Coronavirus as the cause of diseases classified to other chapters	Narrow
SNOMEDCT_US	187467005	[X]Coronavirus infection, unspecified	C0206750	Coronavirus Infections	Narrow
SNOMEDCT_US	187587009	Coronavirus as the cause of diseases classified to other chapters	C0348984	Coronavirus as the cause of diseases classified to other chapters	Narrow
SNOMEDCT_US	243608008	Coronavirus	C0206419	Genus: Coronavirus	Narrow
SNOMEDCT_US	700217006	Suspected coronavirus infection	C3838696	Suspected coronavirus infection	Possible
SNOMEDCT_US	3902339012	2019 Novel Coronavirus			narrow
SNOMEDCT_US	2808671000000110	2019 Novel Coronavirus			narrow
SNOMEDCT_US	2808921000000110	2019 Novel Coronavirus			narrow
SNOMEDCT_US	2833751000000117	2019 Novel Coronavirus			narrow
SNOMEDCT_US	2807491000000115	2019 Novel Coronavirus			narrow
SNOMEDCT_US	2832021000000110	2019 nCOv positive			narrow
SNOMEDCT_US	2808081000000112	2019 nCOv positive			narrow
SNOMEDCT_US	2837991000000116	2019 nCOv positive			narrow
SNOMEDCT_US	2839411000000114	Acute COVID-19 infection			narrow
SNOMEDCT_US	3951290018	Acute bronchitis caused by 2019 novel coronavirus			narrow
SNOMEDCT_US	2838061000000112	Acute bronchitis caused by 2019-nCoV (novel coronavirus)			narrow
SNOMEDCT_US	2838051000000114	Acute bronchitis caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)			narrow
SNOMEDCT_US	3970767016	Acute hypoxemic respiratory failure due to disease caused by 2019 novel coronavirus			narrow
SNOMEDCT_US	2838141000000112	Acute hypoxemic respiratory failure due to disease caused by 2019-nCoV (novel coronavirus)			narrow
SNOMEDCT_US	2838131000000115	Acute hypoxemic respiratory failure due to disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)			narrow
SNOMEDCT_US	3970764011	Acute kidney injury due to disease caused by 2019 novel coronavirus			narrow
SNOMEDCT_US	2838161000000113	Acute kidney injury due to disease caused by 2019-nCoV (novel coronavirus)			narrow
SNOMEDCT_US	2838151000000110	Acute kidney injury due to disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)			narrow
SNOMEDCT_US	3970620012	Acute respiratory distress syndrome due to disease caused by 2019 novel coronavirus			narrow

SNOMEDCT_US	28381810000 00116	Acute respiratory distress syndrome due to disease caused by 2019-nCoV (novel coronavirus)			narrow
SNOMEDCT_US	28381710000 00118	Acute respiratory distress syndrome due to disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)			narrow
SNOMEDCT_US	28080810000 00112	2019-nCoV (novel coronavirus) detected			narrow
SNOMEDCT_US	28379910000 00116	2019-nCoV (novel coronavirus) detection result positive at the limit of detection			narrow
SNOMEDCT_US	28280710000 00119	2019-nCoV (novel coronavirus) qualitative existence in specimen			narrow
SNOMEDCT_US	28371210000 00116	2019-nCoV (novel coronavirus) ribonucleic acid detected			narrow
SNOMEDCT_US	28394110000 00114	Acute COVID-19 infection			narrow
SNOMEDCT_US	3951290018	Acute bronchitis caused by 2019 novel coronavirus			narrow
SNOMEDCT_US	28380610000 00112	Acute bronchitis caused by 2019-nCoV (novel coronavirus)			narrow
SNOMEDCT_US	28380510000 00114	Acute bronchitis caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)			narrow
SNOMEDCT_US	3970767016	Acute hypoxemic respiratory failure due to disease caused by 2019 novel coronavirus			narrow
SNOMEDCT_US	28381410000 00112	Acute hypoxemic respiratory failure due to disease caused by 2019-nCoV (novel coronavirus)			narrow
SNOMEDCT_US	28381310000 00115	Acute hypoxemic respiratory failure due to disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)			narrow
SNOMEDCT_US	3970764011	Acute kidney injury due to disease caused by 2019 novel coronavirus			narrow
SNOMEDCT_US	28381610000 00113	Acute kidney injury due to disease caused by 2019-nCoV (novel coronavirus)			narrow
SNOMEDCT_US	28381510000 00110	Acute kidney injury due to disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)			narrow
SNOMEDCT_US	3970620012	Acute respiratory distress syndrome due to disease caused by 2019 novel coronavirus			narrow
SNOMEDCT_US	28381810000 00116	Acute respiratory distress syndrome due to disease caused by 2019-nCoV (novel coronavirus)			narrow
SNOMEDCT_US	28381710000 00118	Acute respiratory distress syndrome due to disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)			narrow
SNOMEDCT_US	28380810000 00115	Asymptomatic 2019-nCoV (novel coronavirus) infection			narrow
SNOMEDCT_US	3947183016	**Disease caused by severe acute respiratory syndrome coronavirus 2 (disorder)**			narrow

|					
SNOMEDCT_US	3947184010	Disease caused by severe acute respiratory syndrome coronavirus 2			narrow
SNOMEDCT_US	3947185011	COVID-19			narrow
SNOMEDCT_US	3947186012	**Exposure to severe acute respiratory syndrome coronavirus 2 (event)**			narrow
SNOMEDCT_US	3947189017	**Severe acute respiratory syndrome coronavirus 2 (organism)**			narrow
SNOMEDCT_US	3947191013	Severe acute respiratory syndrome coronavirus 2			narrow
SNOMEDCT_US	3947190014	SARS-CoV-2			narrow
SNOMEDCT_US	840539006	Disease caused by severe acute respiratory syndrome coronavirus 2 (disorder)			narrow
SCTSPA	292508471000119105	History of disease caused by Severe acute respiratory syndrome coronavirus 2 (situation)			narrow
SCTSPA	840546002	Exposure to 2019 novel coronavirus (event)			possible
SCTSPA	63211000122105	Patient has had recent contact with case of COVID-19 (finding)			possible
SCTSPA	700217006	Suspected coronavirus infection (situation)			possible
SCTSPA	840544004	Suspected disease caused by 2019 novel coronavirus (situation)			possible
SCTSPA	702547000	Exposure to coronavirus infection (event)			possible
SCTSPA	66301000122106	High clinical suspicion of COVID-19: present (situation)			possible
SCTSPA	64821000122100	Result of PCR test for SARS-CoV-2: inconclusive (finding)			possible
SCTSPA	399150003	Polymerase chain reaction test for SARS (procedure)			possible
SCTSPA	62791000122101	Isolation of person who has had contact with case of COVID-19 infection (procedure)			possible
SCTSPA	63251000122106	Health center as place of recent contact with case of COVID-19 (environment)			possible
SCTSPA	186747009	Coronavirus infection (disorder)			narrow
SCTSPA	63681000122103	Diagnosis of COVID-19 infection confirmed by laboratory testing (disorder)			narrow
SCTSPA	882784691000119100	Pneumonia caused by Severe acute respiratory syndrome coronavirus 2 (disorder)			narrow
SCTSPA	63711000122102	Test result of antibodies against SARS-CoV-2: IgM negative and IgG positive (finding)			narrow
SCTSPA	63901000122102	Patient cured after COVID-19 infection (finding)			narrow
SCTSPA	64121000122109	Procedure for action related to case of disease due to SARS-CoV-2 (procedure)			narrow
SCTSPA	27619001	Disease due to Coronaviridae (disorder)			narrow
SCTSPA	62531000122108	Polymerase chain reaction positive for severe acute			narrow
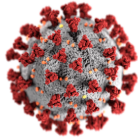
		respiratory syndrome coronavirus 2 (finding)			
SCTSPA	871552002	Detection of Severe acute respiratory syndrome coronavirus 2 antibody (observable entity)			narrow
SCTSPA	63511000122 107	Outcome: case of COVID-19 still under follow-up (finding)			narrow
SCTSPA	64731000122 108	SARS-CoV-2 antigen testing positive (finding)			narrow
SCTSPA	64671000122 103	Testing positive for IgG against SARS-CoV-2 (finding)			narrow
SCTSPA	871553007	Detection of Severe acute respiratory syndrome coronavirus 2 antigen (observable entity)			narrow
SCTSPA	63621000122 102	Positive result of rapid test for detection of IgM and IgG antibodies against SARS-CoV-2 in blood (finding)			narrow
SCTSPA	871562009	Detection of Severe acute respiratory syndrome coronavirus 2 (observable entity)			narrow
SCTSPA	65081000122 106	Fatigue syndrome after COVID-19 (finding)			narrow
SCTSPA	65071000122 108	Sequel of COVID-19 (finding)			narrow
SCTSPA	1119304009	Chronic post-COVID-19 syndrome (disorder)			narrow
SCTSPA	62951000122 108	Positive serologic study for COVID-19 (finding)			narrow
SCTSPA	64031000122 106	Secondary triage for severity level in patient with disease due to SARS-CoV-2 (procedure)			narrow
SCTSPA	18948624100 0119100	Asymptomatic Severe acute respiratory syndrome coronavirus 2 infection (finding)			narrow

11.   Algorithm proposal

<u>Broad Algorithm for background rates (in the absence of vaccine):</u>
Codes including possible and narrow

<u>Narrow Algorithm for background rates (in the absence of vaccine):</u>
<u>Conditions</u>
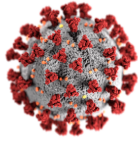
12.   References

1. Lambert PH, Ambrosino DM, Andersen SR, et al. Consensus summary report for CEPI/BC March 12-13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines. *Vaccine*. 2020;38(31):4783-4791. doi:10.1016/j.vaccine.2020.05.064

Draft BC Definition
2. Munoz F et al. Vaccine-associated Enhanced Disease: Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data

3. Final Brighton Collaboration definition
Flor M. Munoz, Jakob P. Cramer, Cornelia L. Dekker, Matthew Z. Dudley, Barney S. Graham, Marc Gurwith, Barbara Law, Stanley Perlman, Fernando P. Polack, Jonathan M. Spergel, Eva Van Braeckel, Brian J. Ward, Arnaud M. Didierlaurent, Paul Henri Lambert
Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data Vaccine, Volume 39, Issue 22, 21 May 2021, Pages 3053-3066