Safety Platform for Emergency vACcines

D2.3 Priority List of Adverse Events of Special Interest: COVID-19

Work Package: WP2 Standards and tools

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TABLE OF CONTENTS

1. Background

To maximize the value of vaccine safety data in clinical trials given their relatively limited sample size, it is essential to standardize their collection, presentation and analysis when possible.

Given serious adverse events following immunization (AEFIs) are fortuitously rare, this need for globally accepted standard case definitions that allow for valid comparisons extend to individual case reports, surveillance systems, and retrospective epidemiologic studies.

This need for standardization was recognized by Dr. RobertChen at a vaccine conference in Brighton, England in 1999. Harald Heijbel, Ulrich Heininger, Tom Jefferson, and Elisabeth Loupi joined his call one year later to launch the Brighton Collaboration as an international voluntary organization, now with more than 750 scientific experts. It aims to facilitate the development, evaluation and dissemination of high-quality information about the safety of human vaccines.[1]

The goals of the Brighton Collaboration in the domain of case definitions have been to:

1. Develop standardized case definitions for specific AEFI's
2. Prepare guidelines for their data collection, analysis and presentation for global use
3. Develop and implement study protocols for evaluation of case definitions and guidelines in clinical trials and surveillance systems.
4. Raise global awareness of their availability and to educate about their benefit, monitor their global use, and facilitate access.

Safety monitoring during clinical trials is a crucial component for vaccine development. Before a vaccine can receive regulatory approval for marketing, rigorous safety monitoring and reporting is required. In the CEPI funded vaccine development programs, the CEPI funded developers are the sponsors and responsible for safety monitoring of their products and have the responsibility to comply with regulatory requirements. Since CEPI funds several developers that develop vaccines for the same target, using different vaccines and platforms, harmonization of safety monitoring is essential to allow for meaningful analysis and interpretation of the safety profiles of CEPI funded vaccines.

CEPI has contracted with the Brighton Collaboration, 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. As part of its landscape analysis of COVID-19, this document describes the methods and results SPEAC used to arrive at the list of adverse events of special interest (AESI).

Adverse events of special interest

An adverse event following immunization (AEFI) is defined as 'any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.'[2]

'Adverse Event of Special Interest' (AESI) is further defined in Council for International Organizations of Medical Sciences (CIOMS) VII[3] as:

"An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to

the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted."

AESI can be specified in the Program Safety Analysis plan (PSAP) early in product development for safety planning, data collection, analysis and reporting on AESI data, and eventually form the base of AESI analysis in Reporting and Analysis Plan.

While the current CEPI vaccine development focus is primarily on phase 1 and 2 clinical trials, which will have very small total sample sizes (likely N < 1000), the ultimate goal is to have vaccines ready for use against emerging, epidemic diseases. Vaccine safety assessment needs therefore to be conducted 1) across the entire life cycle of vaccine development, approval and use, and 2) in a harmonized and standardized manner so that data are comparable across different trials and populations. Many if not most of the AESI identified as relevant to CEPI vaccine programs are likely to be rare events and may never occur in the context of a given trial. Nevertheless, we have to be prepared to maximize the utility of vaccine safety data in case they do occur.

To this end SPEAC has chosen to identify AESI that have been previously identified with immunization in general (e.g. anaphylaxis, Guillain Barré Syndrome) or vaccine platforms in particular (e.g., arthritis following recombinant vesicular stomatitis virus vectored vaccine). In addition, it is important to consider events that may occur during the clinical course or as a complication of the chosen target pathogen. Depending on the platform, a vaccine targeting that pathogen may induce an adverse event with a similar immunopathogenic mechanism; whether this occurs or not can only be assessed by studying this specific AESI (e.g., sensorineural hearing loss after Lassa Fever).

2. Objective of this deliverable

The primary objective is to create and provide lists of potential AESI relevant to development of COVID-19 vaccines recognizing that our understanding of this virus is not fully developed and that this document may need to be updated or changed.

The secondary objective is to harmonize their safety assessment (monitoring, investigation and analysis) by having standard case definitions, tools and informational aides, developing them as needed.

3. Methods

Methods to obtain AESI

Initially, SPEAC vaccine safety experts used their expertise and experience to identify which existing Brighton Collaboration defined adverse events were most likely to be of relevance to CEPI vaccine candidates.

Subsequently, we developed the following scoring system to characterize the nature of evidence linking a given AESI to immunization:

1. Proven association with immunization.
2. Proven association with a vaccine platform and/or adjuvant relevant to CEPI vaccine development.
3. Theoretical concern based on immunopathogenesis.
4. Theoretical concern related to viral replication during wild type disease.
5. Theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.

A given AESI could have more than one rationale. For example, convulsion could be associated with 1, 2 and 4.

It was decided for clarity to present the AESI in 3 separate tables:

1. AESI relevant to a broad range of vaccines.
2. AESI relevant to one or more specific vaccine platforms.
3. AESI relevant to a specific target disease.

One or more of these tables may be amended once the vaccine safety templates are developed for each of the CEPI vaccine platforms or should new evidence for a possible or proven vaccine safety signal be published.

The SPEAC approach to identifying AESIs associated with one of the CEPI target disease has been described in detail for Lassa Fever and MERS (see SPEAC-D2.2). It was necessary to modify this approach for COVID-19 given it only first appeared in December 2019.

Specifically, a PubMed search was performed on 26/01/20 with the terms ("china"[tw] and "coronavirus"[tw]) AND ("2019/01/01"[PDat] : "2021/01/30"[PDat]) in order to pick up all articles published since the beginning of 2019 mentioning both china and coronavirus. There were 65 results. An additional PubMed search was then performed with the terms (("Coronavirus"[Mesh] OR "coronavirus"[tw] OR "coronaviruses"[tw] OR "2019-nCoV"[tw]) AND ("2020/01/26"[PDat] : "2021/01/30"[PDat])) on 2/17/20 to pick up all articles published since the previous search. This new search was then saved and daily email alerts were set up to continuously update the group of any new articles published on the topic.

All articles providing information on the COVID-19 clinical course and complications were selected for expert review as described below.

Evaluation of literature and Decision-Making Process to Finalize List of AESI

All retrieved articles were independently reviewed by two medical experts (B Law and WT Huang). Each expert made summary notes on the target disease clinical course and complications.

Each expert then drafted a list of AESI for consideration, independently. Subsequently the lists were reviewed and discussed in order to have an agreed upon list of potential AESI for subsequent review and approval by the SPEAC executive board. Extracted data were summarized in a PowerPoint slide set.

Once developed the preliminary list of AESI was shared with CEPI.

4. Results

Table 1 lists AESIs considered potentially applicable to COVID-19 vaccines based on known association with vaccination in general. The rationale for including the AESI is further delineated in the last column of table 1.

Adverse events of special interest applicable to COVID-19 vaccines

TABLE 1. AESI RELEVANT TO VACCINATION IN GENERAL (EVENTS LISTED IN RED HAVE EXISTING BC CASE DEFINITIONS) IN THE TOOLBOX.)

BODY SYSTEM	AESI TYPE	RATIONALE FOR INCLUSION AS AN AESI (SEE FOOTNOTE)
Neurologic	Generalized convulsion	1, 2, 4
	Guillain-Barré Syndrome (GBS)	2
	Acute disseminated encephalomyelitis (ADEM)	3
Hematologic	Thrombocytopenia	1, 2
Immunologic	Anaphylaxis	1, 2
	Vasculitides	3, 4
Other	Serious local/systemic AEFI	1, 2

1. Proven association with immunization encompassing several different vaccines
2. Proven association with vaccine that could theoretically be true for CEPI vaccines under development
3. Theoretical concern based on immunopathogenesis.
4. Theoretical concern related to viral replication during wild type disease.
5. Theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.

Table 2 focuses on AESIs relevant to particular vaccine platforms that are being considered in the COVID-19 vaccine development programs.

TABLE 2. AESI RELEVANT TO SPECIFIC VACCINE PLATFORMS FOR COVID-19 VACCINES

BODY SYSTEM	VACCINE PLATFORM SPECIFIC AESIS	KNOWN/POSSIBLE ASSOCIATION WITH
Neurologic	Aseptic meningitis Encephalitis / Encephalomyelitis	Live viral vaccines including measles
Immunologic	Arthritis	r-VSV platform
Other	Myocarditis	MVA platform

AESIs Related to Specific Target Disease of COVID-19

Five articles on the clinical picture and epidemiology of COVID-19 were available for inclusion in the review for relevant AESIs.[5-9] Given the emerging nature of the epidemic in China and elsewhere, this list must be considered preliminary. As new information becomes available it will be updated as frequently as necessary.

The AESI identified for COVID-19 are shown in Table 3 along with the respective specific rationales for their inclusion.

TABLE 3. AESI RELEVANT TO COVID-19

BODY SYSTEM	COVID-19	RATIONALE FOR INCLUSION AS AN AESI (SEE FOOTNOTE)

Respiratory	Acute respiratory distress syndrome (ARDS)	3, 4
	Pneumonitis	3, 4
Immunologic	Enhanced disease following immunization	1 (formalin-inactivated measles/RSV vaccines; HIV vaccine), 2 (Chimeric Yellow Fever Dengue vaccine), 5 (mouse models SARS/MERS-CoVs)
Other	Acute cardiac injury	3, 4
	Arrhythmia	3, 4
	Septic shock-like syndrome	3, 4
	Acute kidney injury	3, 4

[1]Reasons for including listed events as AESI (in order of highest priority)

3. Theoretical concern based on immunopathogenesis
4. Theoretical concern related to viral replication during wild type disease.

While the tables above are the main output for this deliverable, all papers used for each Landscape Analysis will be available in the SPEAC toolbox along with a tabular summary and teaching PowerPoint slide set for each target disease.

5. Recommendations & discussion

SPEAC recommends CEPI and the COVID-19 vaccine developers adopt the list of AESI. SPEAC further recommends that the developers take a uniform approach to the identification, assessment, investigation, analysis and reporting of any AESI should it occur during a clinical trial.

Many of the AESI for COVID-19 vaccines have published BC case definitions available.

A working group is being put together on an urgent basis to develop a case definition for enhanced disease following immunization with a target to have a first draft before the end of Q2 2020.

BC case definitions are not yet developed for arthritis, myocarditis, acute respiratory distress syndrome (ARDS), pneumonitis, acute cardiac or kidney injury, arrhythmia or septic shock-like syndrome.

SPEAC will develop an action plan for each prioritized AESI, in concert with CEPI & vaccine developers to identify specific approaches vis-a-vis planned clinical trials. These could include one or more of:

1. Prioritize development of new Brighton Case Definitions for those AESI that do not yet have one.
2. Prepare tools (tabular checklists and decision trees) that will facilitate standard, harmonized application of Brighton CDs
3. Conduct systematic literature reviews to describe background rates within the target populations.
4. Work with developers to modify or map existing Case Report Forms (CRF)/outcome definitions or draft new ones if desired to achieve, to the extent possible, harmonized and standardized approaches to each AESI.

6. References

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DOCUMENT INFORMATION

Master Service Agreement		Service order	1
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CEPI Project Lead	Nadia Tornieporth / Jakob Cramer		
CEPI Project Manager	Brett Barnett		
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Key words	Toolbox, adverse events of special interest, guidance documents

SIMPLIFIED DOCUMENT HISTORY

NAME	DATE	VERSION	DESCRIPTION
Barbara Law, Matthew Dudley, Wan-Ting Huang	03/02/2020	V1.0 COVID-19	Pertinent articles retrieved, reviewed and AESI list proposed
Barbara Law, Wan-Ting Huang	23/02/2020	V1.1 COVID-19	Revision to AESI list based on Wang-JAMA 2020[8] (arrhythmia added)
Barbara Law	27/02/2020	D2.3 V1.0	Draft deliverable for COVID-19
SPEAC Executive Board	04/03/2020	D2.3 V1.1	Review