Safety Platform for Emergency vACcines

SO1-D2.0 Addendum to SO1-D2.2 & 2.3 Landscape Analyses Priority Tiers for All CEPI Vaccine Development Adverse Events of Special Interest (AESI)

Work Package: WP2 Standards and tools

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THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

DEFINITIONS & ACRONYMS

AESI	Adverse Events of Special Interest
ARDS	Acute Respiratory Distress Syndrome
CEPI	Coalition for Epidemic Preparedness Innovations
CHIKV	Chikungunya Virus
COVID-19	coronavirus disease 2019
ICD	International Classification of Diseases
E. coli	*Escherichia coli*
LF	Lassa Fever
MedRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MISC	Multisystem Inflammatory Syndrome in Children
MVA	Modified Vaccinia Ankara
NiV	Nipah Virus
RSV	Respiratory Syncitial Virus
RVF	Rift Valley Fever
rVSV	Recombinant vesicular stomatitis virus
SARS	Severe Acute Respiratory Syndrome
SPEAC	Safety Platform for Emergency Vaccines
YF	Yellow Fever

1. Background

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.

A key aspect of this harmonization has been creation of lists of priority potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI target diseases.

A key first step towards harmonization was to identify potential vaccine safety issues that could arise in clinical trials based on what has been seen with vaccines in general and certain vaccine platforms in particular. In addition, landscape analyses were done to identify wild type disease clinical course and complications which could theoretically occur following vaccination based on viral replication and/or immunopathogenesis. Landscape analyses have been completed and AESI lists developed. Detailed descriptions of the methodology and results were summarized in several documents all of which can be found within the SPEAC Toolbox for Adverse Events of Special Interest at the link below: https://speacproject.sharepoint.com/:f:/r/sites/Start/SPEAC%20DEVELOPERS/SPEAC%20DEVELOPERS/TOOLBOX/6.%20SPEAC%20Toolbox%20for%20Adverse%20Events%20of%20Special%20Interest/1_Target%20Disease%20Landscape%20Analyses%20%26%20AESI%20lists?csf=1&web=1&e=ioCKuB

SPEAC Work Package 2 has several activities related to the prioritized AESIs including:

1. Creating new Brighton Collaboration case definitions if none already exist
2. Summarizing general guidance on Brighton Collaboration standards for vaccine safety data collection, analysis and presentation as well as specific guidance on real-time investigations relevant to each AESI.
3. Creating tools to facilitate capturing the specific clinical data needed to meet AESI case definitions across a variety of settings applicable to clinical trials, epidemiologic studies and individual case causality assessment. These include:
    a. Data abstraction and interpretation forms to facilitate capturing data from medical charts and applying it to determine a given AESI case definition level of certainty.
    b. Tabular checklists that are a stand-alone tool useful for summarizing key clinical data needed to determine the level of diagnostic certainty for a given case definition.
    c. Tabular logic and pictorial decision tree algorithms, also stand-alone tools, to facilitate correct application of key clinical data to determine the level of diagnostic certainty for each AESI.
    d. Glossary of terms relevant to anaphylaxis and the neurologic AESI.
4. Providing tabular summaries of risk factors and background rates for each AESI.
5. Creating spreadsheet summaries of ICD9/10 and MedDRA codes for each AESI.

In order to guide the above work and ensure clarity as to when it will be available, prioritization of the AESIs identified to date is necessary. This document provides the rationale for the prioritization and distributes the AESIs into 4 different tiers each of which have specific designated timelines for delivering the related WP2 outputs through the end of 2021.

2. Objective of this deliverable

1. To collate all potential AESI identified to date for CEPI vaccine candidates targeting Lassa Fever, MERS, Nipah virus infection, Rift Valley Fever, Chikungunya and COVID-19.

2. To present the order and planned timelines for development of new Brighton case definitions for CEPI AESI.
3. To delineate, for each AESI tier, the scope and timelines for completion of WP2 standards and tools, including new case definitions, data collection and interpretation forms, tools to summarize key case definition criteria, algorithms for assigning case definition levels of certainty, background rates, risk factors and ICD9/10 and MedDRA codes.
4. To assign all CEPI AESI identified to date to one of the four AESI priority tiers.

3. Methods

All AESI lists for CEPI target pathogens were completed by Mar 31, 2020, but the initial COVID-19 list was significantly expanded in version 2.0 as of May 25, 2020. Following adoption of the COVID-19 V2.0, a table was created to capture all AESI identified for all target diseases in order to consider assigning priority for developing WP2 outputs.

The first decision to be made regarding AESI related to whether or not there was a need to create a Brighton Collaboration case definition for the AESI or if one already existed. From the collated list of all prioritized CEPI vaccine potential AESI, those without an existing case definition were prioritized for working group formation in order to create new case definitions. With the exception of Sensorineural Hearing Loss which was prioritized for a new case definition shortly after the SPEAC project began in March 2019, the COVID-19 list of potential AESI drove the timelines for the next 9-10 case definitions to be developed. Up to 6 additional new case definitions will be developed by December 2021 relating to non-COVID-19 CEPI target diseases. These have not all been decided as yet, but several are targeted for development as shown in the results below.

The AESIs identified to date were divided into a total of 4 Tiers (1=highest priority). The first 3 apply to all CEPI target diseases whereas the 4th includes AESI for non-COVID-19 target diseases (Lassa Fever, MERS, Nipah infection, Rift Valley Fever and Chikungunya). This was decided based on the urgent timelines for COVID-19 and the need to have tools ready as soon as possible. That said, depending on the course of the Pandemic and potential signals that might emerge as vaccines are introduced into global populations, it is possible that new AESIs relevant to COVID-19 will be identified and they can be added to the priority Tier 4 if required.

The combined AESI table was reviewed by SPEAC executive board to determine which AESI should be included in Tier 1. The target dates for Tier 1 Standards and Tools fall from September to November 2020. Given these tight timelines, priority was given to AESI with existing case definitions and that were chosen based on an association with immunization in general or some vaccine platforms in particular. As a result, the Priority 1 AESI are relevant to all CEPI vaccines under development.

Given the emergence of the COVID-19 global pandemic with multiple vaccines under development and compressed timelines for phase 1, 2 and 3 studies, priority for Tier 2 AESI was given to COVID-19 associated AESI; particularly those that have either existing published case definitions, or for which new case definitions will be available by the end of November 2020.

Any AESI not assigned to Tier 1 or 2 but relevant to COVID-19 were put into Tier 3. The remaining AESI identified to date were assigned to Tier 3 or 4, based on whether or not case definitions already existed or had yet to be developed as well as the status of CEPI developer vaccine trial timelines.

4. Results

The key outputs for this deliverable are shown in **Tables 1 -4** below.

As shown in **Table 1**, several separate entities are included in acute cardiovascular injury, coagulation disorder and acute and chronic inflammatory rheumatism. Some of the listed target diseases for each may only have one or two related entities. For example, COVID-19 and to large measure, CHIKV include the entire cardiovascular injury spectrum whereas for Lassa Fever it is primarily pericarditis and vascular leakage syndromes that can accompany cardiovascular dysfunction. Similarly, coagulation disorders will cover a broad spectrum of problems including internal/external bleeding as seen in LF and RVF, disseminated intravascular coagulation as seen in MERS, and thromboembolic disorders including stroke as seen in MERS and COVID-19. The working groups will ultimately decide on the scope of each case definition. If entities specific to a given target disease are not covered in the final case definition, another case definition, if needed, can be slated for development.

TABLE 1. COLLATED AESI IDENTIFIED FOR LASSA FEVER(LF), MERS, NIPAH VIRUS INFECTION(NiV), RIFT VALLEY FEVER(RVF), CHIKUNGUNYA(CHIKV) AND COVID-19. AESI in red font have published Brighton case definitions.

BODY SYSTEM	AESI[Rationale for inclusion(see table footnotes for explanation)]	Target Diseases and/or Vaccine Platforms
Immunologic	Anaphylaxis[1]	All vaccines
	Vaccine associated enhanced disease (VAED)[1,2,5]	Formalin-inactivated measles/RSV[2]; HIV vaccine[2]; Chimeric YF Dengue vaccine[2]; SARS/MERS-CoV vaccine, mouse model[5]
	Multisystem inflammatory syndrome in children (MISC)[3,4]	COVID-19
Respiratory	Acute respiratory distress syndrome (ARDS)[3,4]	COVID-19, MERS, NiV
Cardiac	Acute cardiovascular injury [3,4] (includes myocarditis, pericarditis, arrhythmias, heart failure, infarction)	COVID-19, LF, CHIKV, MVA platform
Hematologic	Thrombocytopenia [1,3,4]	COVID-19, CHIKV
	Coagulation disorder [3,4] (includes coagulopathy, thrombosis, thromboembolism, internal/external bleed, stroke)	COVID-19, LF, RVF, MERS
Renal	Acute kidney injury[3,4]	COVID-19, MERS, RVF, CHIKV
Gastrointestinal	Acute liver injury[3,4]	COVID-19, RVF, CHIKV
Neurologic	Guillain Barré Syndrome[3]	COVID-19, RVF, CHIKV, some inactivated vaccines seasonal/pandemic flu, Rabies Semple vaccine, Tetanus
	Acute disseminated encephalomyelitis (ADEM)[3]	COVID-19, MERS, CHIKV
	Aseptic meningitis [2]	COVID-19, LF, NiV, CHIKV, live vaccines
	Meningoencephalitis[2,4]	COVID-19, LF, MERS, NiV, RVF, CHIKV, live vaccines
	Generalized convulsion[1,2,4]	COVID-19, NiV, RVF, CHIKV, live vaccines
	Peripheral facial nerve palsy [1,2,3,4]	COVID-19, CHIKV, E. coli heat labile toxin adjuvanted intranasal influenza vaccine Berna
	Sensorineural hearing loss [3]	LF
	Anosmia, ageusia[3,4]	COVID-19
	Optic neuritis[3]	CHIKV
Eye	Visual loss (including uveitis, retinitis)	RVF, CHIKV

BODY SYSTEM	AESI[Rationale for inclusion(see table footnotes for explanation)]	Target Diseases and/or Vaccine Platforms
Dermatologic	Chilblain-like lesions[3,4]	COVID-19
	Single organ cutaneous vasculitis[3,4]	COVID-19
	Erythema multiforme[3,4]	COVID-19
	Alopecia	COVID-19, LF, CHIKV
Musculoskeletal	Acute aseptic arthritis[2]	rVSV platform
	Acute & chronic inflammatory rheumatism[3,4]	CHIKV
Pregnancy / Foetal / Neonatal	Maternal / Neonatal death [4]	LF, MERS
	Spontaneous abortion / stillbirth [3,4]	LF, MERS, CHIKV
	Miscarriage [4]	RVF
	Neonatal sepsis [3,4]	CHIKV
	Neonatal encephalopathy [3,4]	CHIKV
	Neonatal neurodevelopmental delay [3,4]	CHIKV

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 summarizes the current status and timelines for all new Brighton case definitions that have been slated for development as part of the SPEAC project. As noted, there are some, currently including chilblain like skin lesions, erythema multiforme, optic neuritis and alopecia, that may be replaced in terms of priority for case definition development. Any changes to what are shown below will be communicated to CEPI and the vaccine developers as soon as it is known, and/or all will be invited to provide input as to where the highest priority should be placed. Finally, vaccine safety templates for the many CEPI vaccine platforms are still being developed and completed; it is possible that this process may identify new AESI as could emerging safety signals, especially as COVID-19 vaccine phase 3 and population-based mass campaigns get underway. For this reason, SPEAC has ensured that flexibility is built into the plans for new case definition development.

TABLE 2. AESI NEW CASE DEFINITION DEVELOPMENT TIMELINES

AESI	Working Group Initiation	Submission for Publication
Sensorineural Hearing Loss	July 2019	Published June 2020
Vaccine Associated Enhanced Disease	March 2020	Aug 31, 2020
Multisystem Inflammatory Syndrome in Children (MISC)	July 2020	Oct 15, 2020
Acute Respiratory Distress Syndrome (ARDS)	July 2020	Oct 15, 2020
Acute Cardiovascular Injury	Aug 2020	Nov 15, 2020
Coagulation Disorders	Aug 2020	Nov 15, 2020
Acute Kidney Injury	Sept 2020	Nov 30, 2020
Acute Liver Injury	Sept 2020	Nov 30, 2020
Anosmia / Ageusia	Sept 2020	Nov 30, 2020
Chilblain like skin lesions (or alternate if higher priority)	By Dec 2020	Apr 30, 2021
Erythema multiforme (or alternate if higher priority)	By Dec 2020	Apr 30, 2021
10th COVID associated AESI – yet to be determined	By Feb 1, 2021	Apr 30, 2021
Acute and Chronic inflammatory rheumatism	By mid-Q2 2021	By mid-Q4 2021
Total/partial loss of vision	By mid-Q2 2021	By mid-Q4 2021

AESI	Working Group Initiation	Submission for Publication
Optic neuritis (or alternate if higher priority)	To be determined	By Dec 2021
Alopecia (or alternate if higher priority)	To be determined	By Dec 2021
5th and 6th AESI for LF, MERS, NiV, RVF and/or CHIKV yet to be determined	To be determined	By Dec 2021

Table 3 provides the Tier 1-4 specific timelines for the additional Standards and Tools that SPEAC will be developing.

TABLE 3. TIMELINES FOR AESI STANDARDS AND TOOLS BY PRIORITY TIER 1 THROUGH 4.

Related Standards and Tools	Tier 1	Tier 2	Tier 3	Tier 4
Background rates and risk factors	Sept30/20	Dec31/20	Jun30/21	Dec31/21
ICD 9/10 and MedDRA codes	Sept30/20	Jan15/21	May15/21	Dec 31/21
PDF Tools for case definition data collection and level of certainty (LOC) determination	Sept9/20	Jan15/21	May15/21	Dec 31/21
Guidance on real time AESI investigation	Sept30/20	Feb28/21	Jun 30/21	Dec 31/21
Web based tools for LOC determination and dashboard for background rates	Nov1/20	Mar1/21	Jun30/21	Dec 31/21

Finally, **Table 4** shows the specific assigned priority tier for all potential AESI, identified to date.

TABLE 4. DISTRIBUTION BY TIMELINE TIERS 1-4 OF CURRENTLY IDENTIFIED AESI RELATED TO CEPI VACCINE DEVELOPMENT

Tier 1	Tier 2	Tier 3	Tier 4
Anaphylaxis	Vaccine associated enhanced disease	Sensorineural hearing loss	Acute/Chronic inflammatory rheumatism
Thrombocytopenia	Acute respiratory distress syndrome	Anosmia/ageusia	Total/partial loss of vision
Generalized convulsion	Acute cardiovascular injury	Chilblain like lesions*	Optic neuritis*
Aseptic meningitis	Coagulation disorder	Erythema multiforme*	Alopecia*
Encephalitis	Acute kidney injury	10th COVID19 AESI	Non-COVID-19 CEPI target AESI
Myelitis	Acute liver injury	Acute aseptic arthritis	Non-COVID-19 CEPI target AESI
Acute disseminated encephalomyelitis	Stillbirth	Single organ cutaneous vasculitis	Neonatal sepsis
Guillain Barré & Miller Fisher Syndromes	Spontaneous abortion and ectopic pregnancy	Maternal death	Neonatal encephalopathy
Peripheral facial nerve palsy	Pathways to Preterm birth & Preterm birth	Neonatal death	Neonatal neuro-developmental delay

** May be replaced by not-yet identified AESI if considered of higher priority*

5. Recommendations & discussion

This deliverable has been created so that CEPI and the vaccine developers for all CEPI target diseases including COVID-19, as well as other SPEAC partners and collaborators will know the timelines for development of all AESI related standards and

tools. AESI identified to date have been distributed into one of four timeline related Tiers. The rationale for tier assignment primarily relates to presence or absence of an existing published Brighton case definition, the timelines for new CD development (see Table 2) and whether or not the AESI are related to COVID-19 (Tiers 1-3 only).

In addition to the Priority Tiers, this deliverable presents a singular collated AESI list (Table 1) and summarizes for each the rationale for choosing and the related spectrum of CEPI target disease(s)/vaccine platform(s).

Table 2 identifies the current list of all AESI slated for new Brighton case definitions and provides the planned timelines for establishment of working groups and submission for publication. All newly drafted case definitions are posted for peer-review on the Brighton website two to three weeks prior to the planned submission date and would be available to the vaccine developers for review at that time.

The standards and tools shown in Table 3 will be further delineated in forthcoming deliverable documents including:

- SO1-D2.4 Background rates and risk factors for Tier 1 AESI (Sept 30, 2020)
- SO2-D2.3 ICD 9/10 and MedDRA codes for Tier 1 AESI (Sept 30, 2020)
- SO2-D2.5.1.1 Tools for Tier 1 AESI Data Collection and Interpretation (Sept 9, 2020)
- SO2-D2.2 Dashboard design for COVID-19 AESI background rates (Sept 30, 2020)
- SO1-D2.7 Guidance for vaccine safety data collection, presentation and analysis (Sept 30, 2020)
- SO2-D2.5.2.1 Web-based Tier 1 AESI tools (Nov 1, 2020)

Table 4 provides the distribution of AESI identified to date into the 4 AESI tiers. SPEAC welcomes feedback from CEPI, the developers and other partners regarding this distribution and may consider changes to the allotted timelines for related tools and standards if issues are raised.

Finally, it should be noted that all the AESI lists relevant to individual target diseases may be updated as new evidence emerges. This is particularly true for COVID-19 as more is learned during the global pandemic. Accordingly, SPEAC is continuing to monitor the literature and will be issuing quarterly updates to the AESI list (September / December 2020 and March / June 2021). In addition, as vaccine platform safety templates are updated by SPEAC and individual developers it is possible that new AESI may need to be added. Furthermore, emerging signals related to phase 3 trials and population rollout of COVID19 vaccines could lead to the identification of additional AESIs. Whenever new AESI are added, CEPI and all developers will be notified, and this document adjusted in terms of the specific tier to which they are prioritized.

6. References

1. Report of the Global Advisory Committee on Vaccine Safety, 27-28 May 2020. WHO Weekly epidemiological record, July 10, 2020; Vol 95(28):325-336.