Safety Platform for Emergency vACcines

D2.2 Priority List of Adverse events of special interest

Work Package: WP2 Standards and tools

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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. Robert Chen 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 has been:

1. To develop standardized case definitions for specific AEFI's
2. To prepare guidelines for their data collection, analysis and presentation for global use
3. To develop and implement study protocols for evaluation of case definitions and guidelines in clinical trials and surveillance systems.
4. To raise global awareness of their availability and to educate about their benefit, monitor their global use, and to 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 two CEPI target pathogens, Lassa Fever (LF) and Middle East Respiratory Syndrome (MERS), this document describes the methods and results SPEAC used to arrive at their respective 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 the 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 adverse 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. Objectives

The primary objective is to create and provide lists of potential AESI relevant to development of Lassa Fever and MERS vaccines.

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.

To identify AESI related to events known to be associated with wild type disease, either as a result of viral replication or immunologic mechanisms, a non-systematic PubMed search was conducted in April 2019 to identify 8-10 recently published review articles for each of Lassa Fever and MERS. Search terms included the target disease (Lassa Fever, MERS or Middle Eastern Respiratory Syndrome), complications and clinical course, focusing on review articles or textbooks. In addition, the US Centre for Disease Control and Prevention website was searched for summary fact sheets on each disease.

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

All retrieved review/summary articles were independently reviewed by two medical experts (B Law and WT Huang). Each expert made summary notes on the target disease history, virology, epidemiology, clinical course, complications, pathogenesis, risk factors, therapy and prevention. The main focus of the review was to have a clear and thorough picture of the clinical course and complications of the target disease. To this end additional references were identified by each expert from the citation lists of the primary review publications. The added references were retrieved and reviewed by at least one expert and additional notes made. Each expert then independently drafted a list of AESI for consideration. The two experts reviewed and discussed to merge the preliminary lists. Tabular summaries in Word and/or Excel and a PowerPoint slide set were developed to present to the SPEAC Executive Board for their discussion and approval.

This preliminary list of AESI was next shared with a) CEPI, b) the vaccine developers, and c) the disease clinical experts for their review and feedback. Review was done with one Lassa Fever clinical expert but none for MERS before finalization.

Results

Table 1 lists AESIs considered potentially applicable to both Lassa Fever and MERS 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 both Lassa Fever and MERS 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 Lassa Fever and/or MERS vaccine development programs.

TABLE 2. AESI RELEVANT TO SPECIFIC VACCINE PLATFORMS FOR LASSA FEVER AND/OR MERS 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 Lassa Fever and/or MERS.

For Lassa Fever ten primary review/summary articles[5-14] were retrieved and reviewed independently by each medical expert. An additional twenty-five articles cited in one or more of the primary review articles were identified as germane to the analysis by one or both medical experts[15-39]. Each of these were reviewed and used to add further detail to the Lassa Fever landscape analysis. Further discussion with a clinical expert in Lassa Fever resulted in the addition of alopecia to the AESI list.

Using the same processes for MERS, a total of nine primary articles[40-48] and five secondary articles[49-53] were retrieved and reviewed.

The AESI identified for Lassa Fever specifically are shown in Table 3 and for MERS are shown in table 4 along with the respective specific rationales for their inclusion.

TABLE 3. AESI RELEVANT TO LASSA FEVER\TARGET POPULATION. AESI WITH AN EXISTING BRIGHTON CASE DEFINITION ARE SHOWN IN RED.

BODY SYSTEM	LASSA FEVER	RATIONALE FOR INCLUSION AS AN AESI (SEE FOOTNOTE)
Neurologic	Sensorineural hearing loss	3
	Encephalopathy/cerebellar ataxia	4
	Aseptic meningitis	4
Hematologic	Bleeding (mucosal, urine, fecal, internal)	3, 4
	Vascular leakage (edema of face/neck)	3, 4

Immunologic	Polyserositis (pleural, pericardial, abdominal effusions)	3, 4
	Alopecia*	3, 4
Other	Maternal death, spontaneous abortion, stillbirth, neonatal death	4

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

**Alopecia was added after consultation with a clinical expert. A PubMed search for evidence failed to recover any published evidence. Follow-up with the expert for published evidence is being sought. If none can be found it will be removed from the list.*

TABLE 4. AESI RELEVANT TO MERS DISEASE/TARGET POPULATION. AESI WITH AN EXISTING BRIGHTON CASE DEFINITION ARE SHOWN IN RED.

BODY SYSTEM	MERS	RATIONALE FOR INCLUSION AS AN AESI (SEE FOOTNOTE)
Respiratory	Acute respiratory distress syndrome (ARDS)	3, 4
	Pneumonitis	3, 4
Neurologic	Encephalopathy	3, 4
	Encephalitis	3, 4
	Acute disseminated encephalomyelitis (ADEM)	3
	CNS vasculopathy (stroke)	3, 4
Hematologic	Disseminated intravascular coagulation (DIC)	4
Immunologic	Enhanced disease following immunization	1, 2, 5
Other	Acute renal failure	3, 4
	Death including maternal death, spontaneous abortion, stillbirth, neonatal death	4

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 based on viral replication during wild type disease.
5. Theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccines.

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.

4. Recommendations & discussion

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

Most of the AESI for LF and MERS vaccines have published BC case definitions available. The sensorineural hearing loss case definition has been finalized and provided to the developers.

BC case definitions are not yet developed for arthritis, myocarditis, bleeding, vascular leakage, polyserositis, alopecia, acute respiratory distress syndrome (ARDS), pneumonitis, CNS vasculopathy (stroke), disseminated intravascular coagulation (DIC), enhanced disease following immunization (MERS) and acute renal failure.

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 CRFs/outcome definitions or draft new ones if desired to achieve, to the extent possible, harmonized and standardized approaches to each AESI.

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6. Appendix. Comprehensive document history

NAME	DATE	VERSION	DESCRIPTION
Barbara Law, Wan-Ting Huang, Matthew Dudley	17/07/19	0.10 LF	Landscape analysis for Lassa Fever completed and presented to EB with proposed AESI list.
Barbara Law, Matthew Dudley	14/08/19	0.11LF	Enhanced Disease (ED) following immunization literature review with PowerPoint slide summary presented to EB and ED added to AESI list.
Robert Chen, Marc Gurwith	10/09/19	0.10 LF	First presentation draft LF AESI Table at WHO LF Meeting, Dakar, Senegal. Based on EB/CEPI discussions leading up to meeting, ED removed from the list for lack of strong evidence.
Barbara Law, Wan-Ting Huang, Matthew Dudley	21/10/19	0.1 MERS	Landscape analysis for MERS completed and presented to EB and CEPI with proposed AESI list.
Steve Black, Inovio, Themis	15/11/19	0.12 LF	LF/MERS AESI list shared with CEPI and developers. Based on feedback added an * to neuropsychiatric complications to indicate to be AESI must be: new onset and severe enough to interfere with daily activity.
Daniel Bausch	25/11/19	1.0 LF	Teleconference with clinical LF expert who suggested two changes: 1) remove neuropsychiatric complications as not clear if due to LF or social circumstances for survivors; 2) add alopecia.
Barbara Law, Steve Black	09/11/19	1.1LF 0.11 MERS	AESI lists modified to incorporate a justification for the inclusion of each AESI in the table as suggested by Steve Black during EB discussion
Alimuddin Zumla [Unsuccessful]	5/12/19 16/12/19 20/12/19	0.1 MERS	Attempt to have review by MERS expert(s) by teleconference X2 and email X1 not completed because Dr. Zumla unable to join/provide feedback. Decision to adopt existing MERS list as final output for D2.2
Miriam Sturkenboom, Barbara Law	13/01/2020	1.0 D2.2	Creation & review of detailed description of Landscape Analysis for methods and results for Lassa Fever and MERS.
Miriam Sturkenboom, Barbara Law	06/02/2020	2.0 D2.2	Amended version submitted to EB for review and discussion.
Miriam Sturkenboom, Barbara Law, EB	17/02/2020	3.1 D2.2	Final version of the deliverable discussed, revised and approved for forwarding to TFGH and CEPI. Decision to add this appendix as a document history for this and future landscape outputs.