Safety Platform for Emergency vACcines

D2.3 Priority List of Adverse events of special interest: Chikungunya

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 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 Chikungunya (CHIK), 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 Chikungunya virus (CHIKV) 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 CHIKV disease, either as a result of viral replication or immunologic mechanisms, a non-systematic PubMed search was conducted in December 2019 to identify recently published review articles to serve as the primary review articles. Search terms included the target disease (Chikungunya Fever), complications and clinical course, focusing on review articles or textbooks. Prior to conducting the primary review, the retrieved articles were screened by one of the expert reviewers (B Law) for suitability to the primary objective. Reasons for exclusion of any primary review articles were recorded.

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 Kathy Edwards). 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 CHIKV vaccine developers, and c) the disease clinical exports for their review and feedback.

4. Results

Table 1 lists AESIs considered potentially applicable to CHIKV 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 Chikugunya 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 CHIKV vaccine development programs.

TABLE 2. AESI RELEVANT TO SPECIFIC VACCINE PLATFORMS FOR CHIKV 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 Chikungunya.

Fourteen primary review/summary articles[5-18] were retrieved and initially screened by B Law for relevance to the primary objective. Three articles[16-18] were deemed non-contributory and excluded from the review. Appendix Table 4 provides the rationale for excluding each article. The remaining eleven articles were reviewed independently by each medical expert. An additional fifteen[19-33] articles cited in one or more of the primary review articles were identified as germane to the analysis and added as secondary review articles. Each of these were reviewed by one or both experts and used to add further detail to the Chikungunya landscape analysis.

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

TABLE 3. AESI RELEVANT TO CHIKUNGUNYA. AESI WITH AN EXISTING BRIGHTON CASE DEFINITION ARE SHOWN IN RED.

BODY SYSTEM	CHIKUNGUNYA FEVER	RATIONALE FOR INCLUSION AS AN AESI (SEE FOOTNOTE)
Musculoskeletal	Inflammatory Rheumatism*	3, 4
Neurologic	Meningitis, Encephalitis, Myelitis	4
	Encephalopathy, Myelopathy	4
	Seizure(s)	4
	GBS, ADEM, Optic neuritis	3
	Sensorineural abnormalities, Cranial nerve palsies	3
Cardiovascular	Myocarditis, pericarditis, arrhythmias	3, 4
	Cardiac dysfunction / heart failure, acute MI	3, 4
Eye	Uveitis, Retinitis	3, 4
Skin	Rash (maculopapular, bullous dermatosis), Alopecia	3, 4

Hepatic	Hepatic dysfunction / failure	3, 4
Renal	Renal dysfunction / failure	3, 4
Hematologic	Thrombocytopenia, lymphopenia	3, 4
Pregnancy, Foetus, Newborn	Foetal loss (miscarriage, stillbirth) Neonatal sepsis / encephalopathy via peripartum CHIKV Neurodevelopmental delay	4

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

* **The disease entities falling under *Inflammatory Rheumatism* include ≥ 1 of:** arthritis, spondylitis, degenerative osteoarthritis, persistent/recurrent arthralgia, tenosynovitis, bursitis, tendinitis, enesthitis, compartment syndromes. Any of these occurring within 4-6 weeks after immunization need to be fully characterized at presentation and followed through to resolution. Anything persisting >3 months would be considered Chronic inflammatory rheumatism as defined for CHIKV wild type infection.

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 that the listed AESI be adopted by CEPI and the CHIKV vaccine developers. SPEAC recommends that the developers be prepared to take a uniform approach to the identification, assessment, investigation, analysis and reporting of any AESI should it occur during a clinical trial.

Several of the AESI for CHIKV vaccines have published BC case definitions available.

BC case definitions are not yet developed for inflammatory rheumatism, myocarditis, pericarditis, arrhythmias, cardiac dysfunction (including heart failure and myocardial infarction), alopecia, renal dysfunction / failure, hepatic dysfunction / failure, uveitis, retinitis, lymphopenia, and global developmental delay following neonatal infection.

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.

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7. Appendix.

Table 4. References retrieved in original search but excluded from primary review articles with reasons for exclusion.

REFERENCE	REASON FOR EXCLUDING FROM PRIMARY REVIEW ARTICLES
16. Vu 2017	Focus on diagnostics with minimal clinical information and nothing not already captured in other primary review articles.
17. Muller 2019	Broadly based review of all vector borne-disease with a focus on the impact of climate change. Non-contributory to clinical course or complications.
18. Ganesan 2017	Focus on animal models for CHIKV with minimal information on human disease.

DOCUMENT INFORMATION

Master Service Agreement		Service order	1
Project acronym	SPEAC	Full project title	Safety Platform for Emergency Vaccines
CEPI Project Lead	Nadia Tornieporth / Jakob Cramer		
CEPI Project Manager	Brett Barnett		
CEPI Contract Manager	Nishat Miah		

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Description of the deliverable	This deliverable provides the methods and results of the creation of the Priority List of potential Adverse events of special interest relevant to Chikungunya vaccine trials
Key words	Toolbox, case definitions, guidance documents

SIMPLIFIED DOCUMENT HISTORY

NAME	DATE	VERSION	DESCRIPTION
Matthew Dudley	13 Dec 2019	NA	Retrieval of 14 review articles for Chikungunya
Barbara Law, Kathy Edwards	20 Mar 2020	CHIKV V0.1	Landscape analysis completed and consensus on AESI list V0.1 achieved.
Barbara Law, Kathy Edwards, SPEAC EB	23 Mar 2020	CHIKV V0.1	Landscape analysis presented to EB and AESI list V0.1 approved.
Barbara Law and CEPI	26 Mar 2020	NA	AESI list and slideshow sent to CEPI for review and soliciting clinical expert review
Barbara Law	26 Mar 2020	D2.3 V0.1	Draft deliverable report for Chikungunya based on previous version developed for LF/MERS
Miriam Sturkenboom, Robert Chen	30 Mar 2020		Review
Mark McKinlay	01 Apr 2020		Review