Safety Platform for Emergency vACcines

D2.3 Priority List of Adverse events of special interest: Rift Valley Fever

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 Rift Valley Fever (RVF), 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 Rift Valley Fever Virus (RVFV) 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 RVF 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 (Rift Valley 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. Excluded articles were replaced by relevant citations from the remaining primary review articles (by B Law). Reasons for exclusion / inclusion of all primary review articles were recorded.

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

All included primary review articles were independently reviewed by two medical experts (B Law and S Kochhar). 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 one or both experts 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 RVFV vaccine developers, and c) the disease clinical experts for their review and feedback.

4. Results

Table 1 lists AESIs considered potentially applicable to RVFV 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 RVFV 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 Rift Valley Fever vaccine development programs.

TABLE 2. AESI RELEVANT TO SPECIFIC VACCINE PLATFORMS FOR RVFV 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 Rift Valley Fever.

Twelve primary review/summary articles[5-16] were initially retrieved and reviewed for suitability to the primary objective (creation of an AESI list based on RVF clinical course and complications) by B Law. Three were included as highly relevant to the primary objective.[5-7] Nine were excluded[8-16]: Two were retained as secondary references either because they provided current information on viral taxonomy[8] and structure[8,9]. Appendix 1 Table 4. itemizes the specific reasons the other 7 articles were excluded from primary/secondary reference sets.

B Law identified another 21 references based on what was cited in included primary references and screened each. Ten were chosen to supplement the primary review references because they added to the overview of the clinical disease course and complications .[17-26] Of the remaining 11, six were chosen as supplementary secondary references [27-32] and five were excluded as not adding to the landscape analysis beyond the chosen articles.[33-37] Specific reasons for their exclusion are noted in Appendix 1, Table 5. Two more articles were retrieved and added to the secondary review by B Law.[38, 39]

The final set of primary review articles were reviewed independently by each medical expert. Each of the secondary articles were reviewed by one or both experts and used to add further detail to the RVF landscape analysis.

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

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

BODY SYSTEM	RIFT VALLEY FEVER	RATIONALE FOR INCLUSION AS AN AESI (SEE FOOTNOTE)
Eye	Unilateral or bilateral blindness / decreased vision	3, 4
Hematologic	Hemorrhagic disease (internal/external bleeding)	4
Neurologic	Meningoencephalitis	3, 4
Hepatic	Acute hepatitis Fulminant liver failure	4
Renal	Acute renal failure	4
Pregnancy	Spontaneous abortion, Stillbirth	4

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

[$]Due to ≥1 of: macular/paramacular retinitis; uveitis; retinal vasculitis; chorioretinal scarring; optic disc atrophy; retinal hemorrhage; vascular occlusion; retinal detachment; vitreous reaction; scotoma.

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 Rift Valley Fever 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.

Two of the AESI for Rift Valley Fever vaccines have published BC case definitions available: meningoencephalitis and miscarriage.

BC case definitions are not yet developed for blindness/decreased vision, hemorrhagic disease, acute hepatitis, fulminant liver failure or acute renal failure. BC case definitions are also not available for two platform related AESI: myocarditis and arthritis.

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

1. Bonhoeffer J, Kohl K, Chen R et al. The Brighton Collaboration – enhancing vaccine safety. Vaccine 2004; 22: 2046.
2. Definition and Application of Terms for Vaccine Pharmacovigilance. Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, 2012, Council for International Organizations of Medical Sciences.
3. The Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials: Report of CIOMS Working Group VII, Geneva 2007. https://cioms.ch/shop/product/development-safety-update-report-dsur-harmonizing-format-content-periodic-safety-report-clinical- trials-report-cioms-w orking-group-vii/ (accessed January 14, 2020)
4. 1CH Topic E2F Development Safety Update Report, EMEA/CHMP/ICH/309348/2008, June 2008 https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-2-f-development-safety-update-report-step-3_en.pdf
5. McMillen CM, Hartman. Rift Valley fever in animals and humans: current perspectives. Antiviral Research 2018; 156:29-37.
6. Bird BH, McElroy AK. Rift Valley fever virus: unanswered questions. Antiviral Research 2016; 132:274-80.
7. Hartman A. Rift Valley Fever. Clin Lab Med 2017; 37(2): 285-301.
8. Gaudreault NN, Indran SV, Balaraman V et al. Molecular aspects of Rift Valley fever virus and the emergence of reassortants. Virus Genes 2019; 55:1-11.
9. Lorenzo G, Lopez-Gil E, Warimwe GM, Brun A. Understanding Rift Valley fever: contributions of animal models to disease characterization and control. Molecular Immunology 2015; 66:78-88.
10. Himeidan YE. Rift Valley fever: current challenges and future prospects. Research and Reports in Tropical Medicine 2016; 7:1-0.
11. Lumley S, Horton DL, Hernandez-Triana LLM et al. Rift Valley fever virus: strategies for maintenance, survival and vertical transmission in mosquitoes. J Gen Virology 2017; 98: 875-87.
12. Mansfield KL, Banyard AC, McElhinney L et al. Rift Valley fever virus: A review of diagnosis and vaccination and implications for emergence in Europe. Vaccine 2015; 33:5520-31.
13. Logue J, Richter M, Johnson RF et al. Overview of human viral hemorrhagic fevers. Chapter 2 in Defense Against Biological Attacks, 2019; SK Singh, JH Kuhn eds. Https://doi.org/10.1007/978-3-030-03071-1_2
14. Kenawya MA, Abdel-Hamid YM, Beier JC. Rift Valley Fever in Egypt and other African countries: historical review, recent outbreaks and possibility of disease occurrence in Egypt. Acta Tropica 2018; 181:40-49.
15. Linthicum KJ, Britch SC, Anyamba A. Rift Valley Fever: an emerging mosquito-borne disease. Annu Rev Entomology 2016. 61:395-415.
16. Clark MHA, Warimwe GM, De Nardo A et al. Systematic literature review of Rift Valley fever virus seropresvalence in livestock, wildlife and humans in Africa from 1968-2016. PLoS Negl Trop Dis 2018;
17. Laughlin LW, Meegan JM, Strausbaugh LJ et al. Epidemic Rift Valley fever in Egypt: observations of the spectrum of human illness. Transactions of the Royal Society of Tropical Medicine and Hygiene 1979; 73(6): 630-3.
18. Madani TA et al. RVF epidemic in Saudi Arabia: epidemiological, clinical and laboratory characteristics. Clin Inf Dis 2003; 37(8): 1084-92.
19. Al-Hazmi A, Al-Rajhi AA, Abboud EB et al. Ocular complications of Rift Valley fever outbreak in Saudi Arabia. Ophthalmology 2005; 112(2): 313-8.
20. LeBeaud AD, Pfeil S, Muiruri et al. Factors associated with severe human Rift Valley fever in Sangaiou, Garissa country, Kenya. PLoS Negl Trop Dis 2015; 9, 30003548

21. Shieh WJ et al 2010 Pathologic studies on suspect animal and human cases of RVF from an outbreak in Eastern Africa 2006-7. Am J Trop Med Hyg 83(2Suppl1): 38-42.
22. Baudin M, Jumaa AM, Jomma HJE et al. Association of Rift Valley fever virus infection with miscarriage in Sudanese women: a cross-sectional study. Lancet Glob Health 2016; 4(11): e864-871.
23. Adam I, Karsany MS. Case report: Rift Valley fever with vertical transmission in a pregnant Sudanese woman. J Med Virol 2008; 80(5), 929.
24. Arishi HM, Aqeel AY, Al Haxmi MM. Vertical transmission of fatal Rift Valley fever in a newborn. Ann Trop Paediatr 2006; 26(3): 251-3.2006
25. Meegan JM, Watten RH, Laughlin LW. Clinical experience with Rift valley fever in humans during the 1977 Egyptian epizootic. Contrib Epidemiol Biostat 1981; 3:114-123.
26. Van Velden DJ,et al. 1977; RVF affecting humans in South Africa: a clinicopathological study. S Afr Med J 51(24): 867-71.
27. Ikegami T, Makino S 2011; The pathogenesis of Rift Valley fever. Viruses 3:493-519.Adam AA, Karsany MS, Adam I. Manifestations of severe Rift Valley fever in sudan. Int J Infect Dis 2010; 14: 3179-80
28. Hise AG, Traylor Z, Hall NB et al. Association of symptoms and severity of Rift Valley fever with genetic polymorphisms in human innate immune pathways. PLoS Negl Trop Dis 2015; 9(3), e0003584 PMCID: PMC4355584
29. Mohamed M, Mosha F, Mghamba J et al. Epidemiologic and clinical aspects of a Rift Valley Fever outbreak in humans in Tanzania 2007; Am J Trop Med Hyg 2010; 83:22-7.
30. Newman-Gerhardt S, Muiruri S, Muchiri E et al. Potential for autoimmune pathogenesis of Rift Valley fever virus retinitis. Am J Trop Med Hyg 2013; 89:495-7.
31. McIntosh BM, Russell D, dos Santos I, Gear JH. Rift Valley fever in humans in South Africa. S Afr Med J 1980; 58(20): 803-6.
32. Jansen van Vuren P, Shalekoff S, Grobbelaar AA et al. Serum levels of inflammatory cytokines in Rift Valley fever patients are indicative of severe disease. Virol J 2015; 12, 159 PMCID: PMC4595326
33. Adam AA, Karsany MS, Adam I. Manifestations of severe Rift Valley fever in sudan. Int J Infect Dis 2010; 14: 3179-80:
34. Al-Hazmi 2003 Epidemic RVF in Saudi Arabia: a clinical study of severe illness in humans Clin Inf Dis Off Publ Infect Dis Soc Am 2003; 36:245-52
35. Alrajhi AA, Al Semaria A, Al-Watban J. Rift Valley fever encephalitis. Emerg Infect Dis 2004; 10:554-5
36. Siam AL, Meegan JM, Gharbawi KF RVF ocular manifestations: observations during the 1977 epidemic in Egypt. Br J Opthalmol 1980; 64:366-374.
37. Abdel-Wahab KS et al. 1978. RVF virus infections in Egypt: pathological and virological findings in man. Trans R Soc Trop Med Hyg 72(4): 392-6.
38. WHO fact sheet. https://www.who.int/newsroom/fact-sheets/detail/rift-valley-fever Accessed Feb 27, 2020; updated Nov 2018.
39. CDCP https://www.who.int/news-room/fact-sheets/detail/rift-valley-fever updated Nov2018; accessed Feb27/20.

7. Appendix.

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

REFERENCE	REASON FOR EXCLUDING FROM PRIMARY/SECONDARY REVIEW ARTICLES
10. Himeidan 2016	Focus on outbreak prevention and control with no clinical information.
11. Lumley 2017	Focus on transmission characteristics especially the possibility of vertical transmission in vectors.
12. Mansfield 2015	Focus on methods for diagnosis of RVFV infection, current status of vaccine development and possible implications for RVFV in Europe.
13. Logue 2019	Textbook chapter covering all human viral hemorrhagic fevers.
14. Kenawya 2018	Focus on outbreak patterns in Africa with minimal coverage of clinical disease.
15. Linthicum 2016	Focus on African transmission cycles and vector ecology.
16. Clark 2018	Focus on seroprevalence studies with no clinical information relevant to AESI list

Table 5. References cited in included primary articles, screened and then excluded for possible addition to either primary or secondary review articles, with reasons for exclusion.

REFERENCE	REASON FOR EXCLUDING FROM PRIMARY/SECONDARY REVIEW ARTICLES
33. Adam 2010	Letter to the editor describing critically ill cases in a Sudan outbreak; nothing new
34. Al-Hazmi 2003	Describes a subset of the larger case study reported by Madani, 2003[18] (primary article)
35. Alrajhi 2004	Letter to the Editor, case report of meningoencephalitis; similar to other reported cases
36. Siam 1980	Descriptive case series of 7 cases of ocular disease (Egypt 1977) that offers nothing beyond the much more detailed and updated report from Al-Hazmi 2005(Saudi 2000).[19]
37. Abdel-Wahab 1978	Pathological/virologic findings for one case. Much less informative then Van Velden 1977

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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Work package number	WP2	Title	Standards and tools

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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 Rift Valley Fever Virus vaccine trials
Key words	Toolbox, case definitions, guidance documents

SIMPLIFIED DOCUMENT HISTORY

NAME	DATE	VERSION	DESCRIPTION
Matthew Dudley	13/Dec/2019	NA	Retrieval of 12 primary review articles for RVF
Barbara Law, Matthew Dudley	a. 21/Feb/2020 b. 26/Feb/2020	NA	a. RVF articles screened by BL, 9 excluded as non-contributory for AESI. 21 new articles requested by BL from citations in 3 remaining primary articles. b. 21 new articles retrieved by MD, screened by BL & 9 added to 1° review
Barbara Law, Sonali Kochhar	06/Mar/2020	RVF AESI V0.1	Landscape analysis completed with consensus on proposed AESI
Barbara Law, Sonali Kochhar and SPEAC EB	16/Mar/2020	RVF AESI V0.1	EB discussion and approval of AESI list.
Barbara Law, CEPI	17/Mar/2020	RVF AESI V0.1	List sent to CEPI for review and sending on to clinical experts for review
Barbara Law	26/Mar/2020	D2.3 V0.1	Draft deliverable report for Rift Valley Fever based on previous version developed for LF/MERS
Miriam Sturkenboom, Robert Chen	30/Mar/2020		Review
Mark McKinlay	01/Apr/2020		Review