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# Safety considerations for RVF vaccine candidates undergoing clinical evaluation

**WHO R&D Blueprint Meeting: Scientific Consultation on CORE Clinical Trial Protocol for Rift Valley Fever Vaccine(s) during Outbreaks**

**October 31, 2025**

Eileen Farnon, MD, DTM&H, FACP, FIDSA
Director of Research, Brighton Collaboration
The Task Force for Global Health, Atlanta, USA
*On behalf of the SPEAC Project Executive Board*

# Brighton Collaboration

**History**

- **2000:** Brighton Collaboration (BC) was formed after a vaccine conference in Brighton, England identified the need to improve **harmonization of vaccine safety data**
- **2000 - 2018:** Based at Children's Hospital Basel, Switzerland, funded in part by WHO
- **2005 - present:** BC case definitions (N=104) and guidelines recommended by CIOMS, FDA, and EMA
- **2019:** Relocated to The Task Force for Global Health in Atlanta, U.S.; received funding from the Coalition for Epidemic Preparedness Innovations (CEPI); launched the Safety Platform for Emergency vACcines (SPEAC) project

**Mission**

- Convene a global safety network (>1500 volunteers from 110 countries)
- Create consensus-driven, **standardized adverse event (AE) case definitions & other safety guidelines to assess vaccine safety and create benefit-risk profiles**

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# Safety Platform for Emergency vACcines (SPEAC) Project

- Supports CEPI's mission to make vaccines available within 100 days of a pandemic
  - Provides tools and services to support vaccine safety evaluation for CEPI-funded vaccine developers
  - SPEAC focuses on diseases caused by **priority pathogens:** COVID-19, MERS, Lassa fever, Nipah, Rift Valley fever, Marburg, chikungunya, and mpox
  - Aligned with the mission of CEPI 1.0 (2017-2021) and CEPI 2.0 (2022-2026)

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# Human RVF vaccines under consideration

| Investigational vaccine (Developer) | hRVFV-4s (Wageningen/LARISSA II Consortium) | DDvax (UCDavis/CDC) | ChAdOx1 RVF (Univ. Oxford) | MP-12 (Sabin/USAMRIID) |
|---|---|---|---|---|
| Platform | LAV (single deletion) | LAV (double deletion) | Viral vector (ChAdOx1) | LAV (mutations in 3 segments) [next-gen Rvax-1 in preclinical] |
| Detectable viremia | None | None (animal data) | None | Transient low viremia in some participants; no reversion |
| Phase of development | Phase 1 complete (Belgium)<br>*Phase 2 planned (Kenya/Uganda)* | Preclinical: positive<br>*Phase 1&2 planned* | Phase 1a & 1b complete (Oxford & Uganda)<br>Phase 2a in progress (Kenya) | Phase 1 & 2 complete |
| DIVA (discriminate infection from vaccination) | Yes | | | No |
| Safety | • Well tolerated<br>• AEs mild and self limiting<br>• (Repeat dose Tox, preclinical & Ph1 complete) | • Positive preclinical data (repeat dose tox, preclinical)<br>• No risk of mosquito-borne transmission demonstrated | Well tolerated<br>AEs mild and self limiting<br>(Repeat dose tox and Ph1a & 1b complete)<br>• Possible risks (e.g., VITT) associated with platform require monitoring | • Transient viremia in multiple species<br>• Viral RNA detected in organs<br>• Next-gen Rvax-1 with decreased risk of mosquito-borne transmission |
| Environmental safety | • Negligible risk given absence of viremia in animals and humans | • Minimal infection rates and negligible transmission in mosquito saliva after oral exposure | N/A | • Transmission to mosquitoes (low risk of mosquito-borne transmission due to low viremia) |
| Safety in pregnancy | Not fully characterized - Positive preclinical data. DART studies planned | | Minimal concern – positive preclinical and platform data & DART planned | Evidence of risk (MP-12) (not applicable for Rvax-1) |
| Immunogenicity/Efficacy | Preclinical & Phase 1 (positive) | Preclinical (positive) | Preclinical & Phase 1 (positive) | Very good |

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Adapted from Pete Hart, CEPI; WHO R&D Blueprint meeting 14 October 2025.

# Safety Considerations: TPP for use during outbreaks & long term protection

| Purpose | Reactive use in outbreak settings with rapid onset of immunity (single dose vaccine) | | Long term protection of persons at high ongoing risk | |
|---|---|---|---|---|
| Vaccine characteristic | Optimal Target | Minimally acceptable target | Optimal Target | Minimally acceptable target |
| Indication for use | For active immunization of at-risk persons in an ongoing outbreak for the prevention of Rift Valley Fever; to be used in conjunction with other control measures to curtail or end an outbreak. | | For active immunization of persons considered at-risk including those working with potentially infected animals (herders, farmers, slaughterhouse workers, and veterinarians). | |
| Target population | People living in the area of the outbreak, **including pregnant women**. Those having contact with infected animals or tissues from infected animals, including consuming milk and handling raw meat products. | People living in the area of the outbreak. Those having contact with infected animals or tissues from infected animals, including consuming milk and handling raw meat products. | Persons at high ongoing risk of RVFV infection such as those handling of animal tissue during slaughtering or butchering, assisting with animal births, conducting veterinary procedures, or involved with the disposal of carcasses or fetuses. High risk occupational groups include herders, farmers, slaughterhouse workers and veterinarians.<br>**Suitable for vaccinating pregnant women.** | Persons at high ongoing risk of RVFV infection such as those handling of animal tissue during slaughtering or butchering, assisting with animal births, conducting veterinary procedures, or involved with the disposal of carcasses or fetuses. High risk occupational groups include herders, farmers, slaughterhouse workers and veterinarians. |
| Safety/reactogenicity | • Safety and reactogenicity sufficient to provide a **highly favourable benefit/risk profile in the context of observed vaccine efficacy**; with *mild, transient adverse events related to vaccination.*<br>• **No live attenuated virus vaccine to be used unless reassorting is excluded.** | • Safety and reactogenicity whereby **vaccine benefits clearly outweigh safety risks.**<br>• Usage of an attenuated live vaccine that may allow reassortment is not indicated in an outbreak setting.<br>• **No live attenuated virus vaccine to be used unless reassorting is excluded.** | Safety and reactogenicity at least comparable to WHO-recommended routine vaccines, providing a **highly favourable risk-benefit profile**, ideally with only *mild, transient adverse events related to vaccination* and **no serious AEs related to vaccination, including in individuals with compromised immune function.** | Safety and reactogenicity whereby **vaccine benefit clearly outweighs safety risks.**<br>Safety profile demonstrated *primarily mild, transient health effects and rare serious AEs related to vaccination.* |

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Adapted from: WHO. TPP for Rift Valley fever vaccines – v3, 2019. https://cdn.who.int/media/docs/default-source/blue-print/tpp-rift-valley-fever-vaccines-draft3-2019.pdf

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*"The benefits of a LAV for prevention and control of RVF outbreaks clearly outweigh the theoretical risk of reassortment, which has not been demonstrated to be a safety problem despite marketing of two RVFV LAVs and several others in development."*

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*Monath TP et al, Vaccine 2020. https://doi.org/10.1016/j.jvacx.2020.100060

# Safety Considerations: Concern for reassortment – V3SWG Guidance

## Variables to assess risk of recombination

1. Intrinsic recombination properties of the parent virus used as a vector.
2. Sequence relatedness of vector and wild virus.
3. Host range, pathogenesis and transmission.
4. Replication competency of vector in target host.
5. Mechanism of vector attenuation.
6. Additional factors potentially affecting virulence.
7. Circulation of multiple recombinant vectors in the same target population.

## Principles for vector design and testing

1. Consider the evidence that members of the virus genus do or do not undergo recombination in the wild or under experimental conditions, for example in an animal model or in cell culture.
2. Given the vector design and mode of delivery, assess the magnitude of the opportunity for recombination in a clinical scenario.
3. Given the vector design, evaluate the probability that a recombination event with a wild virus could lead to a virus of increased pathogenicity. Consider the potential mechanisms whereby this could happen, and cite or conduct laboratory studies to evaluate those mechanisms.
4. Consider vector designs that could further reduce the probability of a recombination event, and enhance safety, while leaving the potency of the vector largely intact.
5. Develop an optimized system for recombination and a strategy for detection of recombinants perhaps using current, sensitive assays for detection of expected viruses (e.g. PCR or infectivity assays) and new, broad methods for detection of novel viruses (e.g. degenerate PCR and massively parallel sequencing).

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Condit RC et al. Vaccine 2016. http://dx.doi.org/10.1016/j.vaccine.2016.04.060

# Safety Surveillance Recommendations for RVF Vaccine Clinical Trials

| Safety event | Duration of surveillance |
|---|---|
| Reactogenicity (local, systemic) | 7 days |
| Adverse events | 28 days |
| Serious adverse events | Duration of study |
| Newly diagnosed chronic medical conditions | Duration of study |
| Adverse events of special interest (AESIs) | Duration of study |

- SPEAC offers a pool of DSMB members, and meta-DSMB liaisons for CEPI-funded developers; protocol review; including guidance on special populations (e.g., exposure during pregnancy)

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# AESIs for RVF vaccines under consideration

| Rationale for AESI | AESI | VACCINE | | | |
|---|---|---|---|---|---|
| | | hRVFV-4s | DDVax | ChAdOx | MP12 |
| RVF Disease-associated (direct viral damage or immuno-pathogenesis) | **Acute intraocular inflammation**[#] (Uveitis, Retinal vasculitis, Neuroretinitis) | YES* | YES* | YES* | YES* |
| | **Organ dysfunction** [#]<br>• Hemorrhagic disease<br>• Thrombocytopenia<br>• Acute hepatitis / fulminant liver failure<br>• Acute kidney injury / renal failure | YES | YES | YES | YES |
| | **Encephalitis** [+] | YES | YES | YES | YES |
| Vaccine platform-associated | **TTS-VITT** [+] | | | YES* | |
| | **Guillain Barré Syndrome** [+] | | | YES | |
| | **Transverse myelitis** [+] | | | YES | |
| | **Acute disseminated encephalomyelitis** [+] | | | YES | |
| All vaccines | **Anaphylaxis** [+] | YES | YES | YES | YES |
| | **Generalized convulsive seizure** [+] | YES | YES | YES | YES |
| | **Thrombocytopenia** [+] | YES | YES | YES | YES |

[#] Case Definition under development

[+] Case Definition, Companion Guide, Automated Brighton Classification (ABC) tool

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https://speacsafety.net/tools/aesi-lists/rift-valley-fever/
https://zenodo.org/records/17455987

# AESIs for RVF vaccines under consideration

| Rationale for AESI | AESI | VACCINE | | | |
|---|---|---|---|---|---|
| | | hRVFV-4s | DDVax | ChAdOx | MP12 |
| RVF Disease-associated (direct viral damage or immuno-pathogenesis) | **Acute intraocular inflammation**[#] (Uveitis, Retinal vasculitis, Neuroretinitis) | YES* | YES* | YES* | YES* |
| | **Organ dysfunction** [#]<br>• Hemorrhagic disease<br>• Thrombocytopenia<br>• Acute hepatitis / fulminant liver failure<br>• Acute kidney injury / renal failure | YES | YES | YES | YES |
| | **Encephalitis** [+] | YES | YES | YES | YES |
| Vaccine platform-associated | **TTS-VITT** [+] | | | YES* | |
| | **Guillain Barré Syndrome** [+] | | | YES | |
| | **Transverse myelitis** [+] | | | YES | |
| | **Acute disseminated encephalomyelitis** [+] | | | YES | |
| All vaccines | **Anaphylaxis** [+] | YES | YES | YES | YES |
| | **Generalized convulsive seizure** [+] | YES | YES | YES | YES |
| | **Thrombocytopenia** [+] | YES | YES | YES | YES |

**** Recommended Protocol-specified AESIs:***

- *AESIs that may not be captured in timeframe for routine safety surveillance (e.g. nonserious AEs for 28 days)*
- *AESIs that require systematic data collection to characterize*

[#] Case Definition under development

[+] Case Definition, Companion Guide, Automated Brighton Classification (ABC) tool

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https://speacsafety.net/tools/aesi-lists/rift-valley-fever/
https://zenodo.org/records/17455987

# AESIs for RVF vaccines under consideration: pregnant populations

| Rationale for AESI | AESI | VACCINE | | | |
|---|---|---|---|---|---|
| | | hRVFV-4s | DDVax | ChAdOx | MP12 |
| RVF Disease-associated (direct viral damage or immuno-pathogenesis) | **Stillbirth** | YES* | YES* | YES* | YES* |
| | **Spontaneous Abortion / Miscarriage** | YES* | YES* | YES* | YES* |

[#] Case Definition update under development
[+] Case Definition
*Guidance available (GAIA, maternal checklist)

**** Recommended Protocol-specified AESIs:***

- *AESIs that may not be captured in timeframe for routine safety surveillance (e.g. nonserious AEs for 28 days)*
- *AESIs that require systematic data collection to characterize*

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https://brightoncollaboration.org/global-alignment-of-immunization-safety-assessment-in-pregnancy-gaia/
Muñoz FM et al, Vaccine 2025. https://doi.org/10.1016/j.vaccine.2025.127513
https://speacsafety.net/tools/aesi-lists/rift-valley-fever/
https://zenodo.org/records/17455987

# BC/SPEAC Tools to Implement AESI Data Collection

## Data Collection Form and LOC Aid

**Encephalitis, Myelitis and ADEM: Data Collection Form and aids for Level of Diagnostic Certainty Assessment**
(Brighton CD: Vaccine 2007; 25: 5771-92; form harmonized for Digital Transformation and Companion Guide)

**Step 1. Complete the case data entry form choosing the most appropriate answer as defined below:** Terms with a glossary definition

- 'YES' means there was written or verbal evidence that the criterion was present.
- 'NO' means there was written or verbal evidence that the criterion was not present.
- 'UNKNOWN' means there was uncertainty in interpreting whether the criterion was present or absent, OR nothing was documented about the criterion.
- Questions regarding criteria marked with an asterisk* must be answered.

| Criterion | Question | Possible Answers | | |
|---|---|---|---|---|
| **A – Histopathology of brain or spinal cord tissue** | | | | |
| A0.1* | **Were samples of brain tissue obtained, by biopsy or at autopsy, for histopathology** (microscopic examination)? If YES, answer A0.2 below | ☐ YES | ☐ NO | ☐ UNKNOWN |
| A0.2 | **Were any brain tissue abnormalities reported?** *NOTE: **answer NO** if histopathology reported as 'normal' or 'no abnormalities seen'. **Answer UNKNOWN** if report unavailable or uninterpretable. **Answer YES** if ≥1 abnormality reported **AND complete A 1, 2 and 3*** | ☐ YES | ☐ NO | ☐ UNKNOWN |
| A0.3* | **Were samples of spinal cord tissue obtained, by biopsy or at autopsy, for histopathology** (microscopic examination)? If YES answer A0.4 below | ☐ YES | ☐ NO | ☐ UNKNOWN |
| A0.4 | **Were any spinal cord tissue abnormalities reported?** *NOTE: **answer NO** if histopathology reported as 'normal' or 'no abnormalities seen'. **Answer UNKNOWN** if report unavailable or uninterpretable. **Answer YES** if ≥1 abnormality reported **AND complete A 4 and 5*** | ☐ YES | ☐ NO | ☐ UNKNOWN |
| A | *Check YES if listed finding reported or **NO** if listed finding not mentioned. (review autopsy or biopsy report(s) & clinical notes)* | | | |
| | 1. Brain histopathology showed presence of acute inflammation | ☐ YES | ☐ NO | |
| | 2. Brain histopathology showed presence of multifocal, focal or diffuse demyelination | ☐ YES | ☐ NO | |
| | 3. Brain histopathology reported to be incompatible with or to rule out diagnosis of ADEM | ☐ YES | ☐ NO | |
| | 4. Spinal cord histopathology showed presence of acute inflammation | ☐ YES | ☐ NO | |
| | 5. Spinal cord histopathology showed presence of multifocal, focal or diffuse demyelination | ☐ YES | ☐ NO | |
| **B – Signs and Symptoms of Encephalopathy** | **Were any of the features listed in B (1-9) below present?** | | | |
| B | 1. Depressed level of consciousness for >24 hours | ☐ YES | ☐ NO | ☐ UNKNOWN |
| | 2. Altered level of consciousness for >24 hours | ☐ YES | ☐ NO | ☐ UNKNOWN |
| | 3. Lethargy for >24 hours | ☐ YES | ☐ NO | ☐ UNKNOWN |
| | 4. Personality change for >24 hours | ☐ YES | ☐ NO | ☐ UNKNOWN |
| | 5. Decreased or absent reponse to loud noise or painful stimuli | ☐ YES | ☐ NO | ☐ UNKNOWN |
| | 6. Inconsistent or absent response to other external stimuli | ☐ YES | ☐ NO | ☐ UNKNOWN |
| | 7. Decreased or absent eye contact | ☐ YES | ☐ NO | ☐ UNKNOWN |
| | 8. Decreased arousability | ☐ YES | ☐ NO | ☐ UNKNOWN |

## Automated Brighton Classification (ABC) Tool

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ABC
Automated Brighton Classification

Case Definition Assessments

Go Back

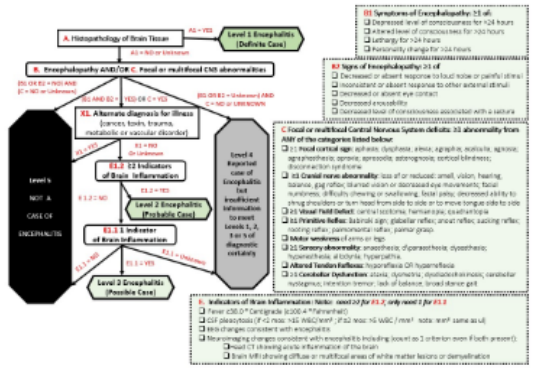
Complete AESI Form

AESI Name: Encephalitis & Myelitis & ADEM | Form Version: V1 | Case Id: EMA-200-30

Encephalitis | Myelitis | ADEM | Final classification

**Encephalitis (Level 2)**

| Criterion | Category | Final Value | Associated Questions |
|---|---|---|---|
| A1 | Microscopic brain inflammation | UNKNOWN | A(0.1-0.2), A(1-2) |
| B1 | Signs and Symptoms of Encephalopathy | YES | B(1-4) |
| B2 | Signs and Symptoms of Encephalopathy | YES | B(5-9) |
| C | Signs and Symptoms of Focal neurologic deficit | NO or UNKNOWN | C(1-9) |
| E1.1 | 1 indicator of brain inflammation | YES | E(0.1-0.5) |
| E1.2 | ≥2 indicators of brain inflammation | YES | E(0.1-0.3), E(0.8) |
| X1 | Exclusionary Criteria | NO or UNKNOWN | X(1) |



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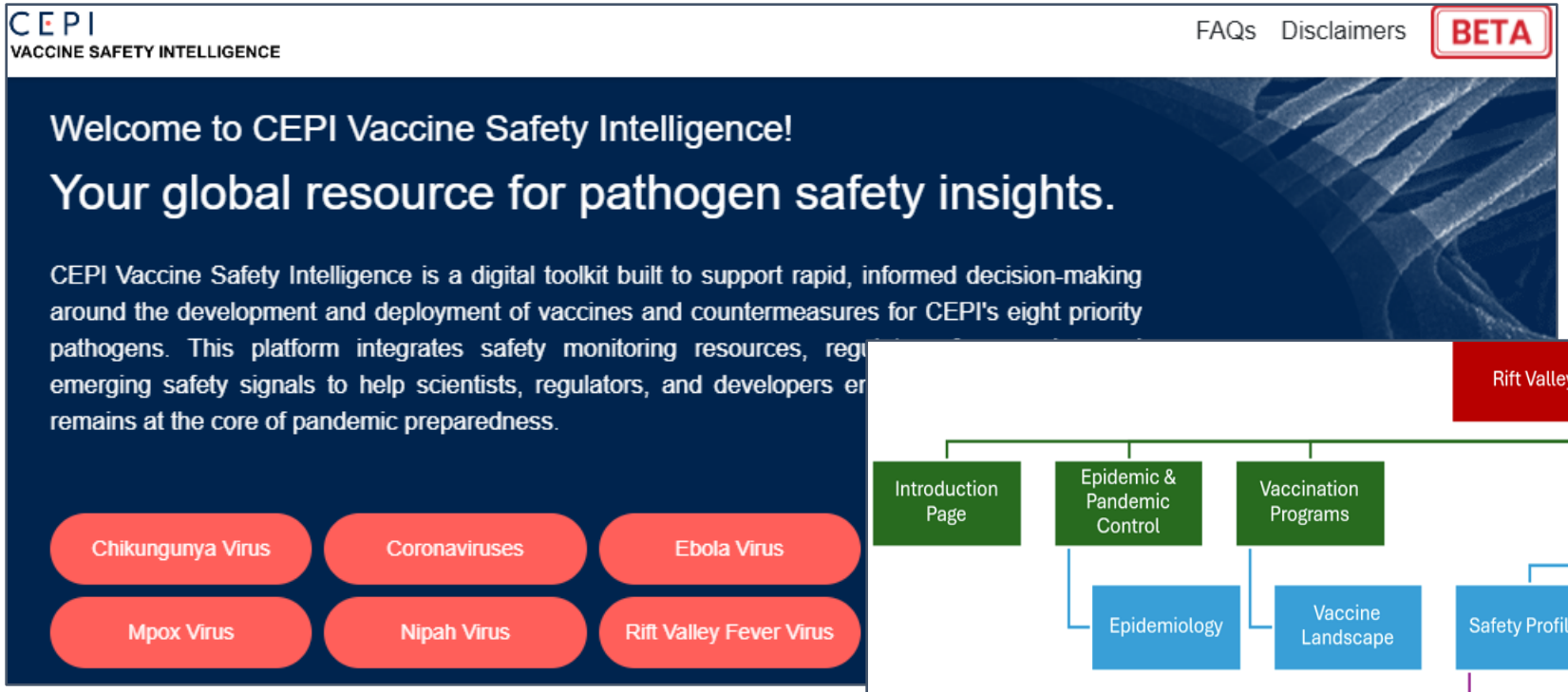
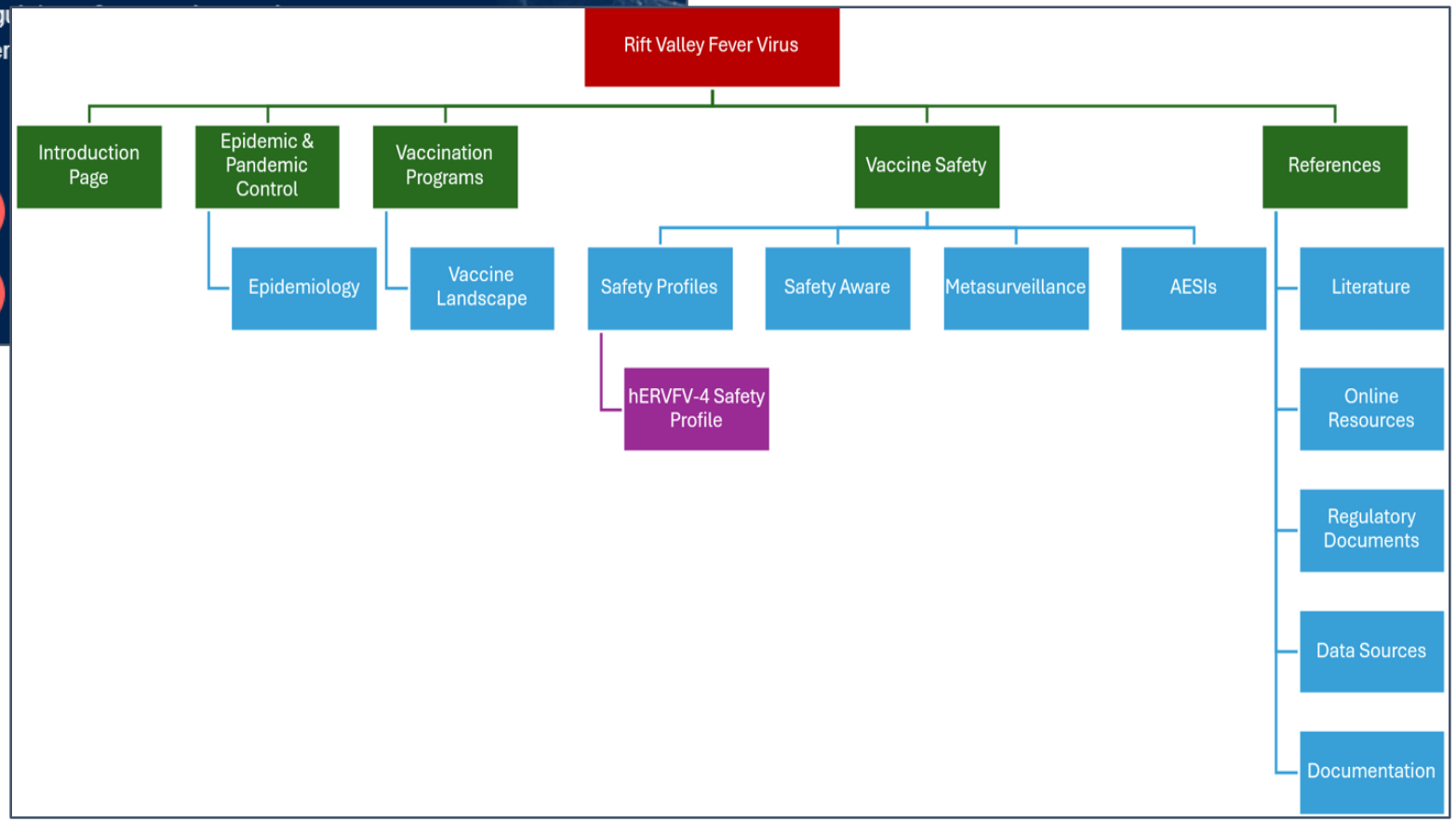
# RVF Digital Toolkit: CEPI Vaccine Safety Intelligence Platform

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https://toolkit.speacsafety.net

# Digital Toolkit for RVF: CEPI Vaccine Safety Intelligence Platform

**AESI Details**

This table presents detailed profiles of AESIs, outlining documentation status such as case definitions, companion guides, and data abstraction tools. It categorizes each AESI by body system and relevance to Rift Valley Fever, highlighting preparedness for surveillance and safety data standardization.

| AESI | Body System | Special Population | Published BCCD | Link to BCCD | Version | Companion Guide | Link to Companion Guide | Simplified Data form | Link to Data Abstraction Form | Disease Specific | Specific to Vaccine Platform |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Acute hepatitis / fulminant liver failure | Hepatic | All | No | TBD | NA | No | TBD | No | TBD | Yes | NA |
| Acute Kidney Injury/renal failure | Renal | All | No | TBD | NA | No | TBD | No | TBD | Yes | NA |
| Anaphylaxis | Immunologic | NA | Yes | | V2 2022 | Yes | | Yes | | | All Vaccines |
| Encephalitis | Neurologic | NA | Yes | | V1 2007 | Yes | | Yes | | Yes | NA |
| Generalized convulsive seizure | Neurologic | All | Yes | | V1 2004 | Yes | | Yes | | Yes | All Vaccines |
| Guillain-Barré Syndrome (GBS) | Neurologic | NA | Yes | | V1 2011 | Yes | | Yes | | | ChAdOx1 Platform |
| Hemorrhagic disease and DIC | Haematologic | NA | No | TBD | TBD | No | TBD | No | TBD | Yes | NA |
| Intraocular inflammation (uveitis, retinal vasculitis, neuroretinitis) | Ophthalmologic | All | No | TBD | TBD | No | TBD | No | TBD | Yes | NA |

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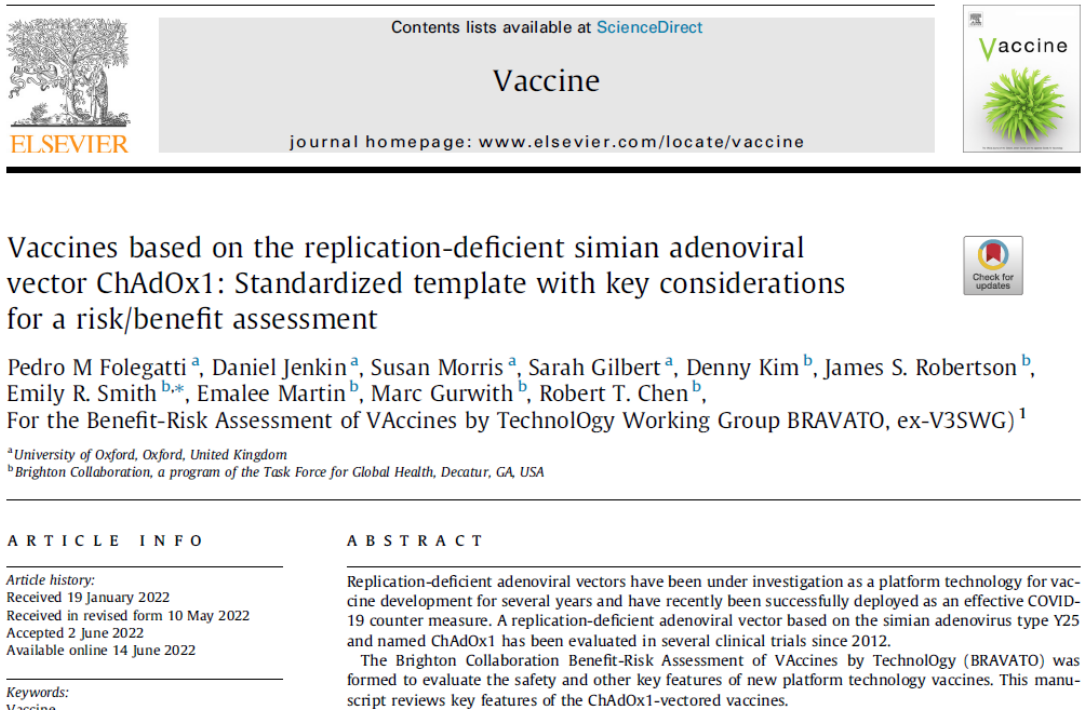
https://toolkit.speacsafety.net/rift-valley/aesis

# BRAVATO Vaccine Profiles for RVF vaccines

- ChAdOx1 platform published 2022 (viral vector template); RVF ChAdOx vaccine template in progress with Oxford
- hRVFV-4s draft template nearly complete with LARISSA II Consortium
- DDvax template planned, pending human clinical trial results (phase 1/2 FPFV anticipated early 2026)



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

## Vaccines based on the replication-deficient simian adenoviral vector ChAdOx1: Standardized template with key considerations for a risk/benefit assessment

Pedro M Folegatti [a], Daniel Jenkin [a], Susan Morris [a], Sarah Gilbert [a], Denny Kim [b], James S. Robertson [b], Emily R. Smith [b,*], Emalee Martin [b], Marc Gurwith [b], Robert T. Chen [b], For the Benefit-Risk Assessment of VAccines by TechnolOgy Working Group BRAVATO, ex-V3SWG) [1]

[a] University of Oxford, Oxford, United Kingdom
[b] Brighton Collaboration, a program of the Task Force for Global Health, Decatur, GA, USA

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ABSTRACT

Replication-deficient adenoviral vectors have been under investigation as a platform technology for vaccine development for several years and have recently been successfully deployed as an effective COVID-19 counter measure. A replication-deficient adenoviral vector based on the simian adenovirus type Y25 and named ChAdOx1 has been evaluated in several clinical trials since 2012.

The Brighton Collaboration Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) was formed to evaluate the safety and other key features of new platform technology vaccines. This manuscript reviews key features of the ChAdOx1-vectored vaccines.

| | Vaccine Safety Template Sections (viral vector vaccines)* |
|---|---|
| 1 | Authorship |
| 2 | Basic vector information |
| 3 | Characteristics of the wild type virus from which the vector is derived |
| 4 | Characteristics of the vector from which vaccine(s) may be derived |
| 5 | Toxicology and potency (pharmacology) of the vector |
| 6 | Adverse event (AE) assessment of the vector |
| 7 | Overall risk assessment of the vector |
| 8 | Target pathogen and population for the vaccine |
| 9 | Characteristics of the vaccine |
| 10 | Toxicology and potency (pharmacology) of the vaccine |
| 11 | Adverse event (AE) assessment of the vaccine |
| 12 | Overall risk assessment of the vaccine |
| 13 | Any other information concerning either the viral vector or the vaccine |

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Folegatti PM et al, Vaccine 2022. https://doi.org/10.1016/j.vaccine.2022.06.008

# Brighton Collaboration Benefit-Risk Assessment Module

- Developed to conduct and communicate formal benefit-risk assessments by vaccine developers, funders, regulators and policy makers in high, middle or low-income countries
- Informs decision-making and facilitate discussions regarding decisions during a vaccine's lifecycle
- Used for planning, conducting, or reporting benefit-risk assessments; or as supplement to BRAVATO vaccine profiles

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ELSEVIER

Benefit-risk assessment of vaccines

Sonali Kochhar [a,b,*], Hector S. Izurieta [c], Rebecca E. Chandler [d], Adam Hacker [d], Robert T. Chen [e], Bennett Levitan [f]

[a] University of Washington, Seattle, USA
[b] Global Healthcare Consulting, India
[c] Center for Biologics Evaluation and Research, Food and Drug Administration, USA
[d] Coalition of Epidemic Preparedness Innovations, London, UK
[e] The Brighton Collaboration, Task Force for Global Health, Decatur, GA, USA
[f] Janssen Research & Development, LLC, USA

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ELSEVIER

The Brighton collaboration standardized module for vaccine benefit-risk assessment

Bennett Levitan [a], Stephen C. Hadler [b], William Hurst [c], Hector S. Izurieta [d], Emily R. Smith [e], Nicole L. Baker [f], Vincent Bauchau [g], Rebecca Chandler [h], Robert T. Chen [e], Danielle Craig [h], Jay King [i], Punnee Pitisuttithum [j], Walter Strauss [k], Sylvie Tomczyk [l], Joseline Zafack [m], Sonali Kochhar [n,o,*]

[a] Janssen Research & Development, LLC, USA
[b] Independent Consultant, Atlanta, GA, USA
[c] Sanofi, Bridgewater, NJ, USA
[d] Center for Biologics Evaluation and Research, Food and Drug Administration, USA
[e] The Task Force for Global Health, Decatur, GA, USA

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Publications:
Digital tool : https://br-module.speacsafety.net/

Slide adapted from Sonali Kochhar, Bennett Levitan, Stephen Hadler

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  - Andrea Berlin
- **Benefit-Risk Module Leads**
  - Sonali Kochhar
  - Bennett Levitan
- **CEPI**
  - Rebecca Chandler
  - Alex Precioso
  - Tom Cole
- **Brighton Collaboration Science Board**



# Thank you!

https://speacsafety.net/
https://brightoncollaboration.org/

efarnon@taskforce.org

bc-coordinator@taskforce.org

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# EXTRA SLIDES

# SPEAC RVF Adverse of Special Interest (AESI) List – v2.1, 17Oct2025

| Body System | AESI | Specific to Rift Valley Fever disease | Specific to vaccine platform | Brighton Case Definition | Brighton CD Companion Guide |
|---|---|---|---|---|---|
| Cardiac | Myocarditis/pericarditis | | MVA | Click to access | Click to access |
| Ophthalmologic | Intraocular inflammation (uveitis, retinal vasculitis, neuroretinitis) | ✅ | | Intraocular inflammation CD pending; click to access draft CD | In development |
| Hematologic | Hemorrhagic disease | ✅ | | Multiorgan dysfunction CD Pending | In development |
| | Thrombocytopenia | ✅ | All vaccines | Click to access | Click to access |
| | Thrombocytopenic Thrombosis Syndrome (TTS) and Vaccine-Induced Immune Thrmobocytopenia and Thrombosis (VITT) | | ChAdOx1 platform | Click to access | Click to access |
| Hepatic | Acute hepatitis / fulminant liver failure | ✅ | | Refer to FDA toxicity grading scales; multiorgan dysfunction CD pending | In development |
| Immunologic | Anaphylaxis | | All vaccines | Click to access | Click to access |
| | Acute aseptic arthritis | | VSV | Click to access | Click to access |
| Neurologic | Encephalitis | ✅ | | Click to access | Click to access |
| | Generalized convulsive seizure | ✅ | All vaccines | Click to access | Click to access |
| | Guillain-Barré Syndrome (GBS) | | ChAdOx1 platform | Click to access | Click to access |
| | Transverse myelitis | | ChAdOx1 platform | Click to access | Click to access |
| | Acute Disseminated Encephalomyelitis (ADEM) | | ChAdOx1 platform | Click to access | Click to access |
| Renal | Acute kidney injury/renal failure | ✅ | | Refer to KDIGO criteria; multiorgan dysfunction CD | In development |
| *Relevant to pregnant populations | | | | | |
| Maternal | Stillbirth | ✅ | | Click to access | NO |
| | Spontaneous Abortion/Miscarriage | ✅ | | Click to access | Click to access |

https://speacsafety.net/tools/aesi-lists/rift-valley-fever/
https://zenodo.org/records/17455987

# Access the RVF Digital Toolkit & CEPI Vaccine Safety Intelligence Platform


## CEPI VACCINE SAFETY INTELLIGENCE

CEPI Safety Intelligence is an interactive, web-based platform that gives public health professionals, researchers, scientists, and regulators the situational awareness needed to act during epidemics and pandemics. By integrating vaccine safety information, immunization program data, and pathogen epidemiology, the platform provides a 360-degree view of the evolving public health landscape.

### VACCINE SAFETY

SPEAC's vaccine safety products including: Case definitions, AESIs/AEFIs, safety profiles, literature reviews and other tools

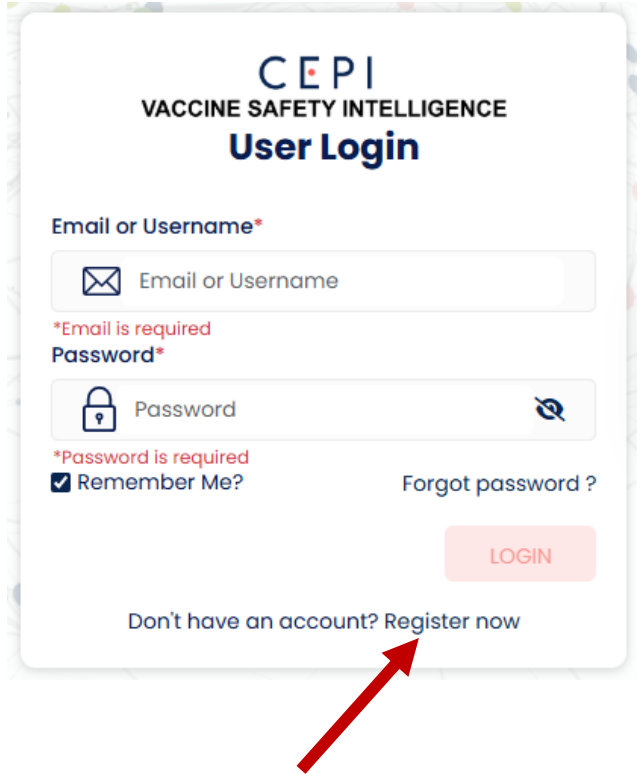
### VACCINATION PROGRAMS

Emergency use authorization tracking, vaccine rollout data, vaccine donations, immunization coverage

### PATHOGEN EPIDEMIOLOGY

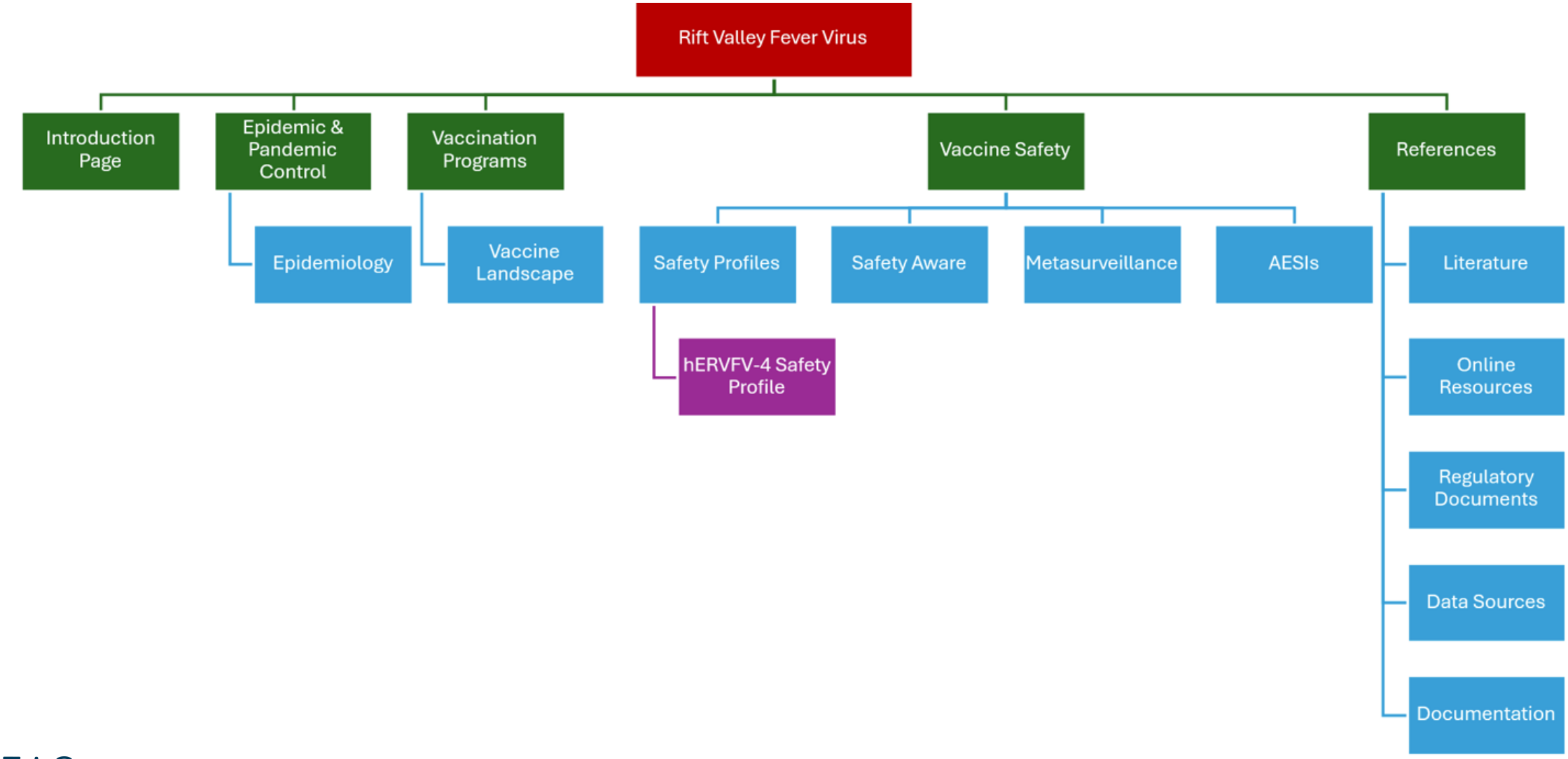
Outbreaks, epidemics, and pandemic pathogen tracking and alerts

LAUNCH CEPI VACCINE SAFETY INTELLIGENCE




https://speacsafety.net/tools/safety-intelligence/

# RVF Digital Toolkit Contents




https://speacsafety.net/tools/safety-intelligence/

# Human Rift Valley fever vaccines
# Clinical (or *near clinical)-stage landscape

| | CEPI-Funded | | | Non-CEPI-Funded | |
|---|---|---|---|---|---|
| **Candidate** | **LARISSA II** | **DD Vax *** | **ChAdOx RVF** | **MP-12** | **TSI-GSD 200** |
| **Platform** | LAV | | Viral Vector | LAV | Formalin-inactivated |
| **Clinical Phase** | Phase 1 complete (Belgium)<br><br>Phase 2a planned (Kenya/ Uganda) | Phase 1 & 2 planned (Tanzania) | Phase 1a & 1b complete (Oxford and Uganda)<br><br>Phase 2a in progress (Kenya) | Status unclear - Phase IIs in progress or completed (No GMP material for MP12) | |
| **Route / Regimen** | 1 & 2 doses being evaluated \| I.M. | | | I.M and SQ | 3 - 4 (S.Q). |
| **DIVA** | Yes | | | No | No |
| **Safety** | Well tolerated<br>AEs mild and self limiting<br><br>(Repeat dose Tox, preclinical and Phase 1 complete) | Positive preclinical data (Repeat dose Tox, preclinical) | Well tolerated<br>AEs mild and self limiting<br><br>(Repeat dose tox and Phase 1a and 1b completed)<br>• Signals (E.g. VITT) warrant further investigation | • Transient viremias in multiple species<br>• Viral RNA detected in organs | • Well tolerated<br>• AEs mild and self limiting |
| **Safety in pregnancy** | Not fully characterised - Positive preclinical data<br>DART Studies planned | | Minimal concern - Positive preclinical and platform data &<br>DART planned | Evidence of risk | Not fully characterised |
| **IG/ Efficacy** | Preclinical and Phase 1 (positive) | Preclinical (positive) | Preclinical & Clinical (Phase 1s) (positive) | Very good | Multiple doses needed |
| **Status/ Dose Readiness** | None currently available | 800 doses GMP CTM1/2 (Release pending) | None currently available - ~6-8 weeks lead time | None available | Unknown |



Source: Pete Hart, CEPI; WHO R&D Blueprint meeting 14 October 2025.

# AESIs: Acute Intraocular Inflammation (DRAFT)

| LOC | Criteria |
|---|---|
| 1 | [Recent onset (≤30 days) of new eye disease **OR** recurrence/worsening of a previously resolved or stable bout of intraocular inflammation]<br>**AND** Meets requirement(s) for at least one of **A1, B1, C1, D1** or **E1** as defined in table below: |
| | **A1. Anterior Uveitis:** — [(blurred **or** reduced vision) **OR** (diffuse eye redness **or** localized ciliary injection) **OR** photophobia] **AND** ≥0.5+ anterior chamber cells by slit lamp bio-microscopy |
| | **B1. Intermediate Uveitis** — [Floaters **or** blurred vision] **AND**<br>[≥0.5+ vitreous cells with haze that obscures view of optic nerve and vessels **or** snowballs] seen with slit lamp bio-microscopy or indirect ophthalmoscopy |
| | **C1. Posterior Uveitis** — Retinal **or** choroidal inflammation evidenced by hypo- or hyper-pigmented, focal or multifocal, lesions in the retina or choroid seen with slit lamp bio-microscopy or indirect ophthalmoscopy or fundus photography |
| | **D1. Retinal Vasculitis** — Focal or widespread arterial **or** venous vascular sheathing based on slit lamp bio-microscopy or indirect ophthalmoscopy or fundus photography. **AND**<br>[(Perivascular sheathing **or** focal areas of cuffing based on fundus photography) **OR**<br>(Blood vessel staining **or** leakage based on fluorescein angiography)]. |
| | **E1. Neuroretinitis** — **[** painless central visual loss **or** blurred vision **or** visual field abnormality**] AND**<br>**[** optic nerve swelling based on fundoscopy, slit lamp bio- microscopy, indirect ophthalmoscopy or fundus photos**] AND**<br>**[** macular edema **or** macular star **or** macular exudates based on indirect ophthalmoscopy or fundus photos**] AND**<br>**[** (>0.5+ vitreous cells based on OCT or fundus photography) **or** (peripapillary vascular obscuration based on fundus photography) **].** |
| 2 | [Recent onset (≤30 days) of new eye disease **OR** recurrence/worsening of a previously resolved or stable bout of intraocular inflammation]<br>**AND** Meets requirement(s) for at least one of **A2, B2, C2 or E2** as defined in table below: *NOTE, there is no level 2 criterion for Retinal Vasculitis)* |
| | **A2. Anterior Uveitis:** — **[** (blurred **or** reduced vision) **OR (**diffuse eye redness **or** localized ciliary injection) **OR** photophobia **]**<br>**AND [** (Posterior synechiae **or** keratic precipitates based on slit lamp bio-microscopy or anterior segment photography **]** |
| | **B2. Intermediate Uveitis** — **[** ≥0.5+ vitreous cells **or** haze based on slit lamp bio-microscopy or indirect ophthalmoscopy **]**. |
| | **C2. Posterior Uveitis** — **[** Decreased vision **or** scotoma **or** metamophopsia **or** serous retinal detachment **or** retinal hemorrhage **] AND [** (hypo- or hyper-pigmented chorioretinal lesions based on fundus photography ) **OR [** hyper-reflective choroidal or retinal lesions based on OCT **]** |
| | **D2. Retinal Vasculitis** — Not applicable |
| | **E2. Neuroretinitis** — **[** painless central visual loss **or** blurred vision **or** visual field abnormality **] AND**<br>**[** optic nerve swelling based on fundoscopy, slit lamp bio- microscopy, indirect ophthalmoscopy or fundus photography **] AND**<br>**[** peripapillary vascular obscuration based on fundus photography **]** |
| 3 | [Recent onset (≤30 days) of new eye disease **OR** recurrence/worsening of a previously resolved or stable bout of intraocular inflammation] **AND** 2 or more of the following:<br>• blurred vision **or** reduced visual acuity<br>• eye redness **or** ciliary injection<br>• ocular pain in one **or** both eyes<br>• floaters<br>• photophobia<br>• macular edema |
| 4 | Reported as a case of aIOI but insufficient information to meet any level of the case definition |
| 5 | NOT a case of aIOI (because not of recent onset **OR** there is an alternate explanation for the clinical presentation). |

**LOC = Level of diagnostic certainty*

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# AESIs: VHF & end organ damage

| Event | BC Case Definition (CD) | Other definitions/ classifications |
|---|---|---|
| VHF | • Multiorgan dysfunction pending | |
| Hemorrhagic disease/DIC | • Multiorgan dysfunction pending | |
| Thrombocytopenia | • Thrombocytopenia | |
| Acute hepatitis/fulminant liver failure | • Multiorgan dysfunction pending | • FDA toxicity grading scales |
| Acute kidney injury/renal failure | • Multiorgan dysfunction pending | • KDIGO criteria |

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[Add references]

# AESIs: Thrombocytopenia, Encephalitis

## Thrombocytopenia

**Level 1 of diagnostic certainty (confirmed TP)**
Platelet count[a] less than $150 \times 10^9\ L^{-1}$
AND
confirmed by blood smear examination OR the presence of clinical signs and symptoms of spontaneous bleeding[b]

**Level 2 of diagnostic certainty (unconfirmed TP)**
Platelet count[a] less than $150 \times 10^9\ L^{-1}$

**Level 3 of diagnostic certainty**
*Not applicable*

[a] Measured by an automated hematology analyzer or assessed by hand count of platelets on a cell count slide.

[b] Presentations of spontaneous (i.e., non-traumatic) bleeding include purpura (i.e., petechiae, purpura *sensu stricto*, ecchymosis), hemorrhagic oozing of skin lesions including rashes, hematoma, bruising, hematemesis, hematochezia, occult bleeding per rectum, epistaxis, hemoptysis, hematuria, vaginal bleeding other than menstruation, conjunctival bleeding, intracranial bleeding.

## Encephalitis

**Level 1 of diagnostic certainty**[3]: Encephalitis

(a) Demonstration of acute inflammation of central nervous system parenchyma (± meninges) by histopathology.

**Level 2 of diagnostic certainty**[4,5]: Encephalitis

(a) Encephalopathy (e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 h),

**AND INCLUDING**

(b) **ONE OR MORE** of the following:
1. Decreased or absent response to environment, as defined by response to loud noise or painful stimuli,
2. Decreased or absent eye contact,
3. Inconsistent or absent response to external stimuli,
4. Decreased arousability,
5. Seizure associated with loss of consciousness [62].

**OR**

(c) Focal or multifocal findings referable to the central nervous system, including one or more of the following:
1. Focal cortical signs (including but not limited to: aphasia,alexia, agraphia, cortical blindness),
2. Cranial nerve abnormality/abnormalities,[6]
3. Visual field defect/defect(s),
4. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex),
5. Motor weakness (either diffuse or focal; more often focal)[6]

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[Add references]

# AESIs: Thrombocytopenia with thrombosis (TTS)

| | |
|---|---|
| **Level 1 (definite case)** | |
| **1.1** | **Thrombocytopenia indicated by ≥ 1 of the following:**<br>• $<150 \times 10^9$/L<br>• Below local laboratory lower limit for normal<br>• ≥50 % decrease from a previously documented count<br>**AND** |
| **1.2** | **Presence of ≥ 1 of the following:**<br>• Acute or new onset thrombus or thromboembolism confirmed by imaging, surgical procedure or pathological examination of autopsy or biopsy material.<br>• Severe, persistent headache with an onset from 5 to 30 days after vaccination with peak D-dimer > 8 x ULN (corresponding to > 4000 ng/mL)<br>**AND** |
| **1.3** | **Symptom onset from 4 to 30 days after vaccination* (day 0).**<br>• If the thrombosis is only DVT or pulmonary embolism, the interval can be up to day 42.<br>**AND** |
| **1.4** | **A more plausible alternative explanation for illness not found** |
| **Level 2 (probable case)** | |
| **2.1** | **Thrombocytopenia (same as defined in 1.1 above)**<br>**AND** |
| **2.2** | **Clinical presentation that is consistent with acute or new onset thrombosis or thromboembolism syndrome**<br>**AND** |
| **2.3** | **Symptom onset from 4 to 30 days after vaccination* (day 0).**<br>• If the thrombosis is only DVT or pulmonary embolism the interval can be up to day 42.<br>**AND** |
| **2.4** | **A more plausible alternative explanation for illness not found** |

* Except for severe and persistent headache which should have an onset from 5 to 30 days after vaccination

[Add reference]

# AESIs: Vaccine-induced immune thrombocytopenia and thrombosis (VITT)

## VITT case definition

| | |
|---|---|
| **Level 1 (definite case)** | |
| **1.1** | **Presence of all five VITT criteria*** |
| | **OR** |
| **1.2** | **A positive functional assay for PF4 dependent antibodies (with or without a positive ELISA test)** |
| | **AND** |
| **1.3** | **Presence of 3 of the other 4 VITT criteria*** |
| **Level 2 (probable case)** | |
| **2.1** | **A positive PF4 antibody ELISA assay without a functional assay result for PF4 dependent antibodies** |
| | **AND** |
| **2.2** | **Presence of three of the other four VITT criteria*** |
| | **AND** |
| **2.3** | **A more plausible alternative explanation for illness not found** |
| **Level 3 (possible case)** | |
| **3.1** | **Presence of any three of the five VITT criteria*** |
| | **AND** |
| **3.2** | **A more plausible alternative explanation for illness not found** |

**1. thrombocytopenia, 2. elevated D-dimer, 3. acute or newly diagnosed thrombosis or thromboembolism, 4. characteristic interval from vaccination to onset, 5. anti-PF4 antibody (see Table 6 for definitions)*

## Criteria for VITT

| Condition | Defined criterion |
|---|---|
| A. Thrombocytopenia | Platelet count that meets ≥ 1 of the following:<br><150 x $10^9$/L<br>Below the local laboratory lower limit for normal<br>≥50 % decrease from a previously documented count |
| B. Elevated D-dimer | A peak D-dimer that is > 8 times the upper normal limit for the testing laboratory (corresponding to > 4000 ng/mL (FEU) D-dimer*) |
| C. Acute or newly diagnosed thrombosis or thromboembolism | ≥1 of the following:<br>Thrombotic event confirmed by pathology, imaging or surgical procedure (equals level 1 of the Brighton Collaboration thrombosis and thromboembolism case definition)<br>Severe, persistent headache with onset from 5 to 30 days after vaccination[1] |
| D. Characteristic interval from vaccination to onset | Symptom onset must fall within 1 of the following intervals:<br>Day 4 to day 30 after vaccination[2]<br>Day 4 to day 42 after vaccination[2] IF the thrombotic event is an isolated DVT or pulmonary embolism |
| E. Anti-PF4 antibody | ≥1 of the following:<br>Positive anti-PF4 antibody ELISA test<br>Positive functional assay for PF4 dependent antibodies. |

[1] Headache and other symptoms occurring in the first days following vaccination are common and rarely have any long-term significance.
[2] Date of vaccination defined as day 0.
* A normal D-dimer level effectively rules out VITT.

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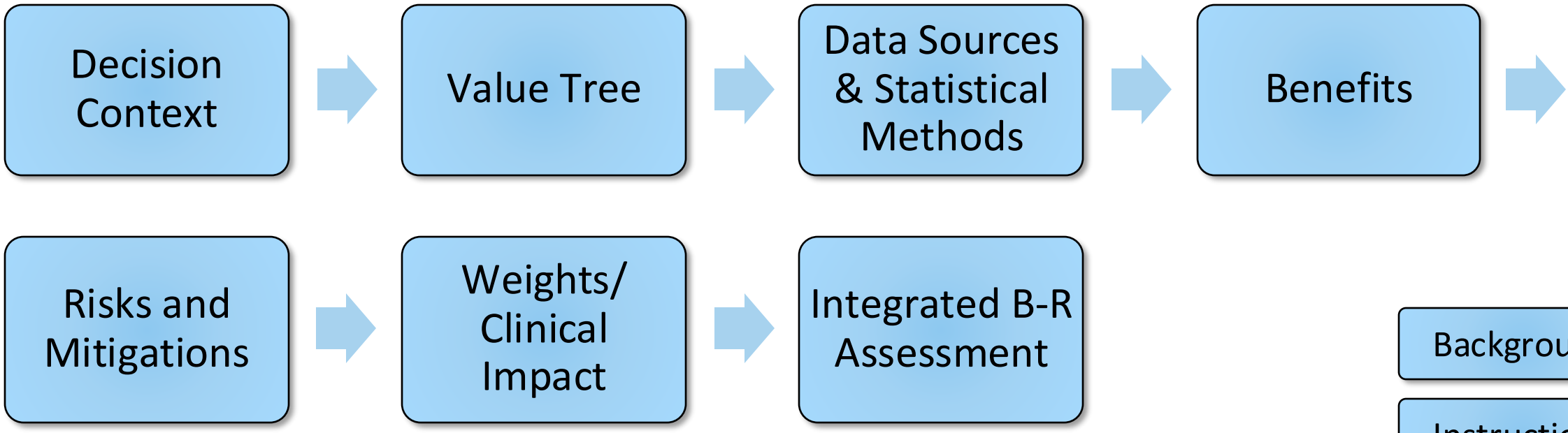
[Add reference]

# Sections of B-R Module




Slide courtesy of Sonali Kochhar, Bennett Levitan, Stephen Hadler

# Integrated B-R Assessment

SPEAC

Benefit-Risk Module

Introduction

M Myocarditis following mRNA COVID-19 Vaccines in Males

- Decision Context
- Endpoints And Value Tree
- Data Sources and Statistical Methods
- Benefits
- Risks and Mitigations
- Clinical Impact / Weighting
- Visualizations
- Integrated B-R Assessment

Glossary

Template Version | Regulatory Framework

1. Integrated B-R Assessment

For the base case analysis, during a period of moderately low COVID-19 incidence in the US, the benefits of mRNA COVID-19 vaccination outweigh the harms for all age groups of males. The balance of benefits and harms is strongest for males > 30 years of age (e.g. per 1,000,000 vaccinated individuals, expected prevention of 2848 341 COVID-19 related hospitalizations, 843 ICU admissions and 341 deaths, compared to expected 2 myocarditis hospitalizations, 1 ICU admission and no deaths). Additionally, the median length of COVID-19 hospitalizations prevented is 4-6 days, while that for myocarditis hospitalizations caused is 1 day. For the youngest age males (16-17-year-old), the balance is less strong, but still favors benefits (e.g. 204 hospitalizations, 69 ICU admissions, and 3 deaths expected to be prevented per million vaccinations, vs. 127 myocarditis hospitalizations, 42 ICU admissions, and no deaths following vaccination). For males 18-29-years-old, benefits also strongly outweigh the risks of mRNA vaccination.
In sensitivity analyses, when COVID-19 incidence is 3-fold higher (moderately high incidence), benefits even more strongly outweigh risks for all age groups.
When COVID-19 incidence is low (⅓ that of the base case, the benefits still outweigh the risks for both males over 30 years-old and 18-29 years-old (for 18-29 years, expected benefits of 212 hospitalizations, 53 ICU admissions and 3 deaths prevented, vs. risks of 76 hospitalizations, 25 ICU admissions and no deaths due to mRNA myocarditis). However, for 16–17-year-old males, the assessment is more complex. The expected risks for hospitalization and ICU admission are greater in number than the benefits - e.g. 128 hospitalizations and 42 ICU admissions expected due to mRNA myocarditis, vs expected benefits fewer 68 hospitalizations, 23 fewer ICU admissions and 1 fewer death due to COVID-19, all per 1,000,000 vaccinated individuals. Given that hospitalization and ICU admissions for myocarditis are mainly for heart monitoring while COVID-19 hospitalization is considerably longer than and much more clinically impactful than for myocarditis, we judge benefits to outweigh risks for the low incidence scenario in the 16-17-year-old males as well.
Based on these analyses with US data, overall, benefits outweigh risks for mRNA vaccines vs. no vaccines in males ages 16 and older.
Limitations of this analysis include the use of US data only. For example, other countries may have different COVID-19 incidence rates, different qualities and uses of medical care, ability to receive second doses, etc.). These expected risks and benefits may also need to consider additional factors, including not just the length of hospitalization (longer for COVID-19 than mRNA myocarditis) but the nature of the hospitalization as well as risks of long COVID (post-acute sequelae of COVID-19) following COVID-19 infection on one hand, versus the long-term impact of mRNA myocarditis, still not clearly defined, on the other.