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Updated Landscape Analysis for Priority List of Adverse Events of Special Interest (AESI): Rift Valley Fever

Work Package: [WP2]

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Safety Platform for Emergency vACcines

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DEFINITIONS & ACRONYMS

SPEAC	Safety Platform for Emergency vAccines
AESI	Adverse Event of Special Interest
CEPI	Coalition for Epidemic Preparedness Innovations
RVF	Rift Valley Fever
AEFI	Adverse Event Following Immunization
CIOMS	Council For International Organizations Of Medical Sciences
DNA	Deoxyribonucleic Acid
CD	Case Definition
DIC	Disseminated Intravascular Coagulation
MVA	Modified Vaccinia
TTS	Thrombocytopenia With Thrombosis Syndrome
VIIT	Vaccine-Induced Thrombocytopenia
VSV	Vesiculostomatitis Virus
FDA	Food and Drug Administration

EXECUTIVE SUMMARY

A key activity of SPEAC (Safety Platform for Emergency vACcines) has been to establish lists of adverse events of special interest (AESI) that have potential to occur during CEPI funded clinical trials. The initial landscape analysis for Rift Valley Fever AESI was completed in March 2020 and was based on a non-systematic literature review of key articles. RVF clinical trials are due to commence within the year in East African sites and thus an update to the RVF AESI list is a high priority for CEPI. The primary objective was to conduct a scoping review of literature published after the previous landscape analysis in order to determine whether or not any new AESI should be added to the previous AESI list for novel Rift Valley Fever vaccines. No new AESI were identified as a result of this updated landscape analysis for Rift Valley Fever as a disease, however several new AESI are associated with vaccine platforms. An updated version of the AESI list is included in the document. This includes additional platform-specific AESI, based on experience with COVID-19 vaccines. It also provides an update as to which AESI have published case definitions and companion guides.

1. Introduction

CEPI–contracted the Brighton Collaboration, through the Task Force for Global Health, to harmonize safety assessment across CEPI funded vaccine development. Since inception, a key activity of SPEAC (Safety Platform for Emergency vACcines) has been to establish lists of adverse events of special interest (AESI) that have potential to occur during CEPI funded clinical trials.

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.[1]

The source definition of 'Adverse Event of Special Interest' (AESI) as described in CIOMS VII[2] is:

"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 early in product development for safety planning, data collection, analysis and reporting on AESI data, and eventually form the base of AESI analysis in the Reporting and Analysis Plan. AESI may also be used to generate or retrieve background rates prior to vaccine launch and be incorporated in risk management plans.

Vaccine safety needs to be conducted across the entire life cycle of vaccine development, approval and use. It is essential that the approach is harmonized and standardized so that data are comparable across different studies and populations. Thus, while several 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, preparations must be made to maximize the utility of vaccine safety data so appropriate risk-benefit decisions can be made.

SPEAC has chosen to identify AESI using 4 main approaches as outlined below. The AESI that were included on the 2020 Rift Valley Fever list are shown for each category below:

1. AESI that have been previously identified with immunization in general:
    a. Anaphylaxis, thrombocytopenia, generalized convulsion
2. AESI associated with specific vaccine platforms:
    a. Live vaccine: aseptic meningitis, encephalitis, myelitis
    b. Vesiculostomatitis virus vaccine platform: acute aseptic arthritis
    c. Modified vaccinia virus platform: myocarditis
    d. Pandemic and some seasonal influenza vaccines: Guillain Barré Syndrome
3. AESI that may occur during the clinical course or as a complication of the chosen target diseases due to viral replication or a host response immunopathogenic mechanism:
    a. Hemorrhagic disease: internal/external (skin, mucosa) bleeding

b. Hepatic disease: acute hepatitis, fulminant liver failure
c. Neurologic disease: meningoencephalitis
d. Ocular disease: unilateral or bilateral blindness / decreased vision
e. Pregnancy: spontaneous abortion, stillbirth
f. Renal disease: acute renal failure

4. Theoretical AESI based on animal models or in vitro experimental data. E.g., vaccine-associated enhanced disease seen in mouse model of SARS1 and MERS vaccines. Not part of the 2020 RVF AESI list.

The initial landscape analysis for Rift Valley Fever AESI was completed in March 2020 and was based on a non-systematic literature review of key review articles (SPEAC SO1 D2.3 Priority list of AESI: Rift Valley Fever March 31, 2020). RVF clinical trials are due to commence within the year in East African sites and thus an update to the RVF AESI list is a high priority for CEPI.

2. Objective of this deliverable

The primary objective was to conduct a scoping review of literature published after the previous landscape analysis in order to determine whether or not any new AESI should be added to the previous AESI list for novel Rift Valley Fever vaccines.

3. Methods

The scoping review followed the PRISMA Guidelines Extension for scoping reviews.[3] The search strategy for MEDLINE was based on the guiding research question: What is the incidence and clinical presentation for Rift Valley Fever? Keywords were chosen for MEDLINE and then adapted to EMBASE and Web of Science. The search covered the period of January 1, 2018 through May 24, 2024. ,

The search strategy for each source is shown below:

Medline (OVID)

"Rift Valley Fever"[MeSH Terms] OR "Rift Valley fever virus"[MeSH Terms] OR "Rift Valley Fever"[MESH] OR "Rift Valley fever virus"[MESH] OR (("rift valley fever"[all] OR "rift valley"[all] OR ("rift valley"[all] AND "fever"[all]) AND (complications[all] OR epidemiology[all] OR physiopathology[all] OR immunology[all] OR "virology*"[all]) OR etiology[all] OR "outbreak*"[all])) AND ("2018/01/01"[Date - Publication] : "3000"[Date - Publication])

Embase (OVID)

((Rift Valley Fever'/exp OR 'Rift Valley Fever' OR 'Rift Valley Fever Virus'/exp OR 'Rift Valley Fever Virus') AND ('complications'/exp OR complications OR 'epidemiology'/exp OR epidemiology OR 'physiopathology'/exp OR physiopathology OR 'immunology'/exp OR immunology OR virology* OR 'etiology'/exp OR etiology OR outbreak*.) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)) AND limit AND date AND [2019-2024]/py

CINAHL (EBSCOHost)

("Rift Valley Fever" OR "Rift Valley fever virus" OR ("rift valley" AND fever)) AND (complications OR epidemiology OR physiopathology OR immunology OR virology* OR etiology OR outbreak*)

Search results were uploaded into EndNote 21 (Clarivate Analytics ©, Thompson Reuters, New York, NY, USA), de-duplicated, and uploaded to Covidence (Veritas Health Innovation Ltd., Melbourne, VIC, Australia) where a second round of deduplication was conducted. No study protocol was published for this effort.

Two medical reviewers independently screened the title and abstract of all uploaded references in Covidence, selecting articles that might inform the AESI list for further full text review. Excluded from further review were the following: non-English article; focus on AESI already included in the 2020 RVF AESI list, with the exception of ocular disease; general description of outbreak without individual clinical data from confirmed cases; report of outbreak with concomitant infections other than RVF; in vitro studies; studies involving animals only except for animal models that focused on neurologic disease in RVF. The rationale for including articles that focused on ocular disease was to gain a better understanding of the nature of ocular complications since the previous AESI list was very broad, mentioning loss of vision or blindness which could have many different causes. Discrepancies in included/excluded articles by the two reviewers were discussed and consensus obtained on the list of articles needing full text review.

The full text of articles screened in by title/abstract review was done by a single medical reviewer (BL) to select articles most likely to contribute to the AESI list. The final group of included articles were then reread in full and detailed notes on relevant clinical data made in a word document (BL).

4. Results

A total of 1083 articles were identified by the literature search and 42 screened out (by ES) because non-English or clearly veterinary focus. Consensus by the two expert reviewers (BL, EF) was reached on excluding 916 articles as irrelevant to updating the AESI list. The full text of the remaining 125 articles was screened (BL) and an additional 113 articles excluded for the following reasons: 72 had information consistent with the previous AESI list but nothing new was found (these included 14 dealing with obstetric / fetal complications, all of which were forwarded to WP 5 Special Populations; including also 9 focused on ocular disease. These were saved, given their relevance to developing an ocular disease case definition, but they did not add anything new regarding AESIs); 31 had no clinical information at all; 2 were meeting abstracts only; 2 were completely unrelated to Rift Valley Fever; 1 was an editorial with no original data and 5 could not be retrieved for review.

A total of 12 articles were included for data abstraction related to updating the AESI list[4-15] and 1 additional article was found from hand search of the citation lists.[16]

Three of the articles focused on clinical Rift Valley Fever disease.[4-6] A systematic review and meta-analysis for clinical course and complications in human Rift Valley Fever screened 3765 articles and included 32 which

presented 30 unique studies of 21 outbreaks in 15 countries from 1933 to 2019.[4] The majority, 25 of 30, were hospital based, with 11 involving both in- and out-patients, 10 including in-patients only and 4 only out-patients. There were 13 case series, 12 cross sectional studies and 5 cohort studies. Sample sizes varied from 3 to 683 cases and ages ranged from 2 to 90 years. The authors identified 9 unique clinical syndromes associated with human Rift Valley Fever:

1. Fever alone
2. Acute kidney injury/renal failure
3. Gastrointestinal (mainly nausea)
4. Hepatic dysfunction/failure
5. Haemorrhagic disease
6. Visual impairment
7. Neurologic involvement (mainly encephalitis)
8. Cardio-pulmonary involvement (mainly cough)
9. Obstetric complications (mainly miscarriage).

All of the above, except fever alone and nausea, were captured in the original landscape analysis.

Two other reviews focused on clinical disease. Anywaine et al[5], reviewed outbreaks in Uganda from Nov 2018 through 2020. One year of follow-up was done for 9 confirmed hospitalized cases and 3 confirmed non-hospitalized cases. Abnormal CBCs and elevated liver function tests all normalized within 3 months of acute disease and remained so through the one year of follow-up. Javelle et al[6] did a general clinical review of Rift Valley Fever in humans. The spectrum of disease manifestations was the same as reported by others with nothing new identified in terms of AESI. They noted the usual timing of abnormalities with liver dysfunction usually occurring from 2 to 21 days from symptom onset; ocular dysfunction from 4 to 20 days after onset, acute encephalitis from 2 to 10 days after onset and delayed encephalitis from 4 to 60 days after onset. They noted that the most frequently seen eye complication was paramacular retinitis.

Four articles focused on RVF pathogenesis.[7-10] Connors et al [7], focused on meningoencephalitis, reviewing several existing animal models including mice, rats, gerbils, ferrets and non-human primates. Human pathology studies showed features typical for encephalitis – namely lymphocytic infiltration with perivascular cuffing. They noted that while it is clear that encephalitis in RVF is due to viral invasion of the brain, the pathway(s) to brain entry are not yet clear. Harmon et al[8], reviewed the relevance of the immune response to encephalitis pathogenesis concluding that innate immunity as well as cell-mediated immunity are likely key to prevent encephalitis following RVF viral infection. Finally Odendaal et al[9], did a detailed review of evidence for RVF virus tissue tropism – both for animals and humans. As human data is primarily gained from post-mortem studies, it is not surprising that cell necrosis and hemorrhage were the main pathologies recognized in liver, kidney, lymphatic organs, and gastrointestinal tract. Hemorrhage without necrosis was also seen in lung and cardiac tissue. None of the articles on pathogenesis suggested any new AESI.

Five articles focused on existing or developing vaccines.[11-15] Several vaccine platforms have been studied in animals and humans including live attenuated virus, viral-vectors, DNA, subunit, viral replicons and virus-like particles. The

main AESI of concern, associated with the first generation live attenuated vaccines using the Smithburn neurotropic strain of RVF virus , were spontaneous abortions and stillbirths in animals.[11] It is beyond the scope of the landscape analysis to review each of these candidates in depth but it is anticipated that whichever platforms are used in RVF trials, a risk-benefit template will be available to summarize evidence regarding possible platform-associated AESI.

5. Discussion & Recommendations

No new AESI were identified as a result of this updated landscape analysis for Rift Valley Fever as a disease, however several new AESI are associated with vaccine platforms. An updated version of the AESI list is shown in Table 1. This includes additional platform-specific AESI, based on experience with COVID-19 vaccines. It also provides an update as to which AESI have published case definitions and companion guides.

TABLE 1. RVF UPDATED AESI LIST BASED ON ALL POSSIBLE MECHANISMS RELATED TO VACCINE, VACCINE PLATFORM OR RVF DISEASE IMMUNOPATHOGENESIS. ABBREVIATIONS (IN ALPHABETICAL ORDER): AESI – ADVERSE EVENT OF SPECIAL INTEREST; CD – CASE DEFINITION; DIC – DISSEMINATED INTRAVASCULAR COAGULATION; MVA – MODIFIED VACCINIA; TTS – THROMBOCYTOPENIA WITH THROMBOSIS SYNDROME; VITT – VACCINE-INDUCED THROMBOCYTOPENIA AND THROMBOSIS; VSV – VESICULOSTOMATITIS VIRUS.

Body System	AESI	Rationale for Potential AESI			Brighton Case Definition	Brighton CD Companion Guide
		All Vaccines	Vaccine Platform	RVF Disease / Immunity		
Cardiac	Myocarditis		MVA	☑	☑	☑
Eye	Uveitis, retinitis, acute optic neuritis			☑	Priority for 2024	Priority for 2024
Hematologic	Hemorrhagic disease & DIC			☑		
	Thrombocytopenia	☑		☑	☑	☑
	TTS / VITT		COVID-19 Adeno vectors		☑	☑
Hepatic	Acute hepatitis / fulminant liver failure			☑		
Immunologic	Anaphylaxis	☑			☑	☑
Neurologic	Aseptic meningitis		Live vaccines		☑	☑
	Encephalitis		Live vaccines	☑	☑	☑
	Generalized convulsive seizure	☑		☑	☑	☑
	Guillain-Barré Syndrome (GBS)		Some vaccines[1]		☑	☑
Musculoskeletal	Acute aseptic arthritis		VSV		☑	☑
Renal	Acute kidney injury/renal failure			☑		

[1]Influenza H1N1 Pandemic vaccine; some seasonal influenza vaccines; ChAdOx-1 COVID-19 vaccine

SPEAC has prioritized inflammatory eye disease (uveitis, retinitis, acute optic neuritis) for development of a Brighton case definition and companion guide before the end of 2024.

Three AESI have no Brighton case definition: hemorrhagic disease & DIC; acute hepatitis / fulminant liver failure; and acute kidney injury / renal failure.[16] With respect to hemorrhagic disease & DIC, the current Brighton case definition for thrombocytopenia incorporates spontaneous bleeding, which is a frequent manifestation of hemorrhagic disease in RVF, into the case definition. SPEAC does not recommend, at this time, developing a separate case definition for hemorrhagic disease or DIC.

Acute hepatitis and fulminant liver failure are diagnosed by abnormal liver function tests (alkaline phosphatase, ALT, AST, bilirubin). As discussed in a prior landscape update for COVID-19 AESIs (link to SO2_D2.1.2_COVID-19_AEIS update_V1.3) there are no international consensus guidelines for acute liver injury (ALI) but the following definition of ALI can be used:

- > 3-fold elevation above the upper normal limit for ALT or AST OR
- > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
- Measuring all 4 liver enzymes (ALT, AST, GGT, ALP) and total bilirubin will enable defining the pattern of injury as hepatocytic, cholangiocytic or mixed and further whether it is a type 1 ALI (ALT/AST > GGT/ALP) or Type 2 ALI (ALT/AST<GGT/ALP).[17]

Also, the FDA toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (downloadable from FDA.gov) can be used to characterize the severity of liver injury as shown below:

TABLE 2. FDA TOXICITY GRADING SCALE FOR ACUTE LIVER INJURY

Serum	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4)
Alkaline phosphate	1.1-2.0 x ULN	2.1-3.0 x ULN	3.1-10 x ULN	>10 x ULN
LFTs: ALT / AST	1.1-2.5 x ULN	2.6-5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in LFT	1.1 – 1.25 x ULN	1.25-1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when LFT is normal	1.1 – 1.5 x ULN	1.6-2.0 x ULN	2.0-3.0 x ULN	>3.0 x ULN

For acute kidney injury and renal failure SPEAC recommends using the consensus Kidney Disease Improving Global Outcomes (KDIGO) guidelines (see https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf). A review by Thomas et al[18] compares KDIGO with prior guidelines and also describes the modified pRIFLE criteria for children. The KDIGO criteria are shown below (note: specific information regarding how Stage 1-3 are defined can be found):

- Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 umol/l) within 48 hours; OR
- Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days OR

- Urine volume ≤0.5 ml/ kg/ hour for 6 hours

6. References

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ANNEXES

Annex 1: Rift Valley Fever Scoping Review

Prepared for Barbara Law, MD and Eileen Farnon, MD, by Tigest F. Mekonnen, MPH, and Erin C. Stone, MPH, Hubert Department of Global Health, Rollins School of Public Health, Laney Graduate School, Emory University.

Methods

This document is a scoping review conducted according to PRISMA Guidelines Extension for scoping reviews[3] to update the Safety Platform for Emergency vACcines landscape analysis to inform the priority list of adverse events of special interest for Rift Valley Fever.

Topic & Question Development

This research question used to guide this review is:

- What is the incidence and clinical presentation for Rift Valley Fever?

Literature Search

One reviewer (E.C.S.) developed a search strategy for MEDLINE from the research question. This strategy was refined using keywords mined from the references of the previous iteration of this document, and then adapted to EMBASE and Web of Science. Searches were performed from the start of 2018 (the date of the last publication) to May 24, 2024. The results of these searches were uploaded into EndNote 21 (Clarivate Analytics©, Thomson Reuters, New York, NY, USA), de-duplicated, and uploaded to Covidence (Veritas Health Innovation Ltd., Melbourne, VIC, Australia) where a second round of deduplication was conducted. No study protocol was published for this effort.

Study Selection

The titles and abstracts of retrieved references were screened by single review (B.L., E.C.F., or E.C.S.). Full-text articles were retrieved if they were relevant to the research question and reporting on Rift Valley Fever disease course, clinical presentation, complications (including viral-host interactions, immunogenic response, or viral replication response), pathogenesis, or immunologic response.

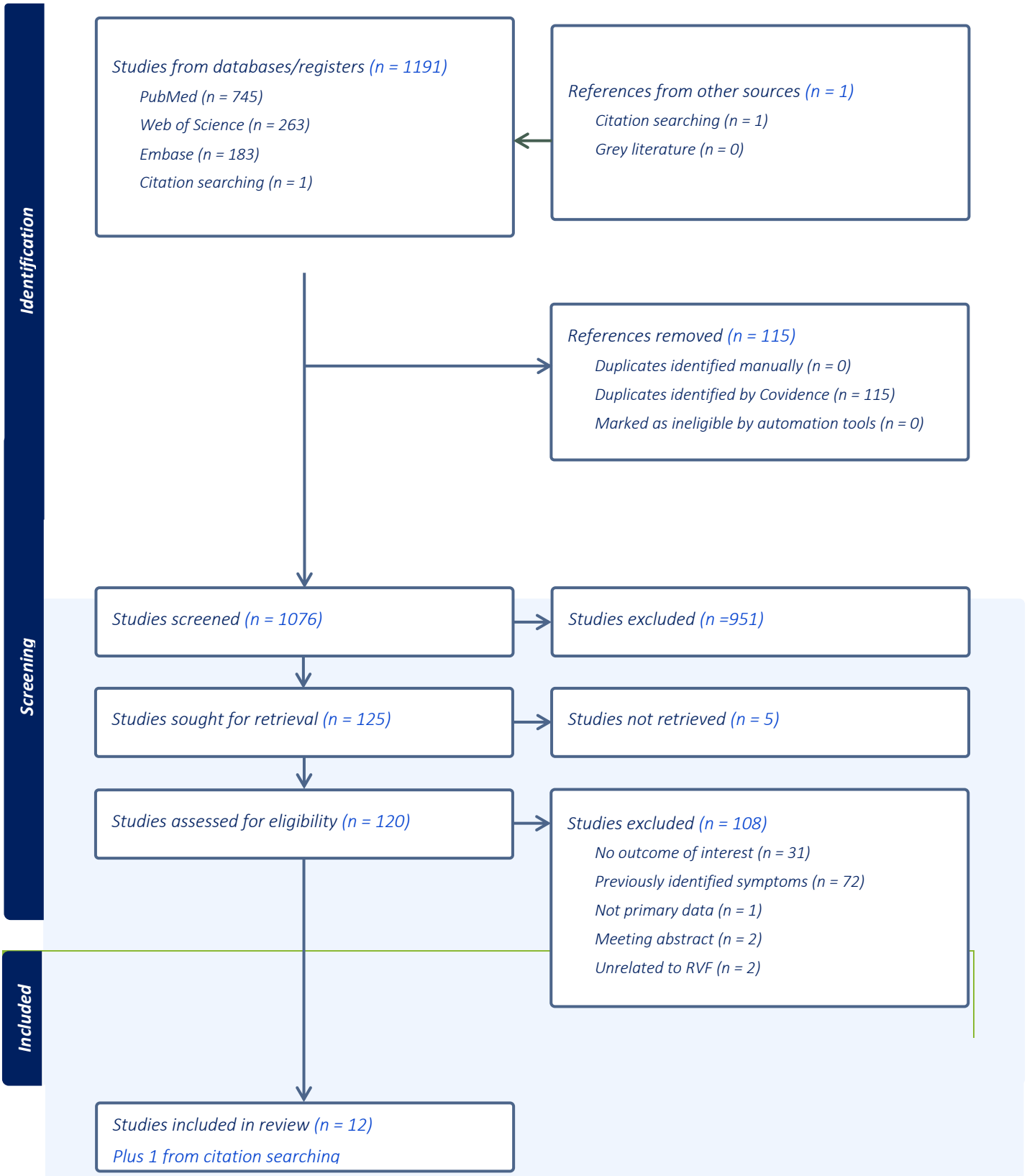
A study was excluded if:

- No full text was available;
- It was in vitro;
- It was not available in English;
- It did not report primary data;
- Reviewers were not able to verify complete methods (e.g., conference abstracts & posters); or
- No exposure or outcome of interest was reported. This included studies reporting only on AESIs already included in the 2020 AESI list for RVF

The full texts of selected articles and the relevant references of selected systematic reviews and narrative reviews were then screened by single review (B.L. or E.C.F.). After the full-text screening was complete, the bibliography of the articles selected for inclusion was vetted with subject matter experts.

The results of the study selection process are depicted in Figure A1.

Figure A1. Results of the Study Selection Process With the exception of the first 2 boxes on Identification, all other numbers added by B Law to reflect the screening and selection process.



Data Extraction and Synthesis

Methodologic data and results of clinically relevant outcomes from the studies meeting inclusion criteria were extracted into standardized evidence tables. Data and analyses were extracted as presented in the studies. For the purposes of this review, statistical significance was defined as $p \leq 0.05$.

TABLE A1. PRIMARY SEARCH STRATEGIES OF DATABASES: 5/24/2024

Database	Strategy	Run Date	Records
Medline (OVID) 1946-	"Rift Valley Fever"[MeSH Terms] OR "Rift Valley fever virus"[MeSH Terms] OR "Rift Valley Fever"[MESH] OR "Rift Valley fever virus"[MESH] OR (("rift valley fever"[all] OR "rift valley"[all] OR ("rift valley"[all] AND "fever"[all]) AND (complications[all] OR epidemiology[all] OR physiopathology[all] OR immunology[all] OR "virology*"[all]) OR etiology[all] OR "outbreak*"[all])) AND ("2018/01/01"[Date - Publication] : "3000"[Date - Publication])	5/22/2024	764 unique records
Embase (OVID) 1974-	((Rift Valley Fever'/exp OR 'Rift Valley Fever' OR 'Rift Valley Fever Virus'/exp OR 'Rift Valley Fever Virus') AND ('complications'/exp OR complications OR 'epidemiology'/exp OR epidemiology OR 'physiopathology'/exp OR physiopathology OR 'immunology'/exp OR immunology OR virology* OR 'etiology'/exp OR etiology OR outbreak*.) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)) AND limit AND date AND [2019-2024]/py	5/24/2024	269 records - 86 duplicates 183- unique records
CINAHL (EBSCOHost)	("Rift Valley Fever" OR "Rift Valley fever virus" OR ("rift valley" AND fever)) AND (complications OR epidemiology OR physiopathology OR immunology OR virology* OR etiology OR outbreak*)	5/24/2024	528 results - 265 duplicates 263 unique records