



Safety Platform for Emergency vACcines

SO1-D2.4 Landscape analysis of background rates
methods

SO2-D2.2 Dashboard to capture background rates
for COVID-19 AESI

Work Package: [2]

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Author(s): Miriam Sturkenboom, Barbara Law

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CONTRIBUTORS

CONTRIBUTOR(S)	DESCRIPTION
Miriam Sturkenboom	Methods for literature search, abstraction and quality control
Barbara Law	Review of abstracts, fine-tuning of search strategy
Marta Rojo Villaescusa	Abstraction of all information from publications and completion of excel sheets
Matthew Dudley	Implementation of Pubmed search
Lisa Chung	Creation of the forest plots
Emalee Martin	Retrieval of additional articles

EXECUTIVE SUMMARY

This deliverable describes the methods for the systematic literature search, screening and the extraction of information from published documents, that capture information on incidence rates for any of the AESI in tier 1-4. It also describes how this information can be displayed visually on the Brighton Collaboration website. The approach chosen for the dashboard was to retain as much information as possible, in the underlying extracted data, which are quite heterogeneous in terms of methodology in particular geographic area, age classification, study years as well as age range, case identification and ascertainment processes. Maintaining that information in a structured manner will allow the user to select as needed.

1. Introduction

Vaccine safety surveillance in the post-licensure setting has several components. Case reporting, statistical analyses of such reporting using disproportionality analyses are the basic components, which may lead to signals. Case reports have their limitations as they may be selectively reported after news or underreported if persons are not aware of the association.

To interpret signals rapidly Observed/Expected analyses may be conducted which calculate the expected number of cases based on the incidence of such events in the absence of the vaccine. *Background rates are incidence rates of events, in the general population in the absence of the vaccine of interest.*

The expected number of cases in a certain interval is calculated as: $\text{Expected} = \text{Incidence} * \text{time interval} * \text{number of vaccine exposures}$. Black *et al.* first alerted to the need of such background rates in 2009 as part of the preparedness for the H1N1 pandemic and recently updated for COVID19¹. Awareness of the background rates of possible adverse events will be a crucial part of assessment of possible vaccine safety concerns and will help to separate legitimate safety concerns from events that are temporally associated with but not caused by vaccination.

¹ Black S, Eskola J, Siegrist CA, Halsey N, MacDonald N, Law B, Miller E, Andrews N, Stowe J, Salmon D, Vannice K, Izurieta HS, Akhtar A, Gold M, Oselka G, Zuber P, Pfeifer D, Vellozzi C. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. *Lancet*. 2009 Dec 19;374(9707):2115-2122.

Black SB, Law B, Chen RT, Dekker CL, Sturkenboom M, Huang WT, Gurwith M, Poland G. The critical role of background rates of possible adverse events in the assessment of COVID-19 vaccine safety. *Vaccine*. 2021 May 6;39(19):2712-2718. doi: 10.1016/j.vaccine.2021.03.016. Epub 2021 Mar 6. PMID: 33846042; PMCID: PMC7936550.

Since then, several programs have focused on estimating background rates and they have been generated to support assessing COVID-19 vaccine safety signals in the USA² and in Europe.³

For vaccine safety monitoring purposes, background incidence rates are also compared to incidence rates of the vaccine following exposure, which requires an estimate of exposure as denominator. Such rates are used in rapid cycle analyses, or for observed /expected analyses as conducted by Pottegård et al.⁴

In its COVID-19 vaccine surveillance guidance, the WHO is recommending the availability of background rates to be able to interpret signals that arise. Whereas such rates can be calculated rapidly using large, linked databases in countries where routine care provision is recorded electronically, such rates may be missing in countries that do not have such resources.

To support vaccine safety surveillance, SPEAC aimed to identify and publish incidence rates for the events of interest. These background rates are summarized in the events specific companion guides and made available on the Brighton Collaboration website.

SPEAC Work Package 2 is creating resources and tools for the AESI including:

1. Providing tabular summaries of risk factors and background rates for each AESI.
2. Guidance on AESI real time investigation, data collection, analysis and presentation.
3. Creating spreadsheet summaries of ICD9/10 and MedDRA codes for each AESI.
4. Creating tools to facilitate capturing the specific clinical data needed to meet AESI case definitions across a variety of settings applicable to clinical trials, epidemiologic studies and individual case causality assessment. These include:
 - a. Data abstraction and interpretation forms to facilitate capturing data from medical charts and applying it to determine a given AESI case definition level of certainty.
 - b. Tabular checklists that are a stand-alone tool useful for summarizing key clinical data needed to determine the level of diagnostic certainty for a given case definition.

² Gubernot D, Jazwa A, Niu M, Baumblatt J, Gee J, Moro P, Duffy J, Harrington T, McNeil MM, Broder K, Su J, Kamidani S, Olson CK, Panagiotakopoulos L, Shimabukuro T, Forshee R, Anderson S, Bennett S. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. *Vaccine*. 2021 May 14;S0264-410X(21)00578-8. doi: 10.1016/j.vaccine.2021.05.016. Epub ahead of print. PMID: 34088506; PMCID: PMC8118666.

³ Willame C, Dodd C, Gini R, Durán CE, Ehrenstein V, Thomsen RM, Kahlert J, Bartolini C, Paoletti O, Droz C, Moore N, Haug U, Schink T, Diez-Domingo J, Mira-Iglesias A, Vergara-Hernández C, Villalobos F, Pallejà M, Aragón M, Perez-Gutthann S, Arana A, Giaquinto C, Barbieri E, Stona L, Huerta C, Martín-Pérez M, García Poza P, de Burgos A, Martínez-González M, Bryant V, Trifiro G, Souverein P, Gardarsdottir H, Siiskonen SJ, Mahy P, Weibel D, Klungel O, Sturkenboom MCJM. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines, an ACCESS study. D3-Draft Final Report, April 30, 2021. <https://vac4eu.org/covid-19-tool/>

⁴ Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, Lidegaard Ø, Tapia G, Gulseth HL, Ruiz PL, Watle SV, Mikkelsen AP, Pedersen L, Sørensen HT, Thomsen RW, Hviid A. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. *BMJ*. 2021 May 5;373:n1114. doi: 10.1136/bmj.n1114. PMID: 33952445; PMCID: PMC8097496.

- c. Tabular logic and pictorial decision tree algorithms, also stand-alone tools, to facilitate correct application of key clinical data to determine the level of diagnostic certainty for each AESI.
- d. Glossary of terms relevant to anaphylaxis and the neurologic AESI.

This deliverable describes the methods for the systematic identification of the background rates and the modality for display.

2. Systematic searches for background rates

2.1 Literature search

The purpose of the systematic literature search was to identify background rates for events of interest. Events comprise the tier 1-4 AESI that have been identified by the SPEAC project and are described in table 1.

TABLE 1. AESI PRIORITIZED BY TIER

Tier 1	Tier 2	Tier 3	Tier 4
Anaphylaxis	Vaccine associated enhanced disease	Sensorineural hearing loss	Acute/Chronic inflammatory rheumatism
Thrombocytopenia	Acute respiratory distress syndrome	Anosmia/ageusia	Total/partial loss of vision
Generalized convulsion	Acute cardiovascular injury	Chilblain like lesions	Optic neuritis
Aseptic meningitis	Coagulation disorder	Erythema multiforme	Alopecia
Encephalitis	Acute kidney injury	Acute aseptic arthritis	Neonatal sepsis
Myelitis	Acute liver injury	Single organ cutaneous vasculitis	Neonatal encephalopathy
Acute disseminated encephalomyelitis	Stillbirth	Maternal death	Neonatal neuro-developmental delay
Guillain Barré & Miller Fisher Syndromes	Spontaneous abortion and ectopic pregnancy	Neonatal death	
Peripheral facial nerve palsy	Pathways to Preterm birth & Preterm birth		

In order to conduct the search synonyms and MesH terms were identified for each of the events. In order to focus on incidence words that would indicate incidence or epidemiology were added.

The search strategy was tested and discussed between the WP2 lead (Barbara Law), Miriam Sturkenboom and Matthew Dudley, who conducted the search (See annex 1 for search strategies for tier 1 and 2).

The search strategy comprised

- 1) Terms for the events, including synonyms, in the title
- 2) & Incidence as title word or MesH
- 3) & English language
- 4) & period 2000-now (this could be extended backwards if not enough results)
- 5) & meta-analysis as publication type (this condition was lifted if there was none)
- 6) & several exclusions (Coronavirus, experimental, not human, not therapy/procedure related in title)

Source of the search was Medline only accessed through Pubmed. PubMed is a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics. The United States National Library of Medicine at the National Institutes of Health maintains the database as part of the Entrez system of information retrieval.

Abstracts of all articles were screened by Barbara Law based on the in- and exclusion criteria. Exclusion criteria were

- Case reports
- Clinical trials
- Incidence in specific population following a procedure or a certain therapy
- Not compliant with inclusion criteria that had not been filtered out in the search (e.g. not English)

If we used meta-analyses original articles included in the meta-analyses were retrieved for data abstraction.

2.2 Abstraction of data

Full articles were retrieved for all abstracts that were retained after screening of the abstracts. Each full article was reviewed and the following information was abstracted by an epidemiologist (Marta Rojo) under supervision of MS. For meta-analyses that were identified, all original articles were retrieved and subsequently abstracted in a structured Excel sheet. A quality assessment and normalization exercise (converting all rates to the same denominator) was conducted prior to the release of the excels sheets for the forest plots.

TABLE 2. VARIABLES EXTRACTED FROM THE INDIVIDUAL ARTICLES

Number	Number of the entry
Methods	
Study reference. (PMID)	The PMID is assigned to each article record when it enters the PubMed system
Specific type	Specific type of event e.g. cause specific anaphylaxis
Country	Country where the study was done
Study years	Range of the study period over which data were obtained
Data source	Type of data source that was used to estimate the incidence rates
Case identification method/codes	The methodology by which cases of the specific event were identified
Method for case ascertainment	The methods by which the identified cases were ascertained/validated
Case definition used	The definition of the event

Age	Age group
Results overall and stratified by gender	
Period strata	The calendar year strata by which the results were published
Age strata	Strata of age, if age specific data were provided
Cases	Number of cases in the period/age strata
person-years	Number of person-year in the period/age strata
rate/100,000	Incidence rate published, transformed to 100,000 PY if needed
95%CI	95%CI confidence intervals as provided in the results

2.3 Dashboard

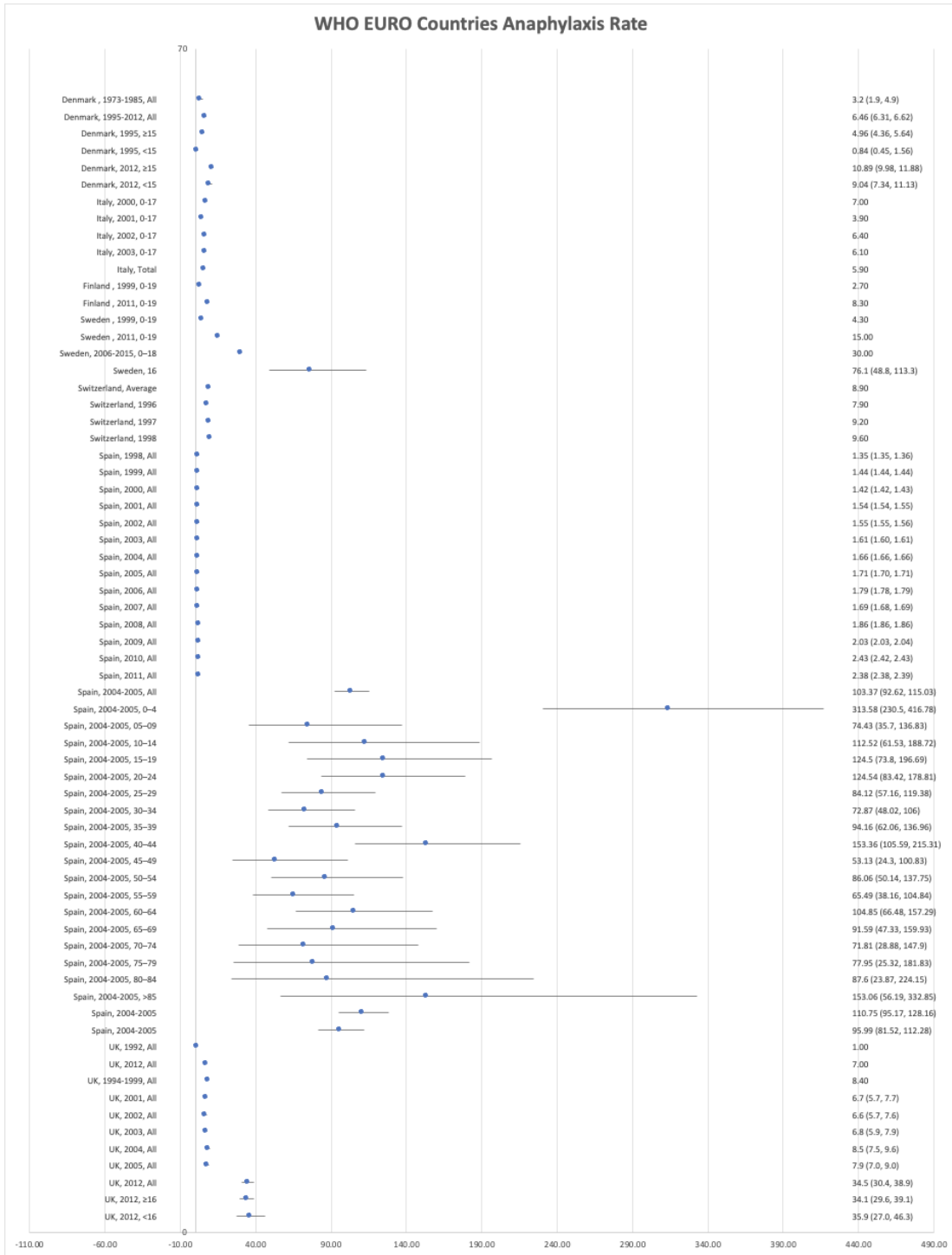
SPEAC aimed to develop a tool that would display the data. The underlying data were heterogeneous regarding many methodological aspects such as geography, calendar time, case identification and ascertainment as well as age. We aimed to maintain this information and at the same time organize it as far as possible. The abstracted incidence rates were organized in worksheets that were continent specific. For display we created forest plots that display the incidence rates and confidence intervals for each specific stratum.

Because the data was abstracted as provided from the original articles, strata can be aggregated if needed. Overall incidence rates were also included in the AESI specific companion guides, in order to have the information available per AESI in one document. Since many of the vaccines are rolled out to specific age groups, it is important to use the proper reference background rates. The dashboard will allow you to aggregate and obtain these.

The dashboard will be publicly available on the Brighton website at this link:

https://docs.google.com/spreadsheets/d/1QqF35nYcsaFN3DZTOtV_IP0TYqQzsDMUQBA5M9brrM/edit#gid=0&fvid=1964086141

Figure 1 shows an example of the display of the anaphylaxis rates on the dashboard.



3. Discussion and next steps

This deliverable describes the methods that were used to systematically identify, abstract and display the available published information on the incidence rates of AESI, which may be used as background rates to interpret the occurrence of reported adverse events following immunization.

The literature is heterogenous and of large volume. Studies on the incidence of the events are conducted in various manners, across whole populations or in specific age categories.

Limitations of the literature search are the need to be restricted in the search of studies by having the conditions in the title, since inclusion of the terms in the abstract or as MeSH yielded a very high number of abstracts. Our attempt was to obtain all relevant articles in an efficient manner. This means that we may have missed publications. To overcome this limitation, we included all original articles from the identified meta-analyses, even if these were conducted prior to 2000. In case we did not obtain a meta-analysis we searched for original articles.

SPEAC provides an abstraction of the overall incidence rates in the AESI companion guides. The detailed data organized by WHO region is available on the Brighton Collaboration website, both the original data as well as the forest plots.

Currently, the forest plots are large. Further aggregation may be conducted and a more interactive display may be made, using a different type of tool. This is proposed as a future IT project.

ANNEXES

ANNEX 1

Search strategy for incidence rates

(Sub-searches with terms for specific AESI, each separated by OR)

AND

(terms for incidence)

AND

(terms for publications in English)

AND

(terms restricting publication date to 2000 and on)

AND

(terms for Meta-Analyses)

NOT

(terms for non-human animal studies)

NOT

(COVID-19 terms)

NOT

(other terms corresponding with articles likely to be irrelevant)

PubMed Search Terms

AESI	Search Terms
Tier 1	
Anaphylaxis	("Anaphylaxis"[Mesh:noexp] OR "anaphylaxis"[ti] OR "anaphylactic"[ti])
Thrombocytopenia	("Purpura, Thrombocytopenic, Idiopathic"[Mesh:noexp] OR "Thrombocytopenia"[Mesh:noexp] OR "ITP"[ti] OR "Werlhof's Disease"[ti] OR "Werlhofs Disease"[ti] OR "Werlhof Disease"[ti] OR "

	morbus werlhof"[ti] OR "thrombocytopenic"[ti] OR "thrombocytopenia"[ti] OR "thrombocytopenias"[ti] OR "thrombopenia"[ti] OR "thrombopenias"[ti] OR "macrothrombocytopenia"[ti] OR "macrothrombocytopenias"[ti])
Seizure	("Seizures"[Mesh:noexp] OR "Seizures, Febrile"[Mesh:noexp] OR "Epilepsy"[Mesh:noexp] OR "Seizure"[ti] OR "Seizures"[ti] OR "Convulsion"[ti] OR "Convulsions"[ti] OR "Epilepsy"[ti] OR "Epilepsies"[ti])
Aseptic Meningitis	((("Meningitis, Aseptic"[Mesh:noexp] OR "Meningitis, Viral"[Mesh:noexp]) OR (("meningitis"[ti] OR "meningitides"[ti] OR "pachymeningitis"[ti] OR "pachymeningitides"[ti] OR "meningomyelitis"[ti]) AND ("aseptic"[ti] OR "viral"[ti])))
Encephalitis	("Encephalitis"[Mesh:noexp] OR "Encephalomyelitis"[Mesh:noexp] OR "encephalitis"[ti] OR "encephalomyelitis"[ti] OR "meningoencephalitis"[ti])
Myelitis	("Myelitis, Transverse"[Mesh:noexp] OR "Myelitis"[ti])
ADEM	("Encephalomyelitis, Acute Disseminated"[Mesh:noexp] OR "acute disseminated encephalomyelitis"[ti] OR "acute disseminated encephalomyelitides"[ti] OR "ADEM"[ti])
GBS	("Guillain-Barre Syndrome"[Mesh:noexp] OR "Guillain Barre"[ti] OR "Guillain-Barre"[ti] OR "Guillain-Barré"[ti] OR "GBS"[ti] OR "Miller Fisher Syndrome"[Mesh:noexp] OR "Miller Fisher"[ti] OR "Miller-Fisher"[ti] OR "Fisher Syndrome"[ti])
Facial Palsy	("Bell Palsy"[Mesh:noexp] OR "facial palsy"[ti] OR "idiopathic facial palsy"[ti] OR "idiopathic peripheral facial nerve palsy"[ti] OR "facial nerve palsy"[ti] OR "Bell palsy"[ti] OR "Bells palsy"[ti] OR "Bell's palsy"[ti])
Tier 2	
VAED	("enhanced disease"[ti] OR "VAED"[ti] OR "enhanced respiratory disease"[ti] OR "VAERD"[ti])
ARDS	("Respiratory Distress Syndrome, Adult"[Mesh:noexp] OR "acute respiratory distress syndrome"[ti] OR "ARDS"[ti])
Myocarditis/Pericarditis	("Myocarditis"[Mesh:noexp] OR "myocarditis"[ti] OR "myopericarditis"[ti] OR "Pericarditis"[Mesh:noexp] OR "pericarditis"[ti])
Cardiac arrest	("myocardial infarction"[ti] OR "cardiac arrest"[ti] OR "Acute Coronary Syndrome"[Mesh:noexp] OR "acute coronary syndrome"[ti] OR "acute coronary syndromes"[ti] OR "ST Elevation Myocardial Infarction"[Mesh:noexp] OR "STEMI"[ti] OR "Death, Sudden, Cardiac"[Mesh:noexp] OR "sudden cardiac death"[ti] OR "asystole"[ti])

Arrhythmia	("Arrhythmias, Cardiac"[Mesh:noexp] OR "arrhythmia"[ti] OR "arrhythmias"[ti] OR "dysrhythmia"[ti] OR "dysrhythmias"[ti] OR "arrhythmic"[ti])
Heart Failure	("Heart Failure"[Mesh:noexp] OR "heart failure"[ti])
Cardiomyopathy	("cardiomyopathy"[ti] OR "Cardiomyopathies"[Mesh:noexp] OR "cardiomyopathies"[ti] OR "Takotsubo"[ti] OR "Tako-Tsubo"[ti])
Thrombosis/TE	("Thromboembolism"[Mesh:noexp] OR "thromboembolic"[ti] OR "thromboembolism"[ti] OR "thrombosis"[ti] OR "thromboses"[ti] OR "thrombotic"[ti])
Bleeding disorder	("Blood Coagulation Disorders"[Mesh:noexp] OR "Coagulation Disorders"[ti] OR "Coagulation Disorder"[ti] OR "coagulopathy"[ti] OR "disseminated intravascular coagulation"[ti] OR "DIC"[ti])
Stroke	("Stroke"[Mesh:noexp] OR "Stroke"[ti] OR "Strokes"[ti] OR "Cerebrovascular Accident"[ti] OR "Cerebrovascular Accidents"[ti])
Kidney injury	("Acute Kidney Injury"[Mesh:noexp] OR "acute kidney injury"[ti] OR "acute renal failure"[ti])
Liver injury	("acute liver injury"[ti] OR "acute liver injuries"[ti])
Stillbirth	("Stillbirth"[Mesh:noexp] OR "stillbirth"[ti] OR "stillbirths"[ti] OR "stillborn"[ti])
Spontaneous Abortion	("Abortion, Spontaneous"[Mesh:noexp] OR "Spontaneous Abortion"[ti] OR "Spontaneous Abortions"[ti] OR "Miscarriage"[ti] OR "Miscarriages"[ti] OR "Early Pregnancy Loss"[ti] OR "Early Pregnancy Losses"[ti] OR "Tubal Abortion"[ti] OR "Tubal Abortions"[ti] OR "spontaneous abortion"[ti] OR "missed abortion"[ti] OR "incomplete abortion"[ti])
Preterm birth	("Premature Birth"[Mesh:noexp] OR "preterm birth"[ti] OR "premature birth"[ti])

AND

("Incidence"[Mesh:noexp] OR "incidence"[tiab])

AND

English[lang]

AND

("2000/01/01"[PDAT] : "3000/12/31"[PDAT])

AND

("Meta-Analysis"[Publication Type])

NOT

("animals"[Mesh:noexp] NOT "humans"[Mesh:noexp])

NOT

("Coronavirus"[Mesh:noexp] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti])

NOT

("therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti]
OR "drug"[ti] OR "drugs"[ti] OR "trial"[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti]
OR "prevents"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti])

ANNEX 2

Updated search strategy for tier 2 AESI incidence rates

(Sub-searches with terms for specific AESI, each separated by OR)

AND

(terms for incidence)

AND

(terms for publications in English)

AND

(terms restricting publication date to 2000 and on)

AND

(terms for study type)

NOT

(terms for non-human animal studies)

NOT

(COVID-19 terms)

NOT

(other terms corresponding with articles likely to be irrelevant)

PubMed Search Terms

AESI	Search Terms
Tier 2	
VAED	("enhanced disease"[ti] OR "VAED"[ti] OR "enhanced respiratory disease"[ti] OR "VAERD"[ti])
ARDS	("Respiratory Distress Syndrome "[Mesh:noexp] OR "acute respiratory distress syndrome"[ti] OR "ARDS"[ti])
Myocarditis/Pericarditis	("Myocarditis"[Mesh:noexp] OR "myocarditis"[ti] OR "myopericarditis"[ti] OR "Pericarditis"[Mesh:noexp] OR "pericarditis"[ti])
Cardiac arrest	("myocardial infarction"[ti] OR "cardiac arrest"[ti] OR "Acute Coronary Syndrome"[Mesh:noexp] OR "acute coronary syndrome"[ti] OR "acute coronary syndromes"[ti] OR "ST Elevation Myocardial

	Infarction"[Mesh:noexp] OR "STEMI"[ti] OR "Death, Sudden, Cardiac"[Mesh:noexp] OR "sudden cardiac death"[ti] OR "asystole"[ti])
Arrhythmia	("Arrhythmias, Cardiac"[Mesh:noexp] OR "arrhythmia"[ti] OR "arrhythmias"[ti] OR "dysrhythmia"[ti] OR "dysrhythmias"[ti] OR "arrhythmic"[ti])
Heart Failure	("Heart Failure"[Mesh:noexp] OR "heart failure"[ti])
Cardiomyopathy	("cardiomyopathy"[ti] OR "Cardiomyopathies"[Mesh:noexp] OR "cardiomyopathies"[ti] OR "Takotsubo"[ti] OR "Tako-Tsubo"[ti])
Thrombosis/TE	("Thromboembolism"[Mesh:noexp] OR "thromboembolic"[ti] OR "thromboembolism"[ti] OR "thrombosis"[ti] OR "thromboses"[ti] OR "thrombotic"[ti])
Pulmonary embolism	("Pulmonary embolism"[Mesh] OR "pulmonary embolus"[ti] OR "pulmonary embolism"[ti] OR "pulmonary thrombosis"[ti] OR "pulmonary thromboses"[ti] OR "pulmonary artery occlusion"[ti])
Sinus thrombosis	("Sinus Thrombosis, Intracranial"[Mesh] OR "sinus thrombosis"[ti] OR "sinus thromboses"[ti])
Bleeding disorder	("Blood Coagulation Disorders"[Mesh:noexp] OR "Coagulation Disorders"[ti] OR "Coagulation Disorder"[ti] OR "coagulopathy"[ti] OR "disseminated intravascular coagulation"[ti] OR "DIC"[ti])
Ischemic Stroke	("Ischemic Stroke"[Mesh] OR "Ischemic Stroke"[ti] OR "Ischemic Strokes"[ti] OR "Cerebral artery occlusion"[ti] OR "Ischemic Cerebrovascular Accident"[ti] OR "Ischemic Cerebrovascular Accidents"[ti])
Hemorrhagic Stroke	("Hemorrhagic Stroke"[Mesh] OR "Hemorrhagic Stroke"[ti] OR "Hemorrhagic Strokes"[ti] OR "Cerebral hemorrhage"[ti] OR "brain hemorrhage"[ti] OR "Hemorrhagic Cerebrovascular Accident"[ti] OR "Hemorrhagic Cerebrovascular Accidents"[ti])
Kidney injury	("Acute Kidney Injury"[Mesh:noexp] OR "acute kidney injury"[ti] OR "acute renal failure"[ti])
Liver injury	("acute liver injury"[ti])
Anosmia and Ageusia	("Anosmia"[Mesh] OR "Ageusia"[Mesh] OR "anosmia"[ti] OR "hyposmia"[ti] OR "ageusia"[ti] OR "hypogeusia"[ti] OR "dysgeusia"[ti])
Stillbirth	("Stillbirth"[Mesh:noexp] OR "stillbirth"[ti] OR "stillbirths"[ti] OR "stillborn"[ti])
Spontaneous Abortion	("Abortion, Spontaneous"[Mesh:noexp] OR "Spontaneous Abortion"[ti] OR "Spontaneous Abortions"[ti] OR "Miscarriage"[ti] OR "Miscarriages"[ti] OR "Early Pregnancy Loss"[ti] OR "Early Pregnancy Losses"[ti] OR "Tubal

	Abortion"[ti] OR "Tubal Abortions"[ti] OR "spontaneous abortion"[ti] OR "missed abortion"[ti] OR "incomplete abortion"[ti])
Preterm birth	("Premature Birth"[Mesh:noexp] OR "preterm birth"[ti] OR "premature birth"[ti])

AND

("Incidence"[Mesh:noexp] OR "incidence"[tiab])

AND

English[lang]

AND

("2000/01/01"[PDAT] : "3000/12/31"[PDAT])

AND

("Observational Study"[Publication Type] OR "Review"[Publication Type] OR "Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type])

NOT

("animals"[Mesh:noexp] NOT "humans"[Mesh:noexp])

NOT

("Coronavirus"[Mesh:noexp] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti])

NOT

("therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR "trial"[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti])