Safety Platform for Emergency vACcines

SO2-D2.1.1 Priority List of COVID-19 Adverse events of special interest: Quarterly update 1

Work Package: WP2 Standards and tools

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1. Background

CEPI has contracted with the Brighton Collaboration, through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key aspect of this harmonization has been creation of lists of priority potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI target diseases.

The initial AESI list for COVID-19 was approved March 5, 2020 based on the first published experiences from China. Subsequently PubMed searches were done on a daily basis and new articles screened for newly emerging COVID-19 clinical patterns and complications. A full description of the methodology and results including citations for the first two COVID-19 AESI lists is available on the Brighton website (https://brightoncollaboration.us/wp-content/uploads/2020/06/SPEAC_D2.3_V2.0_COVID-19_20200525_public.pdf).

The COVID-19 list was presented to the WHO global Advisory Committee on Vaccine safety (GACVS) at a virtual meeting held May 27-28, 2020. The GACVS agreed to adopt the AESI list.[1] At the time it was clearly understood that new AESI could be added to the COVID-19 list as needed based on new knowledge learnt during the global pandemic. Accordingly, SPEAC continues to monitor the literature with quarterly updates to the AESI list planned (September 9 and December 9, 2020; March 10 and June 9, 2021. This deliverable presents the results of the 1st quarterly update and includes modifications to streamline the search strategy.

2. Objective of this deliverable

The primary objective is to present the first quarterly update for the COVID-19 AESI priority list. A detailed description of changes to the ongoing search strategy is included. This was necessitated by the huge volume of new publications on all aspects of COVID-19 spread, clinical presentation, complications, treatment and prevention.

3. Methods

To develop the May 25, 2020 list of potential COVID-19 AESI, a very broad search strategy was used capturing all COVID-19 publications from PubMed as well as pre-prints from bioRxiv and medRxiv. All citation titles were screened by one reviewer (Barb Law) from Feb 17, 2020 and those that addressed the clinical course and complications of COVID-19 were included in a further screen of abstract and/or full text. Duplicates were removed as were non-English articles. Letters to the editor were included as many of these contained relevant case report and case series data that informed the early development of the AESI list. Given the overwhelming volume of publications, the screening was not done in a systematic fashion following PRISMA guidelines. All articles included in the AESI list finalized May 25, 2020 were captured in the appendices of the D2.3 V2.0 deliverable document (available at Brighton website link in Background above).

Searches were discontinued May 16, 2020 in order to develop the final AESI list based on screened in citations and prepare a presentation to the WHO Global Advisory Committee on Vaccine Safety.

From May 16 through the end of May, over 5000 new citations were published. Ongoing review of such a large volume of literature using similar methods as those used to generate the first list was deemed impossible. Accordingly, the screened in articles for the May AESI list were reviewed and key words identified to inform a new search strategy. Also, the nature of the excluded articles which did not inform the AESI list (e.g. therapeutic/prevention strategies, infection control, transmission and other basic virology articles, changes in patterns of healthcare during the pandemic) was used to develop a list of exclusionary terms.

The first revised search strategy is shown in Appendix 1. To ensure that significant articles were not being excluded, all 5000 new citations released from May 16 to early June 2020, were screened in the same manner as used to develop the May 2020 AESI list. Separately, the revised search strategy was also run a) with and b) without exclusionary terms and a file generated with the citations included in (b) but not (a). None of the excluded citations would have contributed to the evolving AESI list. Essentially the revised strategy with exclusionary terms gained efficiency, cutting out 89% of articles captured by prior inclusive search strategies without loss of articles that informed identification of AESI.

The first strategy included 6 separate sub-searches by body system (Neurologic, Multisystem Inflammatory Syndrome, Dermatologic, Cardiac/Hematologic, Pregnancy/Pathology, and a broad category including kidney, gastrointestinal, musculoskeletal, ocular, respiratory and endocrine systems as well as the non-specific terms complications, dysfunction, case reports and case series). Ultimately this strategy decreased efficiency given retrieval of several duplicate publications in the sub-searches. Accordingly, the search strategy was condensed into a single search without changing any of the inclusion or exclusionary terms (Appendix 2).

Searches were conducted using the 1st revised strategy on June 12, July 8th and July 20th. The condensed 2nd revised strategy was used for searches run on July 31st and August 7th. The results from each search were loaded into an excel spreadsheet. A single expert (Barb Law) screened all citations. Several could be screened out based on title alone. Any that could not clearly be screened in or out were then retrieved for abstract and/or full text review.

The brief category name and descriptive rationale for exclusion included:

- 'Duplicate': duplicate of previously captured citation.
- 'Therapy/Testing/Prevention': as implied, articles with the main focus on COVID-19 therapy, testing or prevention of disease.
- 'Healthcare': focus on healthcare during the COVID-19 pandemic.
- 'Unrelated': article unrelated to COVID-19 infection in humans, such as animal model studies or other Coronavirus or related pathogens.
- 'Limited focus': clinical course information included but on a very small scale such as the first case report in a country.
- 'Noncontributory': articles that addressed entities already included on the AESI list with no new information such as an additional case report or limited series of cases.
- 'Non-English': articles in any language other than English.
- 'Comment/Response/Erratum': commentaries including editorials, letters to the editor, author responses to letters to the editor and errata. Of note, full text screening was required for most commentaries because several letters to the editor include case reports, case series and some studies relevant to the AESI list.

For all articles screened out, a distinction was made for whether it was done based on title alone or after abstract and/or full text review.

All screened in articles were categorized according to: 1. Primary topic (mainly by body system); 2. Subgroup 1 (mainly specific diagnosis or population subgroup); and 3. Subgroup 2 (type of article) using the following terms:

1. Primary topic:
    A. Categories from previous AESI list: Cardiac, Neurologic, Dermatologic, Gastrointestinal, Hematologic, Kidney, Liver, Multisystem inflammatory syndromes, Musculoskeletal, Ocular and Respiratory.
    B. Additional categories relevant to AESI list: Autoimmune, Co-infection, Endocrine, Enhanced disease, Pregnancy, Psychiatric, Mixed clinical (for reports, mainly reviews and meta-analyses, of extra-pulmonary manifestations of COVID19) and Other.
    C. Articles to keep for potential relevance to AESI Tools but not to the AESI list per se: Background rate, Risk factor, and Pathology were also categorized and kept but not all reviewed in depth for the AESI list. Within the pathology subgroup, any relating to autopsy findings were to be reviewed in full.
2. Subgroup 1: two groups of terms were used based on whether or not an AESI was already included in the list for COVID19 finalized in May 2020.
    A. Relevant to already identified AESI:
        - Cardiovascular: acute coronary syndrome, aneurysm, arrhythmia, endothelial dysfunction, heart failure, MI, myocarditis (including pericarditis), STEMI (For ST elevation myocardial infarction), sudden death, Takotsubo syndrome (stress cardiomyopathy);
        - Neurologic: acute disseminated encephalomyelitis (ADEM), CNS bleed, encephalitis, encephalopathy, Guillain Barré Syndrome (GBS), myelitis, seizure, Smell/Taste (for anosmia, ageusia, hyposmia, hypogeusia and dysgeusia); Cranial Nerve – other;
        - Dermatologic: angioedema, chilblain, erythema multiforme, urticaria, vasculitis, other rash;
        - Hematologic: coagulopathy, idiopathic thrombocytopenic purpura, ischemia, pulmonary embolus, stroke, thrombocytopenia, thromboembolism, thrombosis;
        - Kidney: injury;
        - Liver: injury;
        - Multisystem inflammatory syndromes: multisystem inflammatory syndrome in children (MISC);
        - Respiratory: ARDS
    B. Entities not on the May AESI list: several were known to have been reported but not in sufficient numbers to merit inclusion on the AESI list; others were added as search results were screened from May 16 to Aug 15. These included:
        - Clinical diagnoses: abscess, adrenal injury, alopecia, arthritis, autoimmune hemolytic anemia, cholecystitis, chronic complication, conjunctivitis, diarrhea, enteritis/colitis, hemophagocytic lymphohistiocytosis, hepatitis, hyperferritinemic syndrome, hyperglycemia, hyponatremia, Kawasaki syndrome, mania, myositis, pancreatitis, parotitis, peripheral neuropathy, pneumomediastinum, pneumothorax, psychosis, retinopathy, rhabdomyolysis, sudden death, thyroiditis, uveo-retinitis;

- Pregnancy/post-partum related: breast milk, ectopic pregnancy, foetal, HELLP syndrome, mortality, neonatal, outcomes, placenta, preeclampsia/eclampsia, transmission;
- Non-specific entities that could lead to identification of new AESI: autopsy, general, mixed clinical, other, outcomes, severity, virus in tissue
- Host-specific other than pregnancy-related: Adult, Geriatric, HIV, Pediatric

3. Subgroup 2: Case Reports (including case series), Commentary (mostly excluded but some kept because of reference to important publications to ensure captured in review), Guideline, Meta-analysis, Pathogenesis, Registry, Review, Study.

For events within the AESI categories identified in May 2020 (subgroup 2A) the number of new articles published for each entity by subgroup and article type were counted but the full article was not reviewed. A spreadsheet for each system group was created to capture all newly published citations.

Nine of the May 2020 COVID-19 AESI had no published case definition. These were prioritized for development of new case definitions. The status as of end of August is shown below. Ultimately up to 10 new case definitions are planned as part of the work for COVID-19.

1. Multisystem inflammatory syndrome in children: Working group established in July and submission for publication due by October 15th, 2020.
2. Acute respiratory distress syndrome: Working group established in July and submission for publication due by October 15th, 2020.
3. Acute cardiovascular injury: Working group established in August and submission for publication due by November 15th, 2020.
4. Coagulation disorder: Working group established in August and submission for publication due by November 15th, 2020.
5. Acute kidney injury: Call for Working group volunteers August 10th, with plans to start work by mid-September and submission for publication by November 30th, 2020.
6. Acute liver injury: Call for Working group volunteers August 10th, with plans to start work by mid-September and submission for publication by November 30th, 2020.
7. Anosmia / ageusia: Call for Working group volunteers August 10th, with plans to start work by mid-September and submission for publication by November 30th, 2020.
8. Chilblain like lesions: deferred start until 2021 and could be replaced by a new AESI of higher priority.
9. Erythema multiforme: deferred start until 2021 and could be replaced by a new AESI of higher priority.

Separate excel spreadsheets were created to capture all newly identified, screened in citations in each of the above categories, for sharing with the Brighton Working groups. These spreadsheets supplement the citations included in the appendices of the May 25th COVID-19 AESI deliverable document.

For events included in subgroup 2B, it is planned to review the articles in full and to prepare tabular summaries in the same way as done for the May 25, 2020 AESIs. These will then be used to prioritize newly emerging entities for addition to the potential COVID-19 AESI list.

4. Results

4.1. Summary of Excluded Publications

From May 16 through August 7, a total of 5 separate searches were run; yielding 4679 citations, of which 1980 (42.3%) were screened in and the other 2699 (57.7%) screened out. Among the articles screened out the decision was based on title alone for 87.3% (2355) and on review of abstract and/or full text article for 12.7% (344). Table 1 summarizes the reason articles were screened for all search dates, separated by whether it was based on title alone or review of abstract/full text. The table also shows variation in distribution of reason excluded for all separate search dates without distinguishing whether exclusion was by title alone or abstract / full text. The single largest reason for exclusion was duplicate publications as a result of the separate searches done by sub-category in the first 3 search dates and then likely overlap in the end date of one search and beginning of the next. Nearly half of the articles excluded by abstract/full text review (166 of 344) involved letters to the editor.

TABLE 1. REASONS FOR EXCLUDING ARTICLES OVERALL AND BY INDIVIDUAL SEARCH DATE

Reason for Exclusion	All Search Dates: Total (%) Excluded by:		Distribution of Reason for Exclusion by Search Date % all excluded (title & abstract/full text)				
	Title alone	Abstract / Full Text	June 12	July 8	July 21	July 31	August 7
Duplicate	979 (36.3%)	4 (0.1%)	25.9%	42.6%	35.8%	39.3%	48.0%
Therapy/Testing/Prevention	286 (10.6%)	29 (1.1%)	9.1%	13.2%	13.6%	13.7%	10.3%
Healthcare	309 (11.4%)	9 (0.3%)	13.9%	11.9%	8.4%	14.3%	9.6%
Unrelated	259 (9.6%)	7 (0.3%)	10.3%	8.8%	8.8%	8.3%	14.2%
Limited focus	76 (2.8%)	8 (0.2%)	4.8%	1.9%	2.7%	3.0%	1.3%
Non-contributory	104 (3.9%)	116 (4.3%)	12.2%	4.6%	10.0%	3.6%	6.3%
Non-English	3 (0.1%)	8 (0.3%)	0.5%	0.5%	0.6%	0.0%	0.0%
Comment/Response/Erratum	339 (12.6%)	166 (6.2%)	23.3%	16.5%	20.1%	17.9%	10.3%
Total excluded/all retrieved (% excluded)	2355/4679 (50.3%)	344/4679 (7.4%)	866/1550 (55.9%)	885/1517 (58.3%)	478/784 (61.0%)	168/357 (47.1%)	302/471 (64.1%)

4.2. Summary of Included Publications for the First Quarterly Update

Table 2 provides a summary by body system of the articles remaining after screening. These are ordered by Primary Topic as described in Methods.

AESI already on COVID-19 list: The vast majority of the recently published articles related to AESI already identified on the COVID-19 list.

- Neurologic: 258 (72%) of 350 new publications.
- Hematologic: 231 (83%) of 278 new publications.
- Cardiac: 178 (92%) of 193 new publications.
- Dermatologic: 63 (45.3%) of 139 new publications. An additional 41 (29.4%) related to entities that were well described but not considered a priority for the AESI list including urticaria, maculopapular, vesicular and livedoid rashes.
- Multisystem inflammatory syndrome: 59 (63%) of 94 articles focused on children.

- Gastrointestinal: 33 (44.6%) of 74 new publications were either for acute liver injury or intestinal thrombosis which is covered under the coagulation disorders.
- Kidney: 100% of the 37 new publications addressed acute kidney injury.

For each of the above, the new publications in the 'General Articles' column focused on the breadth of clinical complications already added to the COVID-19 AESI list. A spreadsheet has been prepared with all new publications listed separately by tab for the body system as noted in the table. This will be made available to the newly formed Brighton Collaboration working groups currently defining ARDS, Multisystem inflammatory disease in children, coagulation disorders, acute cardiovascular injury as well as the next 3 groups to be formed (anosmia/ageusia, acute kidney injury, acute liver injury).

4.3. Entities Not Yet included on the COVID-19 AESI List

While there have been a number of new system-specific complications reported, as shown in Table 2, most involve single or a few case reports. These are listed and will not be discussed further. However, 4 entities were reported in greater number and these are summarized below:

1. Musculoskeletal system- Rhabdomyolysis [2-13]
   - There was a total of 13 case reports from 6 countries (8 USA[2-8]; 1 each: France[9], Spain[10], China[11], Mexico[12], Turkey[13]). All were male, aged 16-88 years. Documented comorbidities were present in at least 9, including type 2 diabetes, obesity, hypertension. Rhabdomyolysis was the presenting complaint for 10 cases and developed during the course of hospitalization for COVID-19 in the other 3. Creatinine kinase elevation ranged from mild (1859 U/L) to massive (276,664 U/L). Six had associated acute kidney injury[2-5,8,9] with 4 needing hemodialysis[2,3,5,8]. All recovered. In the discussions most authors noted that viral infection can account for 5-10% of rhabdomyolysis with influenza virus causing the majority but other known causes including enteroviruses, mumps, adenovirus, orthomyxovirus, EBV, Hepatitis E, HIV, CMV, dengue and rubella. In the original descriptions of COVID-19 clinical disease from China, several reports noted myalgia and or elevated CK in about 10% of cases however the two were not linked. It was noted that acute kidney injury is a relatively common complication of rhabdomyolysis occurring in 7-10% of all cases. This is relevant since it is possible that it might be covered in the acute kidney injury case definition. This will be referred to the working group and is a reason not to add it to the AESI list at present. Additional reports will be found as the literature review continues and if not covered as part of acute kidney injury it could be considered for addition in the future.
2. Endocrine system - Pancreatitis 14[-28]
   - Prior to May 2020 there was a report from China that 17% of 52 COVID-19 patients had evidence of pancreatic injury, defined as any abnormality in amylase or lipase.[14] However, symptoms of pancreatitis were not reported. Since May 16, 2020, pancreatitis was the focus of 13 case reports plus for one report of MISC it was noted that pancreatitis was the presenting complaint.[18] Overall, there were 14 cases reported from 10 different countries. USA had 4 reports[15-18], Denmark 2 from the same family[19], and 1 from each of the remainder: France[20], Portugal[21], Romania[22], UK[23], Israel[24], Iran[25], UAE[26], Pakistan.[27] There were two pediatric cases (7[17] and 10[18] years) and the rest adults ranging from 24 to 68 (8 were aged <50yrs). There were 5 males, 9 females; Comorbidities were noted for 6 (obesity, hypertension most common). Pancreatitis was the presenting complaint for 5, concurrent with COVID19 infection in 2, onset after admission for COVID-19 and couldn't be determined for 1. All recovered. For most of the cases other factors such as alcohol, gallstones, trauma and recent invasive procedures were noted to be absent.
   - One report was an interesting study from the US that identified 339 patients with acute thyroiditis among whom 75 were tested for COVID.[28] They compared the 14 COVID + to the 61 negative; The two groups were similar for age, gender, race and pattern of pancreatitis (10-14% necrotizing and the rest interstitial).

Final diagnosis as to etiology of pancreatitis was significantly different between the two groups. Among the 61 COVID negative cases of acute pancreatitis 64% were alcohol related, 31% with gallstones, 3% other cause and 2% idiopathic. Among the 14 COVID positive 29% were alcohol related, 7% gallstones, 7% other and 57% idiopathic. The COVID positive cases also had higher mortality (21% versus 2%) and higher incidence of both multiorgan failure (14% vs 0) and persistent organ failure (57% vs 8%). Of interest an increased expression of SARS-CoV-1 in pancreatic islet cells was noted during the 2000-2004 SARS outbreak and that some survivors developed acute diabetes.[29 Yang 2010] Also noted by most authors was that up to 10% of acute pancreatitis is thought to have an infectious cause, most commonly viral (mumps, coxsackie, CMV). Also relevant to the setting of COVID-19 was the rarity of drug-related pancreatitis (<5%). That said it can follow use of acetaminophen, dexamethasone, ciprofloxacin, pantoprazole and tocilizumab and there have been two reports of acute pancreatitis with hypertriglyceridemia in COVID-19 patients treated with combination tocilizumab and lopinavir/ritonavir.[24]

3. Endocrine system – Thyroiditis [30-35]

- Thyroiditis is a newly reported entity since May 2020. There were 5 new case reports published, 1 from Singapore[30] and 4 from Italy.[31-34] The Singapore case was a 45-year-old previously healthy man who developed Hashimoto's autoimmune thyroiditis 1 week after a COVID-19 upper respiratory tract infection which had a mild course. In contrast the other case reports involved 4 women, aged 18, 41, 43 and 69 years, with subacute thyroiditis that onset 1-6 weeks following documented COVID-19 infection in 3 and was the sole presenting feature in one with no COVID symptoms but who was COVID PCR positive. All recovered on treatment.
- Muller et al[35] assessed the prevalence of subacute thyroiditis among patients admitted to ICU comparing 2020 during the COVID outbreak in Italy to 2019. They studied 93 consecutive COVID positive patients admitted to their high intensity ICU (HICU-20) as well as another 52 COVID positive admitted to the lower intensity ICU (LICU-20) and 101 patients admitted in 2019 to the high intensity ICU (HICU-19). Thyroid function was assessed on admission to ICU. They found evidence of thyrotoxicosis in 15% of the HICU-20 versus 1% of HICU-19. Of greatest interest was a follow-up study done in 8 HICU-20 patients. Patients were followed for a mean of 55 days post discharge and 2 (25% confirmed to have hypothyroidism and autoimmune thyroiditis features on thyroid scan. The rest had normal thyroid function and no thyroid auto-antibodies. They concluded that a substantial portion of critically ill COVID-19 patients present wtih thyrotoxicosis which is a mix of non-thyroidal illness syndrome related to severe illness and subacute thyroiditis.

4. Hematologic system - Autoimmune hemolytic anemia (AIHA) [36-42]

- By mid-May 2020 there were already 2 reports of AIHA. At the time these were considered insufficient to add this to the COVID-19 list. Lazarian et al described 7 patients (6 French, 1 Belgian hospital) who had their 1st episode of AIHA during acute COVID-19 infection.[36] At least 4 had known predisposing conditions (Chronic lymphocytic leukemia in 2, marginal zone lymphoma in 2). Lopez described a single case in an American 46-year-old female with congenital thrombocytopenia but not active and no other known associations.[37]
- Since May 16 there have been an additional 5 case reports of AIHA – 3 from the USA[38-40], 1 from Belgium[41] and 1 from Spain.[42] Age ranged from 13-62 years with 3 females and 2 males. 4 of the 5 had unusual medical history but not clear if it was associated: a 46 year old female had a history of ITP during pregnancy 27 years earlier; a 17 year old male had a history of refractory chronic ITP; a 51 year old female had a history of ductal breast carcinoma with mastectomy in early 2020; and a 62 year old male had orophyarngeal squamous cell cancer and was on day 3 after the first dose of cisplatin when he presented with COVID-19. The 5th case, a 13-year-old female was previously healthy.[42]

TABLE 2. AESI RELEVANT TO SPECIFIC VACCINE PLATFORMS FOR COVID-19 VACCINES

BODY SYSTEM	Total Articles	AESI (number articles) already on COVID-19 List	Entities (number articles) Not yet on the AESI list	General Articles
Neurologic	350	Anosmia/Ageusia (126), GBS (40), encephalitis (29) encephalopathy (23), brain hemorrhage (16), seizure (13), ADEM (7), myelitis (4)	Vasculitis(3), SIADH(2), Hearing loss(4), ophthalmoplegia(2), facial palsy(2), optic neuritis(1), transient cortical blindness(1), dysphagia(1), myoclonus(1), tremor+ataxia(1), mixed central/peripheral nervous system disorder(1), disrupted sleep quality(1), benign intracranial hypertension(1), hypothermia(1),fulminant cerebral edema(1), dysautonomia(1),	Reviews(32) Studies(12) Pathogenesis(11) Meta-analyses(4) Virus in tissue(5) Registry(3) Guideline(1)
Hematologic	278	Thrombosis(62), Stroke(59), Coagulopathy(42), Pulmonary embolus(39), other thromboembolism(20), Ischemia(7), endothelial dysfunction(2),	Autoimmune hemolytic anemia (5, all case reports)	Reviews(6) Pathogenesis(6)
Cardiac	193	Myocarditis(42), acute cardiac injury(41), STEMI(20), arrhythmia(18), heart failure(18), endothelial dysfunction(13), acute coronary syndrome(9), Takostsubo stress cardiomyopathy(7), MI(7), ruptured aneurysm(2), sudden cardiac death(1),	cardiac tamponade(2), micturition syncope(1),	Reviews(6) Studies(3) Meta-analysis(1) Pathogenesis(1) Virus in tissue(1)
Dermatologic	139	Chilblain(48), cutaneous vasculitis(9), erythema multiforme(4), alopecia(2)	Urticaria(11), maculopapular or vesicular rash(26), livedoid rash(4), necrotic/gangrene skin lesion(3), erythema nodosum(2), atypical Sweet's syndrome(1), lichenoid eruption(1), cutaneous hyperesthesia(1), pruritic papules(1), pityriasis rosea(1), non-genital warts(1), exfoliative toxic-shock like(1), eosinophilic granulomatosis mimicking COVID(1)	Reviews(13) Studies(6) Pathogenesis(1) Registry(1) Guideline(1)
Multisystem inflammatory syndrome(MIS)	94	MIS-Children(59)	MIS-Adult(7), Hemophagocytic lymphohistiocytosis(5), Hyperferritinemic syndrome(2), Macrophage activation syndrome(1),	Studies(4) Pathogenesis(15) Meta-analysis(1)

BODY SYSTEM	Total Articles	AESI (number articles) already on COVID-19 List	Entities (number articles) Not yet on the AESI list	General Articles
Gastrointestinal	74	Acute liver injury(24) GI ischemia/thrombosis(9)	Pancreatitis(13), enterocolitis(6), Acute hepatitis(3), presentation mimicking cute abdomen(2), appendicitis(2), oral mucosal lesions(2), bowel perforation(1), Acute cholecystitis(1)	Reviews(3) Studies(2) Meta-analyses(4) Pathogenesis(1)
Respiratory	38	ARDS(3-autopsy studies, 1 premature infant),	Pneumomediastinum(14) Pneumothorax(13) Lung abscess/cavitation(3), Pulmonary fibrosis(2)	Reviews (2)
Kidney	37	Acute kidney injury(37)		
Musculoskeletal	18		Rhabdomyolysis(11), arthritis(4), myositis(1)	Reviews(2)
Ocular	16		Conjunctivitis(2), retinopathy(2), uveo-retinitis as part of MIS(1), episcleritis(1), papillophlebitis(1), orbital emphysema(1), retro-orbital pain mimicking Dengue(1)	Reviews(2) Studies(5)
Endocrine	15		Thyroiditis(6), adrenal injury(4), hyperglycemia(3), parotitis(2)	
Miscellaneous other				
Co-infection	21	17 case reports (3 H. Zoster, 3 bacterial infection, 3 TB, 2 influenza, 1 respiratory pathogens, 1 RSV, 1 rhinovirus, 1 EBV, 1 parainfluenza, 1 HIV, 1 Dengue); 2 Meta-analyses; 2 Reviews.		
Enhanced disease	5	Case report (1-7 recurrent cases; no evidence for enhanced disease), Pathogenesis(2), Commentary(2);		
Psychiatric	3	Case reports(2; manic episode, psychotic episode); Meta-analysis (1)		
Autoimmune	1	Case report(1-concomitant onset of COVID-19 and new diagnosis of SLE)		
Mixed Clinical	59	Asymptomatic cases: 2 reviews, 1 metanalysis Neonatal/Pediatric cases: 6 case reports, 3 studies, 11 reviews, 2 meta-analyses Pregnancy focus: 7 studies, 1 review, 1 meta-analysis Adult clinical overviews (some include pregnancy): 2 case reports, 4 studies, 10 reviews, 8 meta-analyses, 1 commentary.		
Pregnancy	133	Case reports(50): fetal loss(2), fetal skin edema(1), fetal heart rate changes(1), breast milk non-transmission(1), breast milk antibody(1), placental involvement(4),premature birth(1), vertical transmission(14), neonatal infection(8), maternal mortality(4), maternal COVID complications(13), Meta-analyses/Reviews(40): Outcomes(25), Vertical transmission(12), Fetus(1), maternal mortality(1), thrombocytopenia(1). Studies(32): Outcomes(22), placental pathology(5), maternal mortality(3), vertical transmission(1), preeclampsia/eclampsia(1) Pathogenesis(7): vertical transmission(5), maternal mortality(1), placenta(1) Guidelines(2): Maternal mortality(1), Vertical transmission(1) Commentary(2): Outcomes(1), Neonatal(1)		

BODY SYSTEM	Total Articles	AESI (number articles) already on COVID-19 List	Entities (number articles) Not yet on the AESI list	General Articles
Articles screened in for potential relevance to AESI Tools but not to the AESI list per se				
Pathology	117	Autopsy studies(16; all consistent with AESI on COVID-19 list)	Mortality (99; most focus on case fatality rates by country or as part of systematic review or meta-analysis); Review(1) Pathogenesis(1)/	
Risk Factors	368	▪ For COVID Mortality (230); for COVID Severity(67); COVID mixed outcomes(27) ▪ By population: HIV(9), Children(4), by gender(2), Elderly(1), ▪ By co-morbidity: hematologic(6), autoimmune disease(4), cardiac(4), diabetes(3), kidney(2),myasthenia gravis(2), solid organ transplant(1), malignancy(1), obesity(1), immunocompromised(1), liver(1), multiple system(2).		
Background rate	22	Stroke(4), Acute coronary syndrome(6), Heart failure(3), STEMI(3), Takotsubo syndrome(2), ectopic pregnancy(1), Kawasaki disease(1), ectopic pregnancy(1), maternal/child mortality(1).		

**Review of nucleic acid platforms, and protein platforms has not been conducted since these are novel*

4.4. Pregnancy Outcomes: Maternal, Foetal, Neonatal

As per table 2 there have been 133 publications focused on various aspects of pregnancy outcomes since May 16th. The sheer volume of publications prohibited a detailed review that could be presented here. As noted in 5 below, this will be a priority in the coming month in order to determine whether or not any pregnancy-related AESI should be added to the COVID-19 list.

5. Recommendations & discussion

Based on the updated literature review, covering May 16 through August 7, 2020, SPEAC does not recommend adding any new AESI to the COVID-19 priority list at this time. Four conditions were notable for an increased number of reports including rhabdomyolysis, pancreatitis, subacute and possibly autoimmune thyroiditis and autoimmune hemolytic anemia. At this point in time it is not recommended that they be added to the AESI list. It is quite possible that rhabdomyolysis will be included in the case definition for acute kidney injury. Should there be an increase in new reports or a more definitive link to COVID-19 than currently exists over coming months, SPEAC may change this recommendation and add one or more to the AEIS list.

A priority over the next 1-2 months will be to review the many publications on pregnancy outcomes to determine which if any should be added to the AESI list. Should this happen SPEAC will notify CEPI and the COVID-19 vaccine developers using established communication channels.

6. References

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ANNEXES

Annex I

Revised Search Strategy 2.0 for literature relevant to updates to the potential AESI list for covid-19 (used to retrieve articles from May 16 - July 20, 2020)

Two different searches:

1. Go back to Jan 1, 2020; Update monthly – capture all systematic reviews and meta-analyses for COVID19 without any exclusions – so can capture scope of COVID with methodologic rigor covering more than just the clinical presentation/complications (e.g. compilations of clinical severity by region, risk scores, pathogenesis, immunity, vaccines)

(("Coronavirus"[Mesh] OR "coronavirus"[tiab] OR "nCoV"[tiab] OR "COVID"[tiab] OR "SARS-CoV-2"[tiab]) AND English[lang] AND ("2020/01/01"[PDat] : "2050/01/01"[PDat]) AND (systematic[sb] OR Meta-Analysis[ptyp]))

2. Subsearches – to be done first from May 16 up to Friday June 12 (when requested) and then every 2 weeks, thereafter each Friday
   - May 16 to Jun 12: ~ 11,544 citations in pubmed searches that would need manual screening
     - New strategy retrieved 1290 (11.2%) after removal of duplicates (212) (

Search Terms – looking in Title Only

Strategy
(((Main Terms) NOT (Exclusion Terms)) AND Sub Search X*)
*repeated iteratively for each sub search

Main Terms

(("Coronavirus"[Mesh] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti]) AND English[lang] AND "2020/05/15 15.00"[MHDA]:"2050/01/01 15.00"[MHDA])

Exclusion Terms

("inflammatory bowel disease"[ti] OR "inflammatory bowel diseases"[ti] OR "inflammatory bowel syndrome"[ti] OR "inflammatory bowel syndromes"[ti] OR "tocilizumab"[ti] OR "screen"[ti] OR "screening"[ti] OR "guidance"[ti] OR "guide"[ti] OR "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 "management"[ti] OR "manage"[ti] OR "managing"[ti] OR "pharmacologic"[ti] OR "pharmacological"[ti] OR "murine"[ti] OR "stroke care"[ti] OR "recommendation"[ti] OR "recommendations"[ti] OR "vaccine"[ti] OR "vaccines"[ti] OR "anti-viral"[ti] OR "anti-virals"[ti] OR "nutrition"[ti] OR "anxiety"[ti] OR "telemedicine"[ti] OR "rheumatic"[ti] OR "thromboprophylaxis"[ti] OR "methylprednisolone"[ti] OR "steroids"[ti] OR "corticosteroid"[ti] OR "corticosteroids"[ti] OR "chloroquine"[ti] OR "hydroxychloroquine"[ti] OR "azithromycin"[ti] OR "remdesivir"[ti] OR "ribavirin"[ti] OR "lopinavir"[ti] OR "ritonavir"[ti] OR "azithromycin"[ti] OR "favipiravir"[ti] OR "biomodulator"[ti] OR "biomodulators"[ti] OR "psychosis"[ti] OR "neuropsychiatric"[ti] OR "infection control"[ti] OR "precautions"[ti] OR "aspergillosis"[ti] OR "coccidioidomycosis"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti] OR "multiple sclerosis"[ti] OR "managed"[ti] OR "infusion"[ti] OR "IBD"[ti] OR "predict"[ti] OR "predictor"[ti] OR "predictors"[ti] OR "prediction"[ti] OR "predictions"[ti] OR "predicting"[ti] OR "gene"[ti] OR "genes"[ti] OR "transplant"[ti] OR "transplants"[ti] OR "transplantation"[ti] OR "racism"[ti] OR "ethnic"[ti] OR "racial"[ti] OR "ethnicity"[ti] OR "lifestyle"[ti] OR "chronic inflammation"[ti] OR "chronic inflammatory condition"[ti] OR

"chronic inflammatory conditions"[ti] OR "obesity"[ti] OR "chronic use"[ti] OR "chronic liver disease"[ti] OR "chronic hepatitis"[ti] OR "conference"[ti] OR "conferences"[ti] OR "infliximab"[ti] OR "colchicine"[ti] OR "anakinra"[ti] OR "famotidine"[ti] OR "ruxolitinib"[ti] OR "clozapine"[ti] OR "ocrelizumab"[ti] OR "Chron's"[ti] OR "cigarette"[ti] OR "smoker"[ti] OR "smoking"[ti] OR "vaping"[ti] OR "prognosis"[ti] OR "prognostic"[ti] OR "asthma"[ti])

Sub-Search 1: Neurologic Terms

("brain involvement"[ti] OR "neurological"[ti] OR "neurologic"[ti] OR "seizure"[ti] OR "seizures"[ti] OR "convulsion"[ti] OR "convulsions"[ti] OR "epilepsy"[ti] OR "status epilepticus"[ti] OR "leukoencephalopathy"[ti] OR "olfactory"[ti] OR "gustatory"[ti] OR "neuropathy"[ti] OR "paresthesia"[ti] OR "paraesthesia"[ti] OR "Miller Fisher"[ti] OR "smell"[ti] OR "taste"[ti] OR "nervous system"[ti] OR "stroke"[ti] OR "cerebrovascular"[ti] OR "myoclonus"[ti] OR Guillain*[ti] OR "encephalitis"[ti] OR "encephalopathy"[ti] OR "encephalitic"[ti] OR "encephalomyelitis"[ti] OR "rhomboencephalitis"[ti] OR "meningitis"[ti] OR "myelitis"[ti] OR "meningomyelitis"[ti] OR "meningoencephalitis"[ti] OR "anosmia"[ti] OR "hyposmia"[ti] OR "ageusia"[ti] OR "hypogeusia"[ti] OR "optic neuritis"[ti] OR "viral meningitis"[ti] OR "aseptic meningitis"[ti] OR "palsy"[ti] OR "cranial nerve"[ti] OR "dysphagia"[ti] OR "subarachnoid"[ti] OR "confusion"[ti] OR "confusional"[ti] OR "coma"[ti] OR "comatose"[ti] OR "unresponsive"[ti] OR "neuroinvasive"[ti] OR "neuroinvasion"[ti] OR "neurotropism"[ti] OR "neurotropic"[ti] OR "sensorineural hearing loss"[ti] OR "ataxia"[ti] OR "cerebellitis"[ti] OR "radiculitis"[ti] OR "neuritis"[ti] OR "polyneuritis"[ti] OR "polyneuropathy"[ti] OR "neuralgia"[ti] OR "weakness"[ti] OR "focal deficit"[ti])

Sub-Search2: Multisystem Inflammatory Syndromes Terms

("inflammatory"[ti] OR "hyperinflammatory"[ti] OR "hyper-inflammation"[ti] OR "hyper-inflammatory"[ti] OR "macrophage activation syndrome"[ti] OR "cytokine storm syndrome"[ti] OR "cytokine release syndrome"[ti] OR "kawasaki"[ti] OR "hemophagocytic lymphohistiocytosis"[ti] OR "haemophagocytic lymphohistiocytosis"[ti] OR "shock"[ti] OR "hyponatremia"[ti] OR "inflammation"[ti] OR "hyperferritinaemia"[ti] OR "hyperferritinemia"[ti] OR "hyperferritinaemic"[ti] OR "hyperferritinemic"[ti] OR "multisystem inflammatory syndrome"[ti] OR "inflammatory multisystem syndrome"[ti] OR "viral sepsis"[ti])

Sub-Search 3: Dermatologic Terms

("chilblain"[ti] OR "chilblains"[ti] OR "acral"[ti] OR "acro-ischemia"[ti] OR "urticaria"[ti] OR "urticarial"[ti] OR "rash"[ti] OR "rashes"[ti] OR "skin lesion"[ti] OR "skin lesions"[ti] OR "skin finding"[ti] OR "skin findings"[ti] OR "alopecia"[ti] OR "purpura"[ti] OR "purpuric"[ti] OR "vasculitis"[ti] OR "vasculitic"[ti] OR "angioedema"[ti] OR "Sweet's syndrome"[ti] OR "cutaneous"[ti] OR "Stevens-Johnson"[ti] OR "erythema multiforme"[ti] OR "pernio"[ti] OR "maculopapular"[ti] OR "varicella-like"[ti] OR "chickenpox-like"[ti] OR "papulovesicular"[ti] OR "exanthem"[ti] OR "exanthems"[ti] OR "exanthema"[ti] OR "exanthematous"[ti] OR "morbilliform"[ti] OR "erythema nodosum"[ti] OR "vesicular"[ti] OR "bullous"[ti] OR "bullae"[ti] OR "vesiculobullous"[ti] OR "livedoid"[ti] OR "livedo"[ti] OR "necrotic"[ti] OR "papule"[ti] OR "papules"[ti] OR "macule"[ti] OR "macules"[ti] OR "macular"[ti] or "papular"[ti] OR "petechial"[ti] OR "petechiae"[ti] OR "gangrene"[ti] OR "erythroderma"[ti] OR "pustulosis"[ti] OR "pustular"[ti] OR "pustule"[ti] OR "pustules"[ti] OR "angioedema"[ti] OR "vesicle"[ti] or "vesicles"[ti])

Sub-Search 4: Cardiac and Hematologic Terms

("myocarditis"[ti] OR "cardiomyopathy"[ti] OR "infarction"[ti] OR "infarct"[ti] OR "infarcts"[ti] OR "cardiac arrest"[ti] OR "microangiopathy"[ti] OR "micro-angiopathy"[ti] OR "microvascular inflammation"[ti] OR "vascular inflammation"[ti] OR "cardiogenic"[ti] OR "cardiogenic shock"[ti] OR "right ventricular failure"[ti] OR "cor pulmonale"[ti] OR "aneurysm"[ti] OR "aneurysmal"[ti] OR "mediastinum"[ti] OR "pneumomediastinum"[ti] OR "arrhythmia"[ti] OR "arrhythmias"[ti] OR "dysrhythmia"[ti] OR "dysrhythmias"[ti] OR "arrhythmic"[ti] OR "myopericarditis"[ti] OR "pericarditis"[ti] OR "pericardial effusion"[ti] OR "endotheliitis"[ti] OR "heart failure"[ti] OR "vasculature"[ti] OR "acute coronary syndrome"[ti] OR "acute

coronary syndromes"[ti] OR "STEMI"[ti] OR "wide complex tachycardia"[ti] OR "vascular leak"[ti] OR "vascular leakage"[ti] OR "endothelial dysfunction"[ti] OR "microvascular dysfunction"[ti] OR "myocardial injury"[ti] OR "myocardial damage"[ti] OR "cardiac injury"[ti] OR "tachyarrhythmia"[ti] OR "tachyarrhythmias"[ti] OR "bradyarrhythmia"[ti] OR "bradyarrhythmias"[ti] OR "sudden cardiac death"[ti] OR "ischemia"[ti] OR "ischemic"[ti] OR "pericyte"[ti] OR "pericytes"[ti] OR "tachycardia"[ti] OR "bradycardia"[ti] OR "ventricular fibrillation"[ti] OR "atrial fibrillation"[ti] OR "atrial flutter"[ti] OR "cardiomegaly"[ti] OR "endomyocardial biopsy"[ti] OR "cardiac biopsy"[ti] OR "plaque rupture"[ti] OR "AV block"[ti] OR "bundle branch block"[ti] OR "asystole"[ti] OR "autoimmune hemolytic anemia"[ti] OR "disseminated intravascular coagulation"[ti] OR "lupus anticoagulant"[ti] OR "thromboembolic"[ti] OR "thromboembolism"[ti] OR "thrombosis"[ti] OR "thromboses"[ti] OR "thrombotic"[ti] OR "microthrombus"[ti] OR "microthrombi"[ti] OR "embolism"[ti] OR "emboli"[ti] OR "embolic"[ti] OR "hemostasis disorder"[ti] OR "hemostasis disorders"[ti] OR "hemorrhage"[ti] OR "haemorrhage"[ti] OR "hemorrhagic"[ti] OR "haemorrhagic"[ti] OR "coagulopathy"[ti] OR "hypercoagulability"[ti] OR "microhemorrhage"[ti] OR "microhaemorrhage"[ti] OR "microhemorrhages"[ti] OR "microhaemorrhages"[ti] OR "microhemorrhagic"[ti] OR "microhaemorrhagic"[ti] OR "DIC"[ti] OR "Takotsubo"[ti] OR "Tako-Tsubo"[ti] OR "cardiac tamponade"[ti] OR "thrombocytopenia"[ti] OR "idiopathic thrombocytopenic purpura"[ti] OR "ITP"[ti] OR "antiphospholipid syndrome"[ti] OR "antiphospholipids"[ti] OR "complement-mediated"[ti] OR "complement activation"[ti])

Sub-Search 5: Combined kidney, gastrointestinal, musculoskeletal, ocular, respiratory, endocrine and general terms for complications including case report/case series

("acute kidney injury"[ti] OR "nephritis"[ti] OR "liver injury"[ti] OR "hepatitis"[ti] OR "pancreatitis"[ti] OR "hematochezia"[ti] OR "rhabdomyolysis"[ti] OR "musculoskeletal"[ti] OR "elevated creatinine kinase"[ti] OR "myositis"[ti] OR "follicular conjunctivitis"[ti] OR "keratoconjunctivitis"[ti] OR "retinitis"[ti] OR "uveitis"[ti] OR "pneumothorax"[ti] OR "atypical ARDS"[ti] OR "thyroiditis"[ti] OR "manifestation"[ti] OR "manifestations"[ti] OR "complication"[ti] OR "complications"[ti] OR "dysfunction"[ti] OR "case report"[ti] OR "case reports"[ti] OR "case-reports"[ti] OR "case-report"[ti] OR "first case"[ti] OR "case series"[ti])

Sub-Search 6: Pregnancy/Newborn/Fetus Terms plus pathology/pathogenesis/fatal outcomes

("pregnant"[ti] OR "pregnancy"[ti] OR "pregnancies"[ti] OR "maternal-fetal"[ti] OR "maternal"[ti] OR "maternal morbidity"[ti] OR "gestational diabetes"[ti] OR "antenatal bleeding"[ti] OR "spontaneous abortion"[ti] OR "missed abortion"[ti] OR "incomplete abortion"[ti] OR "chorioamnionitis"[ti] OR "endometritis"[ti] OR "preeclampsia"[ti] OR "HELLP"[ti] OR "congenital"[ti] OR "birth defect"[ti] OR "birth defects"[ti] OR "vertical transmission"[ti] OR "mother-to-newborn"[ti] OR "in utero"[ti] OR "intrauterine infection"[ti] OR "uterine infection"[ti] OR "amnionitis"[ti] OR "funisitis"[ti] OR "postpartum haemorrhage"[ti] OR "postpartum hemorrhage"[ti] OR "neonatal"[ti] OR "neonate"[ti] OR "neonates"[ti] OR "neurodevelopmental"[ti] OR "developmental delay"[ti] OR "disability"[ti] OR "small for gestational age"[ti] OR "growth retardation"[ti] OR "preterm"[ti] OR "premature"[ti] OR "prematurity"[ti] OR "failure to thrive"[ti] OR "fetal"[ti] OR "foetal"[ti] OR "fetus"[ti] OR "foetus"[ti] OR "fetuses"[ti] OR "fetuses"[ti] OR "placenta"[ti] OR "sepsis"[ti] OR "placentas"[ti] OR "placental"[ti] OR "miscarriage"[ti] OR "miscarriages"[ti] OR "stillbirth"[ti] OR "stillbirths"[ti] OR "stillborn"[ti] OR "autopsy"[ti] OR "autopsies"[ti] OR "postmortem"[ti] OR "mortem"[ti] OR "clinicopathological"[ti] OR "clinico-pathological"[ti] OR "clinical pathological"[ti] OR "immunopathology"[ti] OR "antibody-dependent"[ti] OR "mortality"[ti] OR "fatal"[ti] OR "fatality"[ti] OR "fatalities"[ti] OR "death"[ti] OR "deaths"[ti])

ANNEX II

Revised Search Strategy 2.1 for literature relevant to updates to the potential AESI list for covid-19 (used to retrieve articles from July 20 - August 7, 2020)

Updated to one big search on 7/20/20 (to be updated every Friday starting 7/31/20). Exclusionary terms shown in red Font. None of the inclusionary or exclusionary terms were changed from strategy 2.0. Main purpose of the change was to eliminate duplicates generated from multiple sub-searches.

((((("Coronavirus"[Mesh] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti]) AND English[lang] AND "2020/07/08 10.00"[MHDA]:"2050/01/01 15.00"[MHDA]) AND (("brain involvement"[ti] OR "neurological"[ti] OR "neurologic"[ti] OR "seizure"[ti] OR "seizures"[ti] OR "convulsion"[ti] OR "convulsions"[ti] OR "epilepsy"[ti] OR "status epilepticus"[ti] OR "leukoencephalopathy"[ti] OR "olfactory"[ti] OR "gustatory"[ti] OR "neuropathy"[ti] OR "paresthesia"[ti] OR "paraesthesia"[ti] OR "Miller Fisher"[ti] OR "smell"[ti] OR "taste"[ti] OR "nervous system"[ti] OR "stroke"[ti] OR "cerebrovascular"[ti] OR "myoclonus"[ti] OR Guillain*[ti] OR "encephalitis"[ti] OR "encephalopathy"[ti] OR "encephalitic"[ti] OR "encephalomyelitis"[ti] OR "rhomboencephalitis"[ti] OR "meningitis"[ti] OR "myelitis"[ti] OR "meningomyelitis"[ti] OR "meningoencephalitis"[ti] OR "anosmia"[ti] OR "hyposmia"[ti] OR "ageusia"[ti] OR "hypogeusia"[ti] OR "optic neuritis"[ti] OR "viral meningitis"[ti] OR "aseptic meningitis"[ti] OR "palsy"[ti] OR "cranial nerve"[ti] OR "dysphagia"[ti] OR "subarachnoid"[ti] OR "confusion"[ti] OR "confusional"[ti] OR "coma"[ti] OR "comatose"[ti] OR "unresponsive"[ti] OR "neuroinvasive"[ti] OR "neuroinvasion"[ti] OR "neurotropism"[ti] OR "neurotropic"[ti] OR "sensorineural hearing loss"[ti] OR "ataxia"[ti] OR "cerebellitis"[ti] OR "radiculitis"[ti] OR "neuritis"[ti] OR "polyneuritis"[ti] OR "polyneuropathy"[ti] OR "neuralgia"[ti] OR "weakness"[ti] OR "focal deficit"[ti]) OR ("inflammatory"[ti] OR "hyperinflammatory"[ti] OR "hyper-inflammation"[ti] OR "hyper-inflammatory"[ti] OR "macrophage activation syndrome"[ti] OR "cytokine storm syndrome"[ti] OR "cytokine release syndrome"[ti] OR "kawasaki"[ti] OR "hemophagocytic lymphohistiocytosis"[ti] OR "haemophagocytic lymphohistiocytosis"[ti] OR "shock"[ti] OR "hyponatremia"[ti] OR "inflammation"[ti] OR "hyperferritinaemia"[ti] OR "hyperferritinemia"[ti] OR "hyperferritinaemic"[ti] OR "hyperferritinemic"[ti] OR "multisystem inflammatory syndrome"[ti] OR "inflammatory multisystem syndrome"[ti] OR "viral sepsis"[ti]) OR ("chilblain"[ti] OR "chilblains"[ti] OR "acral"[ti] OR "acro-ischemia"[ti] OR "urticaria"[ti] OR "urticarial"[ti] OR "rash"[ti] OR "rashes"[ti] OR "skin lesion"[ti] OR "skin lesions"[ti] OR "skin finding"[ti] OR "skin findings"[ti] OR "alopecia"[ti] OR "purpura"[ti] OR "purpuric"[ti] OR "vasculitis"[ti] OR "vasculitic"[ti] OR "angioedema"[ti] OR "Sweet's syndrome"[ti] OR "cutaneous"[ti] OR "Stevens-Johnson"[ti] OR "erythema multiforme"[ti] OR "pernio"[ti] OR "maculopapular"[ti] OR "varicella-like"[ti] OR "chickenpox-like"[ti] OR "papulovesicular"[ti] OR "exanthem"[ti] OR "exanthems"[ti] OR "exanthema"[ti] OR "exanthematous"[ti] OR "morbilliform"[ti] OR "erythema nodosum"[ti] OR "vesicular"[ti] OR "bullous"[ti] OR "bullae"[ti] OR "vesiculobullous"[ti] OR "livedoid"[ti] OR "livedo"[ti] OR "necrotic"[ti] OR "papule"[ti] OR "papules"[ti] OR "macule"[ti] OR "macules"[ti] OR "macular"[ti] or "papular"[ti] OR "petechial"[ti] OR "petechiae"[ti] OR "gangrene"[ti] OR "erythroderma"[ti] OR "pustulosis"[ti] OR "pustular"[ti] OR "pustule"[ti] OR "pustules"[ti] OR "angioedema"[ti] OR "vesicle"[ti] or "vesicles"[ti]) OR ("myocarditis"[ti] OR "cardiomyopathy"[ti] OR "infarction"[ti] OR "infarct"[ti] OR "infarcts"[ti] OR "cardiac arrest"[ti] OR "microangiopathy"[ti] OR "micro-angiopathy"[ti] OR "microvascular inflammation"[ti] OR "vascular inflammation"[ti] OR "cardiogenic"[ti] OR "cardiogenic shock"[ti] OR "right ventricular failure"[ti] OR "cor pulmonale"[ti] OR "aneurysm"[ti] OR "aneurysmal"[ti] OR "mediastinum"[ti] OR "pneumomediastinum"[ti] OR "arrhythmia"[ti] OR "arrhythmias"[ti] OR "dysrhythmia"[ti] OR "dysrhythmias"[ti] OR "arrhythmic"[ti] OR "myopericarditis"[ti] OR "pericarditis"[ti] OR "pericardial effusion"[ti] OR "endotheliitis"[ti] OR "heart failure"[ti] OR "vasculature"[ti] OR "acute coronary syndrome"[ti] OR "acute coronary syndromes"[ti] OR "STEMI"[ti] OR "wide complex tachycardia"[ti] OR "vascular leak"[ti] OR "vascular leakage"[ti]

OR "endothelial dysfunction"[ti] OR "microvascular dysfunction"[ti] OR "myocardial injury"[ti] OR "myocardial damage"[ti] OR "cardiac injury"[ti] OR "tachyarrhythmia"[ti] OR "tachyarrhythmias"[ti] OR "bradyarrhythmia"[ti] OR "bradyarrhythmias"[ti] OR "sudden cardiac death"[ti] OR "ischemia"[ti] OR "ischemic"[ti] OR "pericyte"[ti] OR "pericytes"[ti] OR "tachycardia"[ti] OR "bradycardia"[ti] OR "ventricular fibrillation"[ti] OR "atrial fibrillation"[ti] OR "atrial flutter"[ti] OR "cardiomegaly"[ti] OR "endomyocardial biopsy"[ti] OR "cardiac biopsy"[ti] OR "plaque rupture"[ti] OR "AV block"[ti] OR "bundle branch block"[ti] OR "asystole"[ti] OR "autoimmune hemolytic anemia"[ti] OR "disseminated intravascular coagulation"[ti] OR "lupus anticoagulant"[ti] OR "thromboembolic"[ti] OR "thromboembolism"[ti] OR "thrombosis"[ti] OR "thromboses"[ti] OR "thrombotic"[ti] OR "microthrombus"[ti] OR "microthrombi"[ti] OR "embolism"[ti] OR "emboli"[ti] OR "embolic"[ti] OR "hemostasis disorder"[ti] OR "hemostasis disorders"[ti] OR "hemorrhage"[ti] OR "haemorrhage"[ti] OR "hemorrhagic"[ti] OR "haemorrhagic"[ti] OR "coagulopathy"[ti] OR "hypercoagulability"[ti] OR "microhemorrhage"[ti] OR "microhaemorrhage"[ti] OR "microhemorrhages"[ti] OR "microhaemorrhages"[ti] OR "microhemorrhagic"[ti] OR "microhaemorrhagic"[ti] OR "DIC"[ti] OR "Takotsubo"[ti] OR "Tako-Tsubo"[ti] OR "cardiac tamponade"[ti] OR "thrombocytopenia"[ti] OR "idiopathic thrombocytopenic purpura"[ti] OR "ITP"[ti] OR "antiphospholipid syndrome"[ti] OR "antiphospholipids"[ti] OR "complement-mediated"[ti] OR "complement activation"[ti]) OR ("acute kidney injury"[ti] OR "nephritis"[ti] OR "liver injury"[ti] OR "hepatitis"[ti] OR "pancreatitis"[ti] OR "hematochezia"[ti] OR "rhabdomyolysis"[ti] OR "musculoskeletal"[ti] OR "elevated creatinine kinase"[ti] OR "myositis"[ti] OR "follicular conjunctivitis"[ti] OR "keratoconjunctivitis"[ti] OR "retinitis"[ti] OR "uveitis"[ti] OR "pneumothorax"[ti] OR "atypical ARDS"[ti] OR "thyroiditis"[ti] OR "manifestation"[ti] OR "manifestations"[ti] OR "complication"[ti] OR "complications"[ti] OR "dysfunction"[ti] OR "case report"[ti] OR "case reports"[ti] OR "case-reports"[ti] OR "case-report"[ti] OR "first case"[ti] OR "case series"[ti]) OR ("pregnant"[ti] OR "pregnancy"[ti] OR "pregnancies"[ti] OR "maternal-fetal"[ti] OR "maternal"[ti] OR "maternal morbidity"[ti] OR "gestational diabetes"[ti] OR "antenatal bleeding"[ti] OR "spontaneous abortion"[ti] OR "missed abortion"[ti] OR "incomplete abortion"[ti] OR "chorioamnionitis"[ti] OR "endometritis"[ti] OR "preeclampsia"[ti] OR "HELLP"[ti] OR "congenital"[ti] OR "birth defect"[ti] OR "birth defects"[ti] OR "vertical transmission"[ti] OR "mother-to-newborn"[ti] OR "in utero"[ti] OR "intrauterine infection"[ti] OR "uterine infection"[ti] OR "amnionitis"[ti] OR "funisitis"[ti] OR "postpartum haemorrhage"[ti] OR "postpartum hemorrhage"[ti] OR "neonatal"[ti] OR "neonate"[ti] OR "neonates"[ti] OR "neurodevelopmental"[ti] OR "developmental delay"[ti] OR "disability"[ti] OR "small for gestational age"[ti] OR "growth retardation"[ti] OR "preterm"[ti] OR "premature"[ti] OR "prematurity"[ti] OR "failure to thrive"[ti] OR "fetal"[ti] OR "foetal"[ti] OR "fetus"[ti] OR "foetus"[ti] OR "fetuses"[ti] OR "fetuses"[ti] OR "placenta"[ti] OR "sepsis"[ti] OR "placentas"[ti] OR "placental"[ti] OR "miscarriage"[ti] OR "miscarriages"[ti] OR "stillbirth"[ti] OR "stillbirths"[ti] OR "stillborn"[ti] OR "autopsy"[ti] OR "autopsies"[ti] OR "postmortem"[ti] OR "mortem"[ti] OR "clinicopathological"[ti] OR "clinico-pathological"[ti] OR "clinical pathological"[ti] OR "immunopathology"[ti] OR "antibody-dependent"[ti] OR "mortality"[ti] OR "fatal"[ti] OR "fatality"[ti] OR "fatalities"[ti] OR "death"[ti] OR "deaths"[ti]))) NOT ("inflammatory bowel disease"[ti] OR "inflammatory bowel diseases"[ti] OR "inflammatory bowel syndrome"[ti] OR "inflammatory bowel syndromes"[ti] OR "tocilizumab"[ti] OR "screen"[ti] OR "screening"[ti] OR "guidance"[ti] OR "guide"[ti] OR "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 "management"[ti] OR "manage"[ti] OR "managing"[ti] OR "pharmacologic"[ti] OR "pharmacological"[ti] OR "murine"[ti] OR "stroke care"[ti] OR "recommendation"[ti] OR "recommendations"[ti] OR "vaccine"[ti] OR "vaccines"[ti] OR "anti-viral"[ti] OR "anti-virals"[ti] OR "nutrition"[ti] OR "anxiety"[ti] OR "telemedicine"[ti] OR "rheumatic"[ti] OR "thromboprophylaxis"[ti] OR "methylprednisolone"[ti] OR "steroids"[ti] OR "corticosteroid"[ti] OR "corticosteroids"[ti] OR "chloroquine"[ti] OR "hydroxychloroquine"[ti] OR "azithromycin"[ti] OR "remdesivir"[ti] OR "ribavirin"[ti] OR "lopinavir"[ti] OR "ritonavir"[ti] OR "azithromycin"[ti] OR "favipiravir"[ti] OR "biomodulator"[ti] OR "biomodulators"[ti] OR "psychosis"[ti] OR "neuropsychiatric"[ti] OR "infection control"[ti] OR "precautions"[ti] OR "aspergillosis"[ti] OR "coccidioidomycosis"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti] OR "multiple sclerosis"[ti] OR "managed"[ti] OR "infusion"[ti] OR "IBD"[ti] OR "predict"[ti] OR "predictor"[ti] OR "predictors"[ti] OR "prediction"[ti] OR "predictions"[ti] OR "predicting"[ti] OR "gene"[ti] OR "genes"[ti] OR "transplant"[ti]

OR "transplants"[ti] OR "transplantation"[ti] OR "racism"[ti] OR "ethnic"[ti] OR "racial"[ti] OR "ethnicity"[ti] OR "lifestyle"[ti] OR "chronic inflammation"[ti] OR "chronic inflammatory condition"[ti] OR "chronic inflammatory conditions"[ti] OR "obesity"[ti] OR "chronic use"[ti] OR "chronic liver disease"[ti] OR "chronic hepatitis"[ti] OR "conference"[ti] OR "conferences"[ti] OR "infliximab"[ti] OR "colchicine"[ti] OR "anakinra"[ti] OR "famotidine"[ti] OR "ruxolitinib"[ti] OR "clozapine"[ti] OR "ocrelizumab"[ti] OR "Chron's"[ti] OR "cigarette"[ti] OR "smoker"[ti] OR "smoking"[ti] OR "vaping"[ti] OR "prognosis"[ti] OR "prognostic"[ti] OR "asthma"[ti]))