Safety Platform for Emergency vACcines

SO2-D2.1.3 Priority List of COVID-19 Adverse events of special interest

Part 1. Long-term effects of COVID-19 Literature Review

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Description of the deliverable	This deliverable is the second of two documents making up the fourth update to the Priority List of potential Adverse events of special interest relevant to COVID-19 vaccine trials. Part 1 focuses on the issue of Long COVID.
Key words	Toolbox, adverse events of special interest, guidance documents, Long COVID

1. Overview

The first reports of potential long term health effects of SARS-CoV-2 infection surfaced in March 2020[1], with acknowledgement by the World Health Organization in September of that year. Subsequently, multiple terms and definitions for this syndrome have been proposed, including long COVID, Post-Acute Sequelae of SARS-CoV-2 infection (PASC), Post-Acute COVID-19 Syndrome (PACS) and others. Although standardized case definitions have not yet been formalized,* the main features encompassed by all these terms include a lack of return to a usual state of health following acute COVID-19 infection; this can include morbidity that persists after acute infection and/or the development of new symptoms or conditions. Due to the lack of a universally accepted term, this review will refer to this entity as long COVID and include symptoms or conditions that are present for four or more weeks after infection with SARS-CoV-2, which is the time criterion common to most current definitions.†

The objectives of this literature review were to:

a. summarize what is currently known about long COVID, including whether it is distinct from previously described syndromes and
b. explore whether similar sequelae could theoretically occur after SARS-CoV-2 vaccination, based on current hypotheses of the pathogenesis of long COVID

The intent of the review was to inform assessment by SPEAC as to whether long COVID or some components of it should be added to the Priority List of COVID-19 Adverse Events of Special Interest (AESI).

* Following completion of this review and report, WHO published a clinical case definition of what they termed post COVID-19 condition based on a Delphi consensus (available at https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1).

† The UK National Institute for Health and Care Excellence (NICE) subdivides post COVID-19 conditions based on duration: Ongoing Symptomatic COVID-19 (signs and symptoms from 4-12 weeks not explained by an alternative diagnosis) and Post-COVID-19 Syndrome (signs and symptoms that continue for >12 weeks).

2. Methods

Literature searches were run on March 9, May 9 and July 12, 2021. The search strategy is shown in Appendix 1. No restrictions were placed on the type of study, so case reports, case series, observational studies, questionnaire surveys, commentaries, letters to the editor and preprints were all eligible for retrieval. Only English language articles were retrieved. The PMIDs of all articles retrieved in each search, regardless of whether or not they were screened in or out for full text review, were added as exclusions for subsequent searches to reduce retrieval of duplicates.

All retrieved articles were loaded into an Excel spreadsheet and screened by a single medical expert (BL) to determine suitability for further full text review. All screened in articles were then reviewed by a separate medical expert (CP).

Full text review of all the screened-in articles was undertaken. Each article was assessed for relevance to the objectives of the project and whether it added new information compared to others reviewed. Screened-in commentaries were reviewed primarily to identify important or commonly referenced citations that had not been included in the list of articles selected for full review; these supplementary articles were retrieved through hand searches and were also reviewed. Additional key references from systematic reviews and sources frequently cited in other articles were obtained through hand search if required to obtain additional details from the original sources. These sources included additional articles from the published literature and preprint servers, as well as government and nongovernmental reports and websites.

A formal assessment of the quality of each reference was not undertaken however, notations were made if a reference had a very small sample size, clear methodological limitations or was a preprint (not peer-reviewed); the findings from these sources were given less weight in contributing to the observations and conclusions of this review. Summary notes for key articles were made, including main points and conclusions.

3. Results

The three searches together identified 266 articles of which 139 (52%) were screened out as noncontributory to the main purpose of the review. The remaining 127 articles were retrieved for full text review and are included in the 'COVID Review Citations Jan2020 to Aug2021'spreadsheet, Tab 'Long COVID'. A further 34 supplementary references were identified through hand searching and are included in the same spreadsheet.

The broad criteria for inclusion of studies in the review resulted in a wide range in the quality of evidence that each contributed. As well, there was significant heterogeneity in:

- criteria for long COVID (time after initial infection, presence of confirmatory SARS-CoV-2 test);
- study participants (hospitalized/severe infections vs those with less severe disease);
- length of follow-up;
- study instruments (symptom assessment, clinical tests, electronic databases)
- investigations to rule out other causes
- measurements of severity and
- sources (patient-led vs researcher driven).

The majority of studies did not have control or comparison groups. There was limited ethnic diversity in the participants of many studies and there were few studies in children or from low or middle-income countries.

For this report, emphasis was placed on findings from larger studies with more robust study designs.

4. What is known about Long COVID?

Overall Prevalence: Estimates of the prevalence of post-acute symptoms following SARS-CoV-2 infection vary considerably. Earlier studies focused on very select patient groups (e.g. patients with severe disease, those presenting to long COVID clinics or members of long COVID patient groups) and reported high prevalence of long COVID, more than 70%[2-6]. Prevalence of ongoing symptoms from more recent population-based studies is much lower (10-40%). In studies that have included control groups, the frequencies of reported symptoms in people with long COVID was higher than those in the control groups (Tables 1 and 2), suggesting a significantly higher rate than would be expected in the general population.

TABLE 1. Prevalence of at least one ongoing symptom

Time after infection	SARS Co-V-2 positive (n=21,622)	Control (n=21,622)
5 weeks	21.0	2.8
12 weeks	13.7	1.7

Source: Adapted from Office for National Statistics[7]. Results from the Coronavirus Infection Survey. Random sample of UK population followed weekly for first month following enrolment then monthly for the next year. Tested at each follow-up regardless of symptoms. Not dependent on availability of testing for the general population

TABLE 2. Presence of at least one symptom at different time points (% of respondents)

	COVID + (n=357)	COVID - (n=5497)	Did not have a COVID test (n=19,095)
Symptoms >30 days	36.1*	11.7	8.4
Symptoms at 60 days	25.3	8.5	6.3
Symptoms at 90 days	14.8	7.0	4.8
>1 Symptom	90.8	60.0	53.5
Median # symptoms during survey period	9	5	4

*21.3% in people with mild or asymptomatic acute COVID-19, 44.9% in people with severe acute disease

Source: Adapted from Cirulli (preprint)[8] Adult participants who had previously consented to participate in research studies were invited to complete online surveys Apr-Oct 2020 about COVID-19 symptoms, with longitudinal follow-up every 4-6 weeks. COVID test results are self-reported.

Estimates of the frequency of persistence of symptoms more than 6 months after initial infection ranged from 14.3% to 61% depending on the population studied and the study design[9-14].

Risk Factors: Although there isn't complete consistency in the literature, risk factors for long COVID found in multiple studies include female sex, severity of initial disease, number of initial symptoms and pre-COVID-19 comorbidities[8,9,15-20] but it also can occur after a mild initial infection. Older age also poses a higher risk for long COVID; however, it is still notably present in younger age groups[18,21,22]. Other risk factors that have been found less consistently include obesity, prior mental health disorders, smoking and the nature of acute symptoms[19,20,22-25].

Common Symptoms: Similar to the estimates of overall prevalence of long COVID, the reported frequency of individual symptoms varied considerably between studies. The most common symptoms are fatigue, shortness of breath, cognitive impairment (memory problems, difficulty concentrating, 'brain fog') and loss of taste/smell[6,9,26,27]. Other commonly reported symptoms include sleep disorders, palpitations, chest pain, cough, muscle pain and joint pain. Table 3 shows the frequencies of the most common symptoms from one systematized review.

TABLE 3. Common Symptoms of Long COVID

Symptom	Median Frequency (%)	Interquartile Range (IQR - %)
Fatigue	40.0	31-57
Dyspnea	36.0	28-50
Sleep disorders	29.4	24-33
Loss of memory	28.3	19-36
Anosmia	23.6	12-41
Anxiety	22.1	10-30
Persistent cough	16.9	14-25
Ageusia/Dysgeusia	15.6	10-24
Depression	14.9	11-18
Aytpical chest pain	13.1	11-18

Source: Adapted from Nasserie systematic review[6]

Few symptoms are distinct, and there is considerable overlap with other conditions. However, in controlled studies the frequencies of each of the most common persistent symptoms were higher in people who had had COVID infection than that in people who had not had COVID. [7] This suggests there are real differences from background rates. For example, despite the pandemic having a significant effect on mental health of the whole population,[9] studies using administrative databases have shown that prevalence of anxiety, depression and PTSD in long COVID patients is higher than those who haven't had COVID.[28] Additionally, the increased frequency of mental health conditions is not limited to just those who had severe acute illness[29].

Different studies have found clustering of symptoms into 2-5 groups with some people having primarily respiratory complaints and others having primarily fatigue or cognitive symptoms[9,19,22,30]. The trajectory of symptoms is variable with some people having ongoing symptoms continuously, others having a symptom-free interval before relapsing, and still others having new symptoms not present in acute phase. Symptoms have a major impact on daily functioning and quality of life[31,32], affecting family life, ability to care for dependents, ability to work and finances[33,34].

Objective findings: The literature related to objective clinical measurements in long COVID patients is conflicting, possibly reflecting different patient populations and diagnostic modalities studied. Findings have included reduced pulmonary diffusion capacity[35,36], reduced performance on standardized cognitive[24,37] and exercise[36] testing, abnormalities in brain imaging[38-40] autonomic testing[41] and inflammatory markers[7,29]. Some studies have shown a correlation between severity of acute COVID-19 disease and objective findings[5,25,35] while others have not[42-45]. However, it is clear that abnormalities have been found even in people with initially mild disease or at low-risk of COVID-19 complications. A prospective cohort (mean age 44 years) found multiorgan impairment in 29% of long COVID participants; long COVID participants had a higher frequency of mild impairment in the heart, lung, liver, kidney and pancreas compared to healthy controls[46].

Other studies have shown higher rates of new diagnoses of hypertension, diabetes, thromboembolism, cerebrovascular events, cardiac events, anxiety, and mood disorders in the months following COVID-19 infection compared to comparison groups (either healthy controls or those with non-COVID health conditions)[40,47-49]. Although excess morbidity is seen with other post-viral syndromes, the frequency and range of excess morbidity following COVID-19 appears to be greater[28].

Children and adolescents: The searches yielded very few studies that specifically focused on children. Similar to the findings for adults, the reported prevalence of long COVID depended on the study design, including setting and age of participants. A cross-sectional study of children with a range of severity of acute illness found two thirds of participants had at least one symptom persisting for 2-4 months, and half had symptoms lasting more than 4 months[50]. A prospective cohort study (preprint) of children hospitalized with COVID-19 found 24% had a least one symptom persisting for more than 5 months[51]. In contrast, a clinic-based study only 8% had post-acute COVID symptoms at 3-6 months and all had returned to baseline health status[52] and a school-based study found only 4% of children had symptoms lasting more than 12 weeks[53]. The most frequently reported symptoms in children were similar to those found in adults: fatigue, dyspnea, sleep disturbances, myalgia, memory and concentration issues[33,50,51,53]. Other similarities with adults include occurrence of long COVID symptoms even in children with mild or asymptomatic acute infection[52] and variation in the presence and severity of symptoms over time.[54].

5. Pathogenesis

The most frequently proposed and overlapping hypotheses for the pathogenesis of long COVID include long term tissue damage arising from the acute infection; viral persistence; immune dysregulation and/or autoimmunity; and autonomic dysfunction.

With respect to long term tissue damage, some authors have proposed direct or indirect invasion of the virus into the brain, with resulting damage being responsible for cognitive impairment or other symptoms. Regarding the mismatch between severity of respiratory symptoms and objective findings several authors have commented that routine radiology may not pick up pulmonary abnormalities that may be responsible for dyspnea[20,30].

Hypotheses on viral persistence suggest this could be either in the form of ongoing virus replication or persistence of non-infectious genetic material or protein in the tissues. This is supported by the finding that

mRNA from SARS-CoV-2 and viral proteins have been detected in the intestines of infected individuals even months after the initial infection[29].

Pathologic inflammation may explain sequelae such as Multisystem Inflammatory Syndrome (MIS) which occurs post-COVID-19 in both children and adults. It has also been proposed as an explanation for thyroid dysfunction in long COVID[20,30]. Neuroimaging in patients with post-infectious syndromes has shown persistent brain inflammation[38] and a low grade neuroinflammatory response has been described as a possible explanation for post-COVID-19 fatigue. Inflammatory markers such as C-reactive protein and antinuclear antibody have been found in some long COVID studies to be more frequently elevated compared to the general population[24,33,55].

Autonomic dysfunction has been associated with other viral infections (e.g. hepatitis C, HIV, Epstein-Barr Virus). Dysautonomia may explain long COVID symptoms such as fatigue and hypoxia and it is not clear if it results directly from cellular damage due to replicating virus or a post-infectious immune-mediated process [56].

Another potential explanatory mechanism may be through ACE2 receptors. It is known that SARS-CoV-2 binds to host cells via ACE2 receptors and presence of these receptors in the gastrointestinal tract with alteration of the gut-brain axis has been raised as an explanation for some long COVID morbidity. Similarly, hypotension and dysautonomia in long COVID, including Postural Orthostatic Tachycardia Syndrome (POTS), have been hypothesized to result from interaction with ACE2 receptors on neurons with disruption of the normal regulation of blood pressure mediated by ACE2[57].

Finally, Epstein-Barr Virus (EBV) reactivation has been hypothesized to have a role in the pathogenesis of long COVID. Globally virtually all people have been infected with EBV by adulthood. The virus persists in a latent state but can reactivate. EBV reactivation has been associated with many symptoms similar to those found in long COVID; in one small study two thirds of patients with long COVID had EBV reactivation compared to only 10% of controls[58]. The accepted role of EBV as one precursor to Chronic Fatigue Syndrome, which has many similar features to long COVID supports this possible mechanism for long COVID.

In summary, while proposed pathogenetic mechanisms overlap considerably with other previously described syndromes, it is possible that COVID-19 triggers persistent symptoms in different or additional ways, for example through ACE2 receptors and more aggressive interactions with the brain, other organs and blood vessels[59].

6. Is long COVID different from Chronic Fatigue Syndrome or other diagnoses?

It has been hypothesized that long COVID is not a single entity but rather multiple conditions with overlapping symptomatology and findings. In more severe cases of acute COVID-19 (i.e. those requiring intensive care and/or ventilation support) there may be overlap with expected sequelae of post-critical illness such as the well-characterized Post Intensive Care Syndrome (PICS) and Post Traumatic Stress Disorder (PTSD). Some long COVID patients fulfill the criteria for Postural Orthostatic Tachycardia Syndrome (POTS), which has previously been hypothesized to be a post-viral infection phenomenon.[49] Additionally, some long COVID patients fulfill the criteria for other conditions such as Chronic Generalized Pain or Fibromyalgia, depending on the constellation of symptoms in an individual.

Common features of long COVID (fatigue, post-exertional malaise, sleep disturbances, cognitive impairment, POTS and persistence of symptoms for 6 months or more) are similar to those of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS, more recently called Systemic Exertion Intolerance Disease or SEID)[60]. In contrast, there are some distinguishing features between long COVID and SEID such as dyspnea and alterations in taste and smell which are not common in published reports of CFS[37,61]. Another contrasting feature is that current definitions of long COVID do not require the minimum six months duration included in most definitions of ME/CFS/SEID.

Symptoms of SEID have been associated with influenza and diphtheria pandemics but the rate post COVID-19 seems much higher than reported for other viruses[28,37]. Higher rates of SEID during pandemics could to some extent be related to general impacts of anxiety and isolation due to restrictive public health measures.

7. Discussion

The understanding of both acute and long COVID is continuously evolving. Findings and conclusions from the literature are dependent on the stage of the pandemic at which they were conducted, which in turn was dependent on local epidemiology as well as the diagnostic and treatment modalities available at the time. In particular, the frequency, nature and severity of post-COVID morbidity may be different following infection with newly emerging SARS-Co-V variants, such as the Delta variant.

A major challenge in synthesizing the literature was the significant heterogeneity in definitions (time after initial infection); populations (select groups such as only hospitalized patients or referrals to specialty clinics); length of follow-up; outcome measurement; investigations to rule out other causes; measurements of severity; and sources (patient-led vs researcher driven). The majority of studies did not have control or comparison groups, making it difficult to determine how or if the findings differed from expected background rates or from the general effects of the pandemic (such as those resulting from isolation, societal disruption or reduced physical activity). Finally, there was limited ethnic diversity in the participants of many studies and there are few studies from low or middle-income countries, limiting the generalizability to the global population.

The above limitations notwithstanding, this review of the literature confirmed that a significant proportion of people who have had SARS-CoV-infection have persistent symptoms; these can be prolonged and debilitating and are not explained simply by general effects of the pandemic on the overall population. Risk factors for long COVID are not always the same as those for severe acute-COVID-19, and long COVID is seen in people of all ages and pre-infection health status. While having many features of other known syndromes such as SEID, long COVID has some different characteristics as currently defined long COVID may not be a single entity but rather several different conditions with different pathogenesis and symptomatology.

The review identified few studies that focused on children; more evidence is needed before a complete picture in this age group emerges.

Given the predominance of immune-related hypotheses for the pathogenesis of long COVID morbidity, it is theoretically conceivable that vaccines could induce similar symptomatology via innate, humoral and/or cellular immune responses. Moreover, post-marketing surveillance has identified increased rates of several immune-mediated adverse events following immunization with COVID-19 vaccines - Vaccine-induced Thrombotic Thrombocytopenia (VITT), myocarditis and pericarditis - which also suggests that the robust

immune response to COVID-19 vaccines could theoretically result in longer-term sequelae. However, a counterargument is the lack of evidence to date that there is an increased rate of new autoimmune disease or autoimmune disease exacerbation following vaccination with mRNA COVID-19 vaccines[62].

While the literature identified in this review has provided much information on what is currently known about long COVID, there are still many unknowns including the pathophysiology, effective treatments, longer term outcomes and impacts of new variants. Research currently underway is likely to provide more insights and ongoing monitoring of new information will be essential.

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Appendix 1

Long COVID-19 Search Strategy

For next update, Dec 21, if required – the colour of the PMIDs reflects the search in which they were retrieved:

- *Yellow Mar 9, 2021*
- *Turquoise May 9, 2021*
- *Green July 12, 2021*

("Coronavirus"[Mesh] OR "COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti])
AND
English[lang]
AND
"2020/01/01 12.00"[MHDA]:"2050/01/01 15.00"[MHDA]
AND
("post-acute COVID-19 syndrome"[Supplementary Concept] OR "post-acute COVID-19 syndrome"[ti] OR "long-COVID"[ti] OR "long-haul COVID"[ti] OR "post-acute sequelae of SARS-CoV-2 infection"[ti] OR "chronic COVID syndrome"[ti] OR "post-acute COVID19 syndrome"[ti] OR "long hauler COVID"[ti] OR "long COVID"[ti] OR "long haul COVID"[ti] OR "post-acute COVID syndrome"[ti])
NOT
(33686318 OR 33684352 OR 33677642 OR 33675686 OR 33664445 OR 33649741 OR 33649174 OR 33633106 OR 33627337 OR 33625001 OR 33622802 OR 33621843 OR 33608317 OR 33580165 OR 33569660 OR 33568362 OR 33548193 OR 33541867 OR 33537155 OR 33538586 OR 33523608 OR 33509811 OR 33502487 OR 33501506 OR 33497610 OR 33497594 OR 33496258 OR 33487628 OR 33479069 OR 33469204 OR 33468452 OR 33462068 OR 33460566 OR 33459404 OR 33453162 OR 33450302 OR 33391730 OR 33428867 OR 33413976 OR 33403997 OR 33401287 OR 33361141 OR 33357467 OR 33342437 OR 33341598 OR 33322316 OR 33320511 OR 33316400 OR 33308453 OR 33288947 OR 33275404 OR 33268328 OR 33252665 OR 33243911 OR 33243837 OR 33220447 OR 33217366 OR 33199035 OR 33173222 OR 33172844 OR 33167766 OR 33095459 OR 33064816 OR 33055076 OR 33051223 OR 33034893 OR 33029005 OR 32998879 OR 32978178 OR 32933925 OR 32895219 OR 32816711 OR 32788251 OR 32769591 OR 32728799 OR 32665317 OR 32975809 OR 33953912 OR 33332756 OR 33729021 OR 33758124 OR 33880442 OR 33444540 OR 33889231 OR 33501596 OR 33657459 OR 33647535 OR 33687143 OR 33731329 OR 33762402 OR 33764205 OR 33847020 OR 33861695 OR 33807869 OR 33683246 OR 33705725 OR 33692189 OR 33692530 OR 33758895 OR 33713306 OR 33722798 OR 33743226 OR 33803690 OR 33740207 OR 33749957 OR 33753937 OR 33765941 OR 33786465 OR 33769552 OR 33791733 OR 33867257 OR 33785926 OR 33817685 OR 33783907 OR 33784738 OR 33785495 OR 33785027 OR 33790036 OR 33807280 OR 33795224 OR 33795319 OR 33822179 OR 33813593 OR 33834529 OR 33835507 OR 33850105 OR 33898792 OR 33919537 OR 33875508 OR 33875855 OR 33879882 OR 33892403 OR 33897909 OR 33923972 OR 33890344 OR 33894903 OR 33893710 OR 33925784 OR 33948602 OR 33911230 OR 33912905 OR 33914346 OR 33926872 OR 33930983 OR 33939462 OR 33941600 OR 33688670 OR 33199025 OR 33887749 OR 34007978 OR 33836148 OR 34035105 OR 33532785 OR 34218857 OR 32915650 OR 33159640 OR 34099197 OR 33880955 OR 33966266 OR 33987484 OR 34035919 OR 34096013 OR 34096390 OR 34163217 OR 34192271 OR 34231404 OR 34234065 OR 34248921 OR 33587889 OR 33846012 OR 33755344 OR 33794106 OR 34041295 OR 33811451 OR 33860871 OR 33464757 OR 33958788 OR 34192289 OR 33992951 OR 34030861 OR 33977626 OR 33983062 OR

33983522 OR 34068009 OR 33990122 OR 33992686 OR 33993490 OR 34063463 OR 34015528 OR 34003294 OR 34006526 OR 34019842 OR 34009992 OR 34011495 OR 34036244 OR 33965645 OR 34024217 OR 34039662 OR 34073342 OR 34045207 OR 34050501 OR 34062184 OR 34059034 OR 33413026 OR 33735380 OR 33901039 OR 34045738 OR 34060675 OR 34076561 OR 34108700 OR 34115558 OR 34090980 OR 34205086 OR 34091456 OR 34104285 OR 34204032 OR 34092779 OR 34102037 OR 34110078 OR 34117474 OR 34128623 OR 34129734 OR 34138696 OR 34140704 OR 34142114 OR 34142116 OR 34204243 OR 34143277 OR 34153235 OR 34145211 OR 34160836 OR 34162532 OR 34162747 OR 34163090 OR 34172475 OR 34215435 OR 34219856 OR 34181102 OR 34183705 OR 34192429 OR 34193506 OR 33958429 OR 34131092 OR 34185758 OR 34210789 OR 34215626 OR 34215639 OR 34237305 OR 34237471 OR 34234251 OR 34244323 OR 34245450 OR 34247285)