

23 OCTOBER 2020

Long Covid: what is it, and what is needed?

This paper is provided to SAGE and UKRI to raise awareness of the emerging syndrome that has become known as Long Covid, among both the public, the medical profession and politicians, and to promote investigation of the predisposing factors, the clinical features and the pathogenesis of the condition, in order to lead to better diagnosis and clinical management. The Royal Society identifies questions that need urgent attention in clinical and laboratory research.

This paper is a pre-print and has not been subject to formal peer-review.

A) Background and rationale

1. It is now clear that, while most people infected with SARS-CoV-2 either remain asymptomatic or recover quickly and completely, a proportion of infected people develop persistent symptoms, which can be severely disabling¹⁻³. For brevity, this phenomenon will be called Long Covid here; see B.3 below.

The precise fraction that fall in this group is poorly understood at present, as are the factors that predispose to this prolonged ill health after initial apparent recovery from the infection. The duration and the long-term sequelae of Long Covid are also unknown, the pathogenesis is not understood, and satisfactory treatment is lacking. These difficulties are compounded by a lack of awareness of the syndrome, especially among the public. A wider appreciation of the incidence and nature of the syndrome is likely to influence behaviour, in particular compliance with measures to minimize transmission of the virus. It is becoming apparent that Long Covid may impose a significant health burden worldwide.

2. The remarkably wide range of persistent or recurrent symptoms reported by individuals following SARS-CoV-2 infection includes the following:

- severe fatigue
- reduced exercise capacity
- breathlessness
- chest pain or heaviness
- fever
- palpitations
- cognitive impairment – “brain fog”
- anosmia or ageusia
- vertigo and tinnitus
- headache
- peripheral neuropathy
- metallic or bitter taste
- skin rash
- joint pain or swelling

The syndrome is often accompanied by anxiety and depression, associated with the protracted and unpredictable course of the symptoms⁴.

3. These symptoms can appear either immediately after apparent recovery from an acute illness, or several weeks later, and can occur in patients whose initial illness was mild or even asymptomatic. Cases are reported (anecdotally) in patients ranging in age from the very young (under 10 years old) to the elderly; the risk of Long Covid rises with age⁵. The symptoms characteristically vary widely within one person from day to day. The diversity of symptoms and their variable and unpredictable course have generated confusion and uncertainty in both the medical profession and the public. Consequently, many patients have had their disabling or alarming symptoms ascribed to anxiety or depression, or simply dismissed. Long Covid bears a strong resemblance to an ill-defined syndrome usually called post-viral fatigue, whose pathogenesis remains obscure and which is thought by some to lack an organic basis. The pathophysiology of Long Covid, which may differ from that in the acute illness, warrants detailed investigation.
4. The purpose of this paper is to raise awareness of this emerging syndrome, Long Covid, among both the public, the medical profession and politicians, and to promote investigation of the predisposing factors, the clinical features and the pathogenesis of the condition, in order to lead to better diagnosis and clinical management. We identify questions that need urgent attention in clinical and laboratory research.
5. Data. Until recently, the published information on Long Covid was largely confined to anecdotal reports. In October 2020 the National Institute of Health Research published a paper⁶ with vivid descriptions by patients of their symptoms of Long Covid, and a summary of links to current work on the management and counselling of patients, to observational studies on Long Covid, and a small number of studies of the involvement in the syndrome of specific organs or systems, such as the heart.

In addition, a number of retrospective observational studies in Europe have been published describing persistent symptoms in patients discharged from hospital following apparent recovery from acute SARS-CoV-2 infection. These studies, from Italy, France, the UK and Switzerland portray a consistent picture of persistent symptoms, most commonly fatigue and breathlessness, in a high proportion of individuals (Table 1).

A prospective study of 201 individuals (mean age 44 years) who were experiencing persistent symptoms 4 months (median 140 days) after the initial onset of illness found impairment in one or more organs (using blood investigations, quantitative MRI and questionnaires) in 70% of the cohort¹¹. This study emphasizes the importance of the condition in the relatively young. Similar observations of multiorgan involvement were

TABLE 1:

Persistent symptoms in Covid-19 survivors

t ^a	N	Persistent symptoms (%)	Fatigue (%)	Breathlessness (%)	Reference
30	116	63	67	56	7
60	143	87	53	43	1
48 ^b	100	61 ^c	64	50	8
111	120	^d	55	42	9
75 ^e	58	>64 ^f	55	64	10

^a Mean time since onset of symptoms (days)

^b Mean time since discharge from hospital (days)

^c Individuals with significant reduction in EQ5D (standardized measure of quality of life)

^d Total number not given; mean EQ5D = 0.86

^e 'Two to three months'

^f Individual symptoms not listed; this study focused on MRI, exercise tolerance, spirometry, cognitive function, mental health, and questionnaires.

made by MRI in a study of 58 patients by Raman et al¹⁰ (see Table 1 and notes ^{e,f} above). In survivors of COVID-19, 3 months after discharge from hospital, Savarraj et al¹² found persistent fatigue with or without other neurological symptoms in 71% of 48 subjects.

These results contrast sharply with a study from Wuhan, China¹³, in which 86% of 131 COVID-19 patients were asymptomatic 3 to 4 weeks after discharge from hospital; none had fatigue and only 1.5% had shortness of breath. In a prospective study in the UK of self-reported symptoms⁵, the estimated rates of persistent symptoms for longer than 28, 56 and 90 days were 14.5%, 5.1% and 2.2% of initially symptomatic cases respectively. The reasons for these differences are not clear.

B) Questions that need to be answered on Long Covid

1. Is it a distinct syndrome or a set of syndromes? It is not yet clear whether there is a continuous distribution of disease duration in the SARS-CoV-2-infected population, or whether the symptoms described constitute a qualitatively distinct syndrome or syndromes.
2. Are there identifiable subgroups of symptoms? Phenotypic heterogeneity can complicate or confound studies of pathogenesis and treatment. A longitudinal mobile phone-based survey of self-reported symptoms in 4,182 individuals⁵ reported two groups of symptoms in Long Covid in addition to fatigue and headache. One group consists of predominantly respiratory symptoms – cough, breathlessness – and the other suggests multiorgan involvement, with cognitive, gastrointestinal and cardiac symptoms (cf. Table 1 and refs. 10-12).
3. What is a satisfactory working case definition of Long Covid? A working definition is needed to enable systematic investigation of the incidence, duration and pathogenesis of Long Covid, and to develop effective treatments. This working definition may change as understanding develops, and more than one phenotypic subgroup may be identified. Definition of the syndrome is complicated by the diverse number and type of symptoms reported^{14,15}; see Section A.2.

For example: Long Covid may be defined as the onset of persistent or recurrent episodes of one or more of the following symptoms, within x* weeks of infection with SARS-CoV-2 and continuing for y* weeks or more [see list of symptoms in Section A.2].

*The maximum period between acquisition of the infection (if known) and the onset of symptoms, and the minimum duration of symptoms, should be specified in the definition.

This working definition is necessarily broad and is therefore open to the criticism levelled at early definitions of AIDS, viz. that it is a collection of diverse signs and symptoms that may not constitute a single entity. However, unlike AIDS at the start of the HIV epidemic it is clear that Long Covid has a single precipitating cause, SARS-CoV-2 infection; and a working definition is essential as a starting point for investigation.

In consultation with NHS England and the World Health Organisation, NICE is currently formulating definitions of the syndrome according to the length of persistence of symptoms. While the general term Long Covid is likely to continue in use, it may be helpful to distinguish between two or three categories: for example, *COVID* for symptoms persisting up to 3 weeks; *Ongoing COVID* for symptoms lasting between 3 and 12 weeks; and *Post-COVID [syndrome]* for symptoms persisting longer than 12 weeks.

4. What is the incidence of Long Covid, i.e. what percentage of infected people develop the syndrome and over what period? And what are the factors that increase or diminish the risk of Long Covid? The King's College London survey⁵ found that one in 20 people with COVID-19 had symptoms for at least two months: risk factors included age, female sex, asthma, and a greater number of symptoms in the acute disease.
5. Prevention and therapy. Does optimized supportive management in the acute disease (fluid balance; control of asthma, diabetes and other co-morbidities) reduce the risk of Long Covid? Do corticosteroids or antivirals provide benefit in Long Covid? What are the best strategies of physical and psychological rehabilitation?
6. Is there a correlation between the risk of Long Covid and the viral titre over time?
7. What is the prognosis of Long Covid? How should recovery from Long Covid be defined?
8. What are the mechanisms of pathogenesis? Investigation into the pathogenesis is of prime importance: again, it is complicated by the diverse nature of the symptoms and the organ systems involved. Although there is minor sequence variation in the virus¹⁶, it is more likely that the variation between patients in the symptoms of Long Covid result from differences in the host than from different strains of the virus. It follows that most effort in research on the pathogenesis is likely to be given to the clinical physiology of the condition and to the host response and host genetics^{17,18}. Evidence is needed on the following:

i) Clinical physiology.

- cardiovascular function. There is MRI evidence of cardiac abnormalities following SARS-CoV2 infection¹⁹. Signs and symptoms of impaired cardiovascular function are frequently reported, especially a severe reduction in exercise capacity
- pulmonary function
- neurology
- renal function. The kidneys are often involved in severe Covid-19; the long-term effects are not yet known
- muscle strength and function
- mental health

ii) Pathology.

- virology: is there evidence of persistence of the virus, for example in the blood vessel endothelium, or in myocardium, or other end organs?
- immunology: does the acquired or innate immune response to SARS-CoV-2 differ between individuals with Long Covid and those who make a full recovery?
- inflammation: are there acute or chronic abnormalities in cytokines, chemokines or other correlates of the inflammatory response associated with Long Covid?
- biochemistry: are there identifiable differences in standard analytes in blood by chemistry between those with Long Covid and those who recover?
- haematology: severe COVID-19 is often accompanied by widespread thrombosis: does thrombosis also contribute to Long Covid?
- genetics: are there identifiable genetic polymorphisms associated with the risk of Long Covid?

C. Action required

1. Agree on a working case definition of Long Covid, either as a single entity, or in a small number of subtypes: see B.3 above. Strong evidence would be required to justify such subdivision at this stage.
2. Cohort studies with appropriate controls. Well-planned and large-scale cohort studies (repeated examination of patients over time post infection) are required, stratified by the key known risk factors including age, gender, ethnicity, past medical conditions, body mass index and others; this list of variables will expand over time as more is understood about the diseases

caused by COVID-19 infection. Some cohort studies are now in the planning stages, both within the UK and internationally^{6,20}. Clear and detailed protocols are required, and their development should take account of other studies planned and underway internationally, to facilitate comparisons and to increase sample sizes in order to improve understanding of the rarer conditions. Protocols should include both individuals with a diagnosis (PCR based) and matched controls. Such studies will follow individuals over time and the protocols in development should specify what investigations will be made (e.g. blood samples to measure virological and immunological markers, chest X rays, genetic measures, etc) and the precise nature of any consultation with a clinician or completion of a questionnaire. Such studies need to be planned for the long term (> 5 years) and ensure that the participants accurately represent the diverse UK population. What is measured in such studies will change over time as the understanding of the infection and associated disease improves. These long-term studies should also investigate the possible long-term sequelae of COVID-19: physiological insults in the acute disease may reduce physiological reserve which result in secondary conditions, especially in the elderly.

Sampling in these cohort studies should be randomized where possible, to minimize bias due to self-selection and to take account of the fall-out of participants over time as is typical in long term cohort studies.

3. Raise awareness of Long Covid in the general public: to make them aware that Covid is not always a disease from which a quick return to full health can be assured, and that people of any age may develop Long Covid. The purpose is to improve reporting of the syndrome and to encourage public support for the measures aimed at suppressing transmission of the coronavirus. This information campaign will require sensitive design and handling, to present the information in a neutral and objective way in order to avoid any impression of persuasion by spreading fear.
4. Patient engagement. Involvement of patient groups in the work at the earliest stages and cooperation in development of the work plan will help ensure the outputs are sensitive to the needs of patients and their families.

References

1. Carfi A, Bernabei R, Landi F. 2020 Persistent Symptoms in Patients After Acute COVID-19. *JAMA* 324, 603. (doi:10.1001/jama.2020.12603)
2. NHS. 2020 After-care needs of inpatients recovering from COVID-19. Available from: <https://www.pcrs-uk.org/sites/pcrs-uk.org/files/nhs-aftercarecovid.pdf>
3. Public Health England. 2020 COVID-19: long-term health effects. Available from: <https://www.gov.uk/government/publications/covid-19-long-term-health-effects/covid-19-long-term-health-effects>
4. Tomasoni D et al. 2020 Anxiety and depression symptoms after virological clearance of COVID-19: A cross-sectional study in Milan, Italy. *J Med Virol* (doi:10.1002/jmv.26459)
5. Sudre CH et al. 2020 Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App. *MedRxiv* (doi: 10.1101/2020.10.19.20214494)
6. NIHR. 2020 Living with Covid19. Available from: <https://evidence.nihr.ac.uk/themedreview/living-with-covid19/>
7. Pellaud C et al. 2020 Characteristics, comorbidities, 30-day outcome and in-hospital mortality of patients hospitalised with COVID-19 in a Swiss area – a retrospective cohort study. *Swiss Med Wkly* (doi:10.4414/smw.2020.20314)
8. Halpin SJ et al. 2020 Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* (doi:10.1002/jmv.26368)
9. Garrigues E et al. 2020 Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *Journal of Infection* (doi:10.1016/j.jinf.2020.08.029)
10. Raman B et al. 2020 Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *MedRxiv* (doi: 10.1101/2020.10.15.20205054)
11. Dennis A et al. 2020 Multi-organ impairment in low-risk individuals with long COVID. *MedRxiv* (doi: 10.1101/2020.10.14.20212555)
12. Savarraj JPJ et al. 2020 Three-month outcomes in hospitalised COVID-19 patients. *MedRxiv* (doi: 10.1101/2020.10.16.20211029)
13. Wang X, Xu H, Jiang H, Wang L, Lu C, Wei X, Liu J, Xu S. 2020 Clinical features and outcomes of discharged coronavirus disease 2019 patients: a prospective cohort study. *QJM: An International Journal of Medicine* 113, 657–665. (doi:10.1093/qjmed/hcaa178)
14. Alwan NA. 2020 Track post-COVID sickness, not just cases and deaths. *Nature* 584, 170–170. (doi:10.1038/d41586-020-02335-z)
15. 2020 Long COVID: let patients help define long-lasting COVID symptoms. *Nature* 586, 170–170. (doi:10.1038/d41586-020-02796-2)
16. The Royal Society. 2020 The SARS-CoV-2 genome: variation, implication and application. Available from: <https://royalsociety.org/-/media/policy/projects/set-c/set-c-genome-analysis.pdf?la=en-GB&hash=CF1883F618E851FF269487B02AB19CF8>
17. The Royal Society. 2020 COVID-19: the immune response, inflammation, and vascular disease. Available from: <https://royalsociety.org/-/media/policy/projects/set-c/set-c-immunology.pdf>
18. The Royal Society. 2020 ABO Blood Groups and COVID-19. Available from: <https://royalsociety.org/-/media/policy/projects/set-c/set-c-blood-groups.pdf?la=en-GB&hash=BF406C30925D04D88EF89568CBE11F75>
19. Puntmann VO et al. 2020 Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* (doi:10.1001/jamacardio.2020.3557)
20. Imperial College London. 2020 Real-time Assessment of Community Transmission (REACT) Study. Available from: <https://www.imperial.ac.uk/medicine/research-and-impact/groups/react-study/>

DISCLAIMER

This paper has drawn on the most recent evidence up to 23 October 2020 and has not been subject to formal peer-review. Further evidence on this topic is constantly published and the Royal Society may return to this topic in the future. This independent overview of the science has been provided in good faith by subject experts and the Royal Society and paper authors accept no legal liability for decisions made based on this evidence.

THANKS

The Royal Society is grateful to the Leverhulme Trust for its support for the Society's pandemic response work.

The text of this work is licensed under the terms of the Creative Commons Attribution License which permits unrestricted use, provided the original author and source are credited. The license is available at: creativecommons.org/licenses/by/4.0

Issued: October 2020 DES7217 © The Royal Society