Long COVID: Summary of key evidence

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- Long COVID is a complex condition, with an emerging but limited evidence base. It is characterised by the existence of symptoms for several weeks or months after acute COVID-19. It can have a severe impact on quality of life.
- Symptoms are wide ranging with relapse commonly reported. Fatigue is the most recurrent theme across the published literature, with other common symptoms including headache, cough, shortness of breath, cognitive dysfunction, anxiety/depression and sleep difficulties. This list does not capture the breadth of lived experience of 'long haulers'.
- The prevalence of long COVID remains unclear, with issues of study quality and varied study design (incl. sample selection and time point) leading to very varied estimates. E.g. 2.3% at 12 weeks in one largely non-hospitalised pop vs 76% at 6 months in a hospitalised cohort.
- Limited evidence means there is no clear case definition of long COVID. The NICE/SIGN/RCGP 'living' guideline currently utilises:
  - Ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4-12 weeks.
  - Post-COVID-19 syndrome: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.
- The currently limited data issue extends to treatment and service organisation. Whilst NICE/SIGN/RCGP suggest a one-stop multidisciplinary clinic approach as one option, they acknowledge no single model will suit all areas of the UK or all patients. They found only seven service descriptions and no outcomes data to guide such decisions.
- In the face of this lack of outcomes data, there are guiding principles for services suggested by NICE/SIGN/RCGP and qualitative research conducted with long COVID patients that could be given consideration e.g.:
  - Provision of integrated, multidisciplinary rehabilitation services
  - The burden of co-ordinating care should be minimised for patients, care pathways should be clear and referral criteria explicit.
  - Specialist investigation and management of specific complications is important, but one clinician should take care of the whole patient and provide continuity of care.
- Long COVID research is being planned/conducted to counter the limited evidence base:
  - The CSO's office has recently awarded funding to nine long COVID research proposals - £2.466 million over an average project duration of 24 months.
  - The NIHR/UKRI have launched a UK-wide call of up to £20 million on the longer term, physical and mental health effects of COVID-19 in non-hospitalised individuals.
- Key research gaps are many, but include:
  - Epidemiology
  - Diagnostic, prognostic and precision medicine approaches
  - Development and evaluation of treatment and rehabilitation strategies
  - Lived experience
- There is an active patient community with long COVID, many of whom are healthcare professionals and academics. Their engagement, both through driving patient-led research and though involvement in shaping and participating in large studies, has been and will continue to be, central to advancing the evidence base.

Introduction

Patients and reports in the media(1–3), have increasingly highlighted lived experience of symptoms that exist, often in a relapsing-remitting way, for several weeks or months after acute COVID-19 (known or suspected). The condition can have a severe impact on quality of life, including the ability to work. Symptoms can be very varied, though fatigue seems to be a particularly common theme, according to experts(4) and larger recent studies(5–8). Other common symptoms identified by the same studies include headache, cough, shortness of breath, cognitive dysfunction, anxiety/depression and sleep difficulties. This list does not capture the breadth of lived experience of 'long haulers'.

The term 'long covid' was coined for this phenomenon by patients(9) and will be used in this brief evidence review. However, other terms have also been used, such as 'post-acute covid-19'(10), 'ongoing symptomatic COVID-19'(11) and 'post-COVID-19 syndrome'(11).

This is a highly debated area with many unknowns(12), from the preferred nomenclature(13) to the underlying cause(14). After a review of some key evidence, this paper will highlight planned research and suggest future research needs. Addressing these will be crucial to create the robust evidence base needed to answer the many questions of patients, clinical staff and policymakers.

Prevalence and key characteristics

The diversity of symptoms identified by long COVID patients is significant - one patient led survey of 1,567 'long haulers' captured 98 symptoms (15). The symptoms can vary from day to day, as articulated in a BMJ Opinion piece by Prof Paul Garner 7 weeks into his journey (16):

The illness went on and on. The symptoms changed, it was like an advent calendar, every day there was a surprise, something new. A muggy head; acutely painful calf; upset stomach; tinnitus; pins and needles; aching all over; breathlessness; dizziness; arthritis in my hands; weird sensation in the skin with synthetic materials.

- Prof Paul Garner, Director of the Centre for Evidence Synthesis in Global Health at the Liverpool School of Tropical Medicine and Co-ordinating Editor of the Cochrane Infectious Diseases Group.

The diversity in symptoms has led the NIHR to suggest there may even be several different syndromes in action (e.g. Post-Intensive Care syndrome, Post-Viral Fatigue syndrome and Long-Term Covid syndrome)(17).

Literature reviews

Two literature reviews were identified, which sought to assess the prevalence and key characteristics of long COVID. They found a limited and heterogeneous evidence base:

- **NICE** (18) Dec 2020: 8 studies reported on symptoms 4 to 12 weeks from onset of acute COVID-19 or hospital discharge, in those hospitalised for known or suspected COVID-19. Even amongst the most common symptoms, symptom prevalence was wide ranging e.g. cough 7% to 43%. This variation was also pronounced across the 13 studies of non-hospitalised people e.g. loss of smell 7% to 51%. Even less data were found for symptoms

beyond 12 weeks, with just 3 very low quality studies identified. These too had very wide-ranging symptom prevalence e.g. breathlessness 6.7% to 94.6%.

NICE attributed this variation to several points: the studies were not necessarily designed to assess prevalence, had varied recruitment strategies and had relatively small sample sizes (majority with n <500). They considered all the studies to be at high or moderate risk of bias.

- **Michelen et al** (19) Dec 2020: In a preprint, they identified 28 studies, but stated that "the limited evidence base currently precludes a precise definition of its symptoms and prevalence". They found a "wide range of systemic, cardiopulmonary, gastrointestinal, neurological, and psychosocial symptoms". The most common were "breathlessness, fatigue, smell and taste disturbance, and anxiety."

Like NICE, they highlighted the low quality of the evidence, which had a high risk of bias, was largely not designed to assess prevalence and had inconsistent data collection methods.

Key recent primary research

Since Michelen and NICE's reviews, four larger studies have emerged. Fatigue is the most recurrent theme across them, with other common symptoms including headache, cough, shortness of breath, cognitive dysfunction and sleep difficulties. Many other symptoms were also identified by patients.

Most focus on symptoms, with only one providing evidence from investigations, which is an area in need of further study. For instance, in one relatively small study (n=100) 78% patients who had recovered from COVID-19 had abnormal findings on cardiac MRI (median of 71 days after diagnosis). Only 33% of the total sample had been hospitalised for acute COVID-19 and the findings were independent of pre-existing conditions, severity and overall course of the acute illness (20).

1. The ONS(8) used 8,193 responses to the Coronavirus (COVID-19) Infection Survey (a nationally-representative sample of the UK community population) to estimate the prevalence of long COVID in those testing positive:

    - Around 20% had symptoms for 5 weeks or longer
    - Around 10% had symptoms for 12 weeks or longer

    The most common symptoms at 5 weeks (% of those who ever tested positive):

- Fatigue (11.5%)
- Cough (11.4%)
- Headache (10.1%)

From these data, they estimated that around 186,000 people in private households in England were living with symptoms that had persisted for between 5 and 12 weeks (estimate for w/c 22 Nov 2020). However, they highlight this analysis as "very much a work in progress".

2. The Covid Symptoms Study App(5) looked at 4,182 incident cases of COVID-19 who reported positive test results and logged their symptoms prospectively in the app. Respondents were predominantly from the UK, but also came from the US and Sweden. 13.9% reported visiting a hospital at some point during the study. They found lower rates of long COVID than the ONS:

- 13.3% had symptoms lasting 4 weeks or more
- 4.5% for 8 weeks or more
- 2.3% for 12 weeks or more

The most common symptoms reported beyond 4 weeks (% of those who had symptoms at 4 weeks or more) were:

- Fatigue (68%)
- Headache (40%)
- Breathlessness (37%)
- Loss of sense of smell (39%)
- 81% entered free-text symptoms not covered by the app

The authors suggested two main patterns amongst those with symptoms lasting 4 weeks or more: those exclusively describing fatigue, headache and upper respiratory complaints (e.g. shortness of breath, sore throat) and those with additional multi-system complaints (e.g. ongoing fever and gastroenterological symptoms). They found long COVID was more likely with increasing age, BMI, female sex and experiencing more than five symptoms during the first week of illness. They also developed a long COVID prediction model using symptom number in the first week, age, and sex.

The authors noted that the study was limited by being necessarily restricted to users of the app, who were disproportionately female and under 70 years old. In addition, they only included cases who started on the app "feeling physically normal". Taken together with other factors, they suggest their estimates may be conservative.

3. Davis et al(6), in patient-led research supported by UCL, surveyed 3,762 individuals with long COVID (illness >28d, with or without a positive test) from 56 countries (41.2% US, 35% UK). They traced 66 symptoms over 7 months, in a population that was predominantly female (78.9%) and non-hospitalised (91.6%).
   - 96% reported symptoms beyond 90 days

The most commonly reported symptoms after 6 months, were:

- Fatigue (77.7%)
- Post-exertional malaise (72.2%)
- Cognitive dysfunction (55.4%)

85.9% reported relapse, 45.2% reported requiring a reduced work schedule compared to pre-illness and 22.3% were not working at the time of survey due to their health.

This is a large study that forms a useful piece of the emerging evidence; however, these data likely reflect a sampling bias toward long COVID patients who were active participants of support groups at the time, which limits extrapolation to the wider long COVID population.

4. Huang et al (7) published a cohort study of the 6-month consequences of COVID-19 in the Lancet, finding far higher prevalence of ongoing symptoms than the aforementioned studies,

potentially due to the focus on hospitalised patients. They enrolled 1733/2469 individuals with confirmed COVID-19 who had been discharged from Jin Yin-tan Hospital (Wuhan) from Jan 7-May 29 2020. Patients were predominantly male (52%).

- 76% of patients reported at least one symptom at 6 months after symptom onset

The most common symptoms at 6 months were:

- Fatigue or muscle weakness (63%, 1038 of 1655)
- Sleep difficulties (26%, 437 of 1655)
- Anxiety or depression (23%, 367 of 1617)

The authors report that more severely ill patients had increased risk of fatigue or muscle weakness, and anxiety or depression at 6 months. However, the results suggest more complexity. Whilst patient who did NOT require supplemental oxygen were less likely to develop fatigue/muscle weakness than those on invasive/non-invasive ventilation or high-flow nasal cannula (HFNC), they were more likely to develop fatigue/muscle weakness than those who DID need supplemental oxygen without ventilation/HFNC. Similarly, they were less likely to have anxiety/depression than those who needed ventilation/HFNC, but there was no statistical difference between them and the group that needed supplemental oxygen without ventilation/HFNC.

They also conducted investigations:

- 23% (n=392/1692) walked below the normal distance range in a 6min walking test
- 353 had a chest CT at follow-up, and approx. 50% had at least one abnormality

Evidence from a subset of ~350 patients who underwent lung function tests and imaging, found patients who were more severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and worse chest CT scores at 6 months.

Case definition

Given the above uncertainty, it is unsurprising that there is no clear case definition for long COVID at present. For instance, neither the CDC nor the WHO have offered any definition as yet. In December 2020 NICE/SIGN/RCGP crafted a guideline which includes case definitions, but their nature reflects the limited evidence base. NICE/SIGN/RCGP describe the existing advice as a 'living guideline' that "will be continuously reviewed and updated in response to emerging evidence". They acknowledged long COVID as a commonly used term for symptoms beyond 4 weeks, but offered the following terminology for clinical case definitions(11):

- Acute COVID-19: signs and symptoms of COVID-19 for up to 4 weeks.
- Ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4 to 12 weeks.
- Post-COVID-19 syndrome: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.

This is a challenging and rapidly evolving area, for all guideline developers. The above case definition has been criticised in an editorial in the BMJ for being a diagnosis of exclusion (21) and in another in the Lancet for lacking clarity with regards the symptoms and being an 'arbitrary construct'(13). The

latter editorial highlighted that the WHO is expected to update its guidance on the clinical management of COVID-19 to include long COVID, which may include a clinical case definition.

Treatment and service organisation

The limited data problem faced by long COVID extends to optimal treatment and service organisation. Presently, there is no single, specific treatment for long COVID. Instead, NICE/SIGN/RCGP focus on self-management and multidisciplinary rehabilitation, with mention of specialist referral where necessary for specific complications (11).

The organisation of services is also a point of variation. Whilst NICE/SIGN/RCGP suggest a one-stop multidisciplinary clinic approach as one option (such as those in some areas of England(22)), in the evidence review document, they acknowledge no single model will suit all areas of the UK or all patients(23).

In that evidence review document, NICE found only seven service descriptions (from the UK, Austria and Italy) which were all proposed or in the early stages of implementation. They found no outcomes data to guide service organisation for long COVID. They also noted the strain on existing services, and advised that "resources should not be diverted from these services to new COVID-19 rehabilitation services".

Below are edited highlights of the general principles included in the final guidance(11), which drew on the aforementioned limited review data, expert testimony, the panel's expertise and the patient lived experience data:

- Provide access to multidisciplinary services (these could be 'one-stop' clinics) for assessing physical and mental health symptoms and carrying out further tests and investigations. They should be led by a doctor with relevant skills and experience and appropriate specialist support, taking into account the variety of presenting symptoms.
- Provide integrated, multidisciplinary rehabilitation services.
- Share knowledge, skills and training between services.
- Agree local, integrated referral pathways between primary and community care, multidisciplinary rehabilitation services and specialist services, multidisciplinary assessment clinics and specialist mental health services.

Similar key points were also identified by a large qualitative study led by Ladds et al from the University of Oxford (24). Through focus groups and interviews they spoke to 114 UK long COVID patients (defined as having symptoms beyond 3 weeks). Notably, almost half were health professionals.

From these conversations, six patient-generated quality principles were derived for long COVID services. There are limitations to this study, for instance they note they may not have fully captured the perspectives of people from some minority ethnic groups, and speed and resource issues necessitated doing only partial transcription for 45 out of the 55 interviews. Nevertheless, given the currently extremely limited evidence base, their advice may offer a useful resource to inform a range of approaches to long COVID management:

- Access: Should not necessitate a positive lab test for Covid-19 or a hospital admission.
- Burden of illness: The burden on the patient for accessing, navigating and coordinating their own care should be minimised. Care pathways should be clear and referral criteria explicit.

- Clinical responsibility and continuity of care: Whilst specialist investigation and management of particular complications is important, one clinician should take care of the whole patient and provide continuity of care.
- Multi-Disciplinary rehabilitation services: Patients requiring a formal rehabilitation package should be assessed by a multi-disciplinary team including (e.g.) rehabilitation, respiratory and cardiac consultant, physiotherapist, occupational therapist, psychologist and (if needed) neurologist.
- Evidence-based standards: Standards and protocols should be developed, published and used so that investigation and management is consistent wherever care is received.
- Further development of the knowledge base and clinical services: Clinical teams should proactively collect and analyse data on this new disease so as to improve services and build the knowledge base. Patients should be partners in this endeavour.

Research

On October 5th the CSO launched a call dedicated to long COVID, with nine projects ultimately awarded funding, represent a commitment of £2.466 million over an average project duration of 24 months. The projects are to be led by five different Scottish Universities, with a range of topics represented, including lived experience, symptom tracking, an exercise trial and an exploration of the frequency, nature, and impact of 'long COVID' in the Scottish population.

In November, the NIHR/UKRI launched a UK-wide joint research call of up to £20 million to fund "research into understanding, mitigating and addressing the longer term, physical and mental health effects, of COVID-19 in non-hospitalised individuals."(25) Details on which projects were awarded funding is expected in Jan 2021.

In addition to these dedicated funding calls, data is already being gathered on longer-term COVID-19 outcomes in several studies, such as the COVIDENCE UK Study and ISARIC-4C Moreover, there are several key studies that have been planned/begun both in the UK and elsewhere, including:

- PHOSP-COVID: Aims to recruit 10,000 patients who have been hospitalised with COVID-19. Over the course of a year, clinical assessments will track patients to gain a comprehensive picture of the impact COVID-19 has had on longer term health outcomes across the UK.
- ONS: Early this year, a new long COVID question will be added to the COVID-19 Infection Survey (CIS), allowing respondents to state the impact long COVID has had on their daily activities, and an expanded list of symptoms. Plan to estimate the prevalence of long COVID symptoms using the CIS and make use of linked healthcare and Census datasets.
- COVID-19 Patient Experience Survey #2: Building on their earlier patient-led research, members of the Body Politic online COVID-19 support group (and sponsored by UCL) have launched a second survey to better describe and understand long COVID. The focus includes participants' backgrounds, testing, symptoms, and psychological wellbeing.
- NIHR Living with COVID-19 review: A substantive update of this review is due in Feb 2021.

These and other studies will hopefully provide the evidence to answer the questions being posed by patients, clinical staff and policymakers. Key gaps, as identified as priority areas in the CSO's long COVID call include:

- Epidemiology
- Clinical evaluation of diagnostic, prognostic and precision medicine approaches
- Development and evaluation of treatment and rehabilitation strategies
- Lived experience

Captured within these headings are a litany of fundamental questions, such as those highlighted by NICE/SIGN/RCGP(11). These include:

- What factors, including identifiable clusters of symptoms, influence the risk of developing post-COVID-19 syndrome and its trajectory?
- Are there clusters of symptoms that identify response to interventions in post-COVID-19 syndrome?
- What is the prevalence and incidence of post-COVID-19 syndrome? Does it differ across different population groups (for example in black, Asian and minority ethnic group communities)?
- What symptoms do children, young people, pregnant women and older people with suspected post-COVID-19 syndrome present with?

Several of these were also noted in an editorial in the Lancet in December(12), which also highlighted the need for large and long-term cohort studies to answer these questions (with diverse populations - hospitalised and non-hospitalised patients, patients from primary and secondary care, and patients from a range of countries, ethnicities and demographics).

The editorial also counselled on the need to include patient perspectives on study designs. There is an active long COVID patient community, (e.g. LongCovidSOS, Long Covid Support) many of whom are healthcare professionals and academics. Their engagement, both through driving patient-led research and though involvement in shaping and participating in large studies, has been and will continue to be, central to advancing the evidence base.

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