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'Long Covid': evidence, recommendations and priority research questions

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Summary and recommendations

1. Long Covid is a distinct condition affecting approximately 60,000 people in the UK and characterised by persistent and fluctuating fatigue, breathlessness, cognitive blunting ("brain fog") and pain. The cause is unknown but it is likely to be due at least partly to an inflammatory reaction. Many cases remain undiagnosed, since clinicians may incorrectly require a positive test for Covid-19.

2. Most people with long Covid slowly get better over time, but a minority (perhaps 10%) are left with significant organ damage and their long-term outlook is unknown.

3. The principles of management are a) confirm the diagnosis; b) exclude serious complications; c) support and monitor the patient while avoiding over-investigation and over-referral; d) develop and supervise a rehabilitation plan and exercises; e) direct to specialist clinics if appropriate.

4. Long Covid services are currently patchy and overstretched. This is partly because funding was diverted away from rehabilitation and towards the acute sector as an emergency response to the pandemic. Specialist rehabilitation services designed for patients recovering from a hospital admission (e.g. oriented to restoring normal breathing after pneumonia) have become swamped with referrals from general practice (who often have more general symptoms such as fatigue).

5. Clinical guidance and local protocols for long Covid are currently highly variable. This is likely to be contributing to the patient experience of inconsistent and fragmented care. We recommend that the development of NICE guidelines and that these are reviewed periodically as new evidence emerges.

6. We recommend that a 4-tier clinical service be developed:
   a) Tier 1: resources and support for self-care.
   b) Tier 2: generalist care including a therapeutic relationship in general practice and a community-based interdisciplinary rehabilitation service led by allied health professionals.
   c) Tier 3: specialist care including system-based investigation, management and rehabilitation.
   d) Tier 4: specialist management of specific complications.

7. There is a significant research agenda on this new disease. We suggest five priority areas for research:
   a) Basic science studies on upstream causes, including genetics and metabolomics.
   b) Observational studies of long-term outcome, especially in non-hospitalised patients.
   c) Trials of interventions, including different rehabilitation protocols.
   d) Studies to optimise and evaluate the service model, including virtual wards and remote care.
   e) Interdisciplinary studies of how socio-economic and racial disadvantage affects the development, course and outcome of long Covid.

What is long Covid?
Long Covid is the name patients gave to Covid-19 that hasn't got better yet. A recent BMJ review defined **post-acute Covid-19** as symptoms lasting 3-12 weeks and **chronic Covid-19** as symptoms beyond 12 weeks.[1] Importantly, some people whose initial Covid-19 was mild (and who were never hospitalised) may go on to develop chronic symptoms and vice versa.

Broadly speaking, patients with long Covid fall into three groups:

A. People who were very ill (perhaps on ITU) with acute Covid-19 and now have significant long-term organ damage (e.g. lungs, heart, brain, kidneys) along with weakness and debility;
B. People who were not so ill in the acute stage but who also now have some evidence of long-term organ damage; and
C. People who have persistent symptoms after Covid-19 but who don't have persisting organ damage.

Whist the first two groups account for considerable illness and suffering, they comprise a **relatively small proportion of long Covid patients**. For example, a study of 110 patients discharged from hospital after acute Covid-19 found that three-quarters still had symptoms (usually of breathlessness and fatigue) at 12-week follow-up but only one in eight still had an abnormal chest X-ray.[2]

What are the symptoms?
People with long Covid experience a wide range of persistent (and often fluctuating) symptoms including **cough, breathlessness, fatigue, fever, sore throat, chest pains ("lung burn"), cognitive blunting ("brain fog"), muscle pains, anxiety or depression, skin rashes, and diarrhoea**.[1-5] Control of

chronic conditions such as diabetes, inflammatory bowel disease, or rheumatological conditions may deteriorate.

Relatively rarely, patients may develop thrombo-embolic complications including **heart attack, stroke and venous thrombosis** (DVT), or other serious conditions such as **heart failure or heart rhythm abnormalities**. It is, of course, important to identify (or, more commonly, exclude) these serious complications.

How common is it?
Estimates vary (e.g. those based on self-surveys of patients recruited from Facebook groups imply higher incidence,[5] presumably because people who got better didn't join a group). The figures we trust most suggest that of people who have had Covid-19:[6,7]

- **10-20%** are still unwell after 3 weeks (though many of these are in group C above and essentially 'on the mend')
- **1% are still significantly unwell** after 12 weeks

Of this 1%, the predominant symptom varies depending on which if any organs are affected (e.g. fatigue, fatigue and breathlessness, cognitive blunting, palpitations or dizziness from fluctuating blood pressure, chronic pain, depression or anxiety).

Based on these figures, approximately 60,000 people in the UK probably have long Covid. A GP practice with 20,000 patients in an area of high Covid-19 incidence (e.g. London, Leicester) is likely to have:

- Up to 2000 patients who have had Covid-19 (whether test-confirmed or not)
- Up to 200 patients whose Covid-19 required a sick note for more than 3 weeks
- Up to 100 patients with *some form of* chronic Covid-19 (i.e. not completely better by 12 weeks)
- 10-20 patients with *seriously debilitating* chronic Covid-19 (e.g. unable to work or take part in normal family life or leisure activities)

How is Long Covid diagnosed?
Long Covid is a clinical diagnosis – i.e. it's **based on a medical assessment and does not need a positive swab or antibody test** (more specifically, a positive test is helpful if present but of no value if absent or negative). This is because

a. back in March-May 2020, most people were never offered swab tests even if they had symptoms;
b. an antibody (blood) test indicates past infection – it does *not* confirm that the person's current symptoms are due to long Covid;
c. the tests aren't 100% accurate – in particular, false negative results are common (and a positive antibody test may become negative over time).

Long Covid is therefore best diagnosed by **a history consistent with acute Covid-19 followed by a prolonged recovery**. This manifests in a variety of ways but is usually dominated by fatigue and breathlessness, particularly on

minimal exertion (and therefore causing severe functional limitation). Note that other diseases (e.g. asthma) have no definitive laboratory test; they are diagnosed clinically.

What causes it?

We don't know exactly, but there is evidence that long Covid is associated with a powerful **inflammatory (immune) reaction**,[8] involving **vasculitis** (swelling of the inner lining of the blood vessels).[9]

How serious is it?

For some people, the sequelae of Covid-19 are very serious and potentially life-threatening – mostly because of **thrombo-embolic complications** (clots in the blood vessels of the brain, lungs, heart and other organs as a result of inflammatory reaction). For others, the problem is more **post-viral fatigue** (prolonged exhaustion that prevents them getting back to work and normal activities – which, while debilitating, is rarely if ever life-threatening). However, biopsy and scan studies suggest that even patients without symptoms of thrombo-embolic disease after Covid-19 may show signs of organ damage.[10] Because of this, people with long Covid need **careful monitoring and a cautious approach to rehabilitation**.

What are the risk factors?

There is remarkably little peer-reviewed data on risk factors for long Covid. People with **pre-existing conditions** are at greater risk of severe disease and more likely to require hospitalisation; these patients are likely to have a prolonged recovery time.[11,12] In one study, 87% of the hospitalised population, who had significant rates of **hypertension, thyroid disease, immune disorders, chronic obstructive pulmonary disease, and diabetes**, still exhibited some symptoms at 60 days.[11] However, many patients with long Covid had no pre-existing conditions.

The self-survey from a large online patient community found that **58% of respondents had at least one pre-existing condition**, with the commonest being asthma, vitamin D deficiency, acid reflux disease, and autoimmune disorders.[3] Of that sample, only 4.4% had been hospitalised. Medical conditions such as diabetes, heart disease and kidney disease predispose to thrombo-embolic complications after Covid-19, but previously healthy people also get them.

What is the chance of recovery?

Reassuringly, **most people seen in Covid-19 rehabilitation clinics slowly recover** (unpublished data, MK). Because Covid-19 is a new disease, the long-term outlook in the minority whose symptoms persist beyond 6 months is unknown. However, there may be parallels with other coronavirus diseases. Some patients with SARS went on to develop a **long-term illness with widespread pain, fatigue, depression and sleep disturbance**.[13,14] **Post-traumatic stress disorder** has also been described after SARS.[15]

Hence, whereas the acute and post-acute manifestations of Covid-19 were **predominantly respiratory**, the **longer-term sequelae may turn out to be more systemic** and (for some who have been traumatised) psychiatric. The

overlap with myalgic encephalomyelitis (a syndrome of profound tiredness, generalised pain and difficulty functioning, probably due to several different underlying causes) is unknown.

What do patients say?
Thousands of **people with long Covid have come together in online communities**, many of whom feel dismissed by their physicians as over-reacting to "mild" illness. They have undertaken and published their own research studies (which have informed the list of symptoms listed above).[3,16]

Research interviews by the Oxford team with over 100 people with long Covid (currently being written up for publication) have identified **five key 'touch points'** in current service provision:

a. **Dismissal:** patients are told there is nothing wrong with them or that they are just anxious (absence of positive test may be misinterpreted as evidence that the patient does not have Covid-19).
b. **Unclear lines of responsibility** – e.g. GP triage service tells patients to call NHS111 (because they have mentioned the word Covid); NHS111 says call the GP (because it's not acute).
c. **Fragmented care:** specialist services look at "one bit of me" (and confirm, for example, no heart attack) but no clinician considers the disease as a whole.
d. **Gaps in services:** patients are told there is no rehabilitation service locally or that it has exclusionary referral criteria (e.g. must have had a positive swab or antibody test, must have been admitted to hospital in the acute illness).
e. **High burden borne by the sick patient:** organising appointments and tests requires considerable effort and persistence (e.g. one patient we interviewed took 12 phone calls to secure a simple repeat prescription of an asthma inhaler).

How are patients with long Covid currently being managed?
Care of the patient with long Covid is **extremely variable** across the country. Covid-19 rehabilitation **services have typically arisen ad hoc** and in a locally path-dependent way in both secondary and community care, perhaps led by a local clinician with an interest. Referral criteria and management protocols are inconsistent and feature **both under- and over-investigation**. Whilst **paced activity**, as recommended by the Royal College of Occupational Therapists,[17] appears to be an important component of management at all levels, there is much uncertainty around who should receive what kind of rehabilitation.

General practitioners are still **operating largely remotely** in a service structure designed for infection control in the acute phase of the pandemic. All **requests for appointments are triaged** and channelled to self-care (i.e. the patient is refused a consultation), NHS111 (the patient is advised to call the NHS phone line), telephone or video call-back appointment, or a face to face appointment. In this context, **many patients fail to secure a full clinical assessment** (history, physical examination, baseline blood tests) a clear management plan, or ongoing follow-up; in some cases the GP does not accept the diagnosis of long Covid.

In our view, there is an **urgent need for interdisciplinary guidelines**, spanning both primary and secondary care, to be developed at national level, preferably by the National Institute for Health and Clinical Excellence, and for these to be reviewed and updated promptly as new evidence emerges.
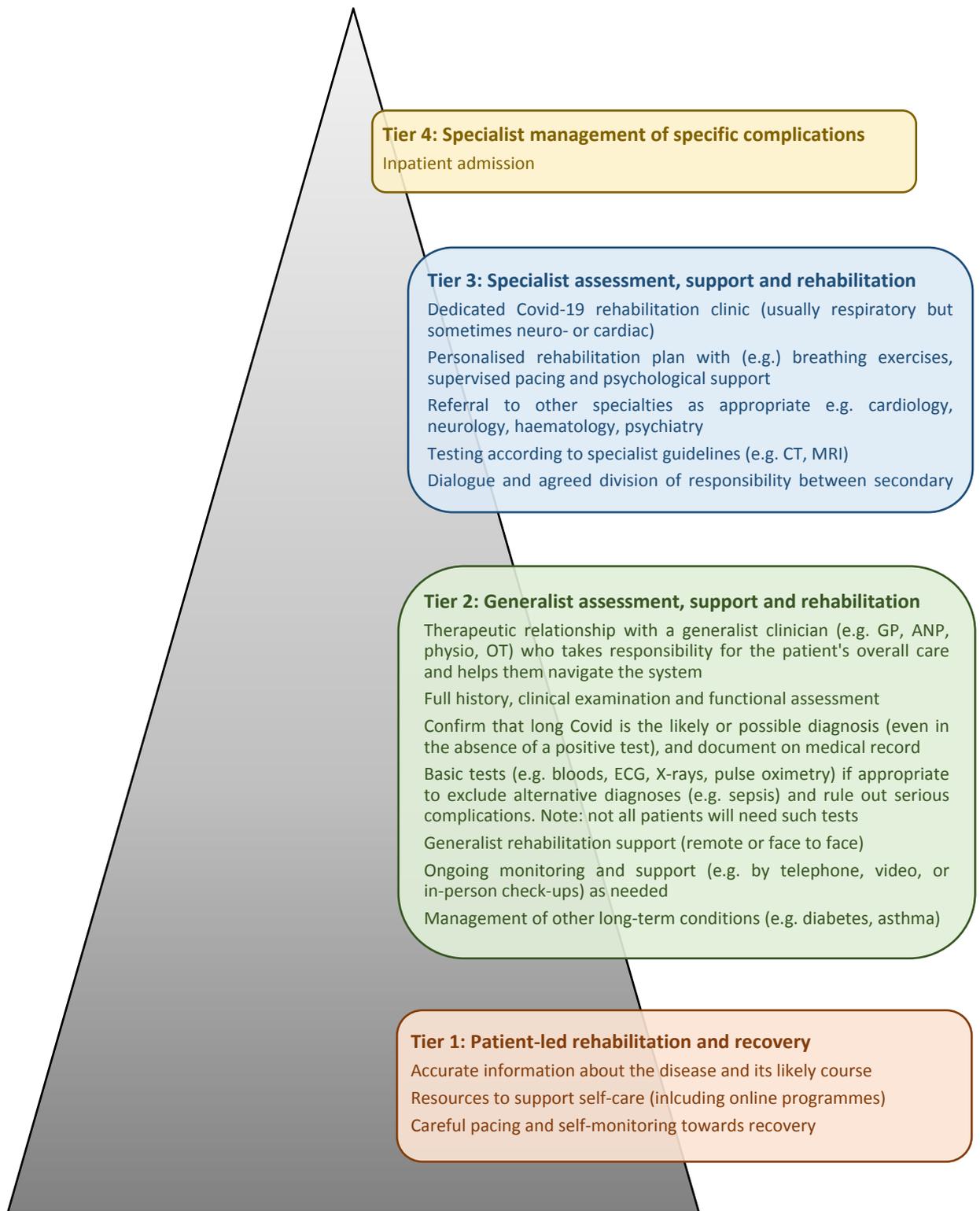

How should services for long Covid be organised?
Whilst there remain many uncertainties around the diagnosis and management of long Covid, there is already considerable evidence to support a **new service model**. We propose a **4-tier service** comprising self-care, generalist care, specialist care and specialist management of specific complications. Assessment should be designed to **identify and fast-track people with severe illness** and complications while **not over-investigating or over-medicalising** the majority. Tiered care models are increasingly used (e.g. in chronic pain[18] and diabetes[19]). Patients may move between tiers as symptoms become more or less troublesome.

Almost all patients with Long Covid will require **Tier 1 support for self-care**. The YourCovidRecovery online service (https://www.yourcovidrecovery.nhs.uk) may be helpful to guide self-care.

Perhaps 80% of patients will need **Tier 2 support from a generalist team**. Patients do not just need tests on their different bodily systems; they need a **therapeutic relationship with a clinician** who recognises their diagnosis, affirms their experience and takes responsibility for their care.

Around 10% of patients will need **Tier 3 specialist care**, though this should be carefully targeted. Early thinking and planning depicted Covid-19 as a disease of the lungs (because it caused a cough and obvious acute problems like pneumonia), so **rehabilitation and follow-up services emerged mostly in respiratory clinics**. We now know that long Covid is a **multi-system disease** and that most patients recover spontaneously without extensive investigation or specific treatment.[2,6] Whilst we acknowledge that NHS England's early guidance 'Aftercare needs of inpatients recovering from Covid-19' provides important baseline recommendations in the different clinical specialties (respiratory, cardiology etc),[20] it is also the case that we need to **avoid the pitfalls seen in other comparable conditions**, where patients with multisystem Covid-19 symptoms, especially less severe cases, enter **a cycle of fragmented secondary care pathways**, sometimes leading to increasing anxiety, overdiagnosis, labels and lengthy waits to get assurance and care.

Tier 4: Specialist management of specific complications
Inpatient admission

Tier 3: Specialist assessment, support and rehabilitation
Dedicated Covid-19 rehabilitation clinic (usually respiratory but sometimes neuro- or cardiac)
Personalised rehabilitation plan with (e.g.) breathing exercises, supervised pacing and psychological support
Referral to other specialties as appropriate e.g. cardiology, neurology, haematology, psychiatry
Testing according to specialist guidelines (e.g. CT, MRI)
Dialogue and agreed division of responsibility between secondary

Tier 2: Generalist assessment, support and rehabilitation
Therapeutic relationship with a generalist clinician (e.g. GP, ANP, physio, OT) who takes responsibility for the patient's overall care and helps them navigate the system
Full history, clinical examination and functional assessment
Confirm that long Covid is the likely or possible diagnosis (even in the absence of a positive test), and document on medical record
Basic tests (e.g. bloods, ECG, X-rays, pulse oximetry) if appropriate to exclude alternative diagnoses (e.g. sepsis) and rule out serious complications. Note: not all patients will need such tests
Generalist rehabilitation support (remote or face to face)
Ongoing monitoring and support (e.g. by telephone, video, or in-person check-ups) as needed
Management of other long-term conditions (e.g. diabetes, asthma)

Tier 1: Patient-led rehabilitation and recovery
Accurate information about the disease and its likely course
Resources to support self-care (inlcuding online programmes)
Careful pacing and self-monitoring towards recovery

Figure: Suggested tiered approach for a long Covid service

The 1% of patients requiring **Tier 4 care for specific complications** should be readily identified by either GPs or specialist clinicians on the basis of acute (perhaps red-flag) symptoms.

In sum, we need to **retain specialist respiratory rehabilitation** for survivors of acute Covid-19 pneumonia but also supplement this with a new tier of **generalist**

(ideally, primary care based) rehabilitation and follow-up services, and provide **resources and support for self-care**.

What is needed to support a tiered long Covid service?
On the basis of the estimates in the previous section, to deliver these services, for every Clinical Commissioning Group population of 225,000, new-blood staff would be needed as follows:

- One FTE physiotherapist or equivalent (see below)
- One FTE occupational therapist
- One FTE consultant-grade clinician (e.g. sessions divided between respiratory physician, GP or advanced nurse practitioner, liaison psychiatry, rehabilitation specialist, pain specialist)
- One FTE social support (e.g. sessions divided between social prescriber, health coach, community link worker as appropriate locally) – this workforce may be linked to the new NHS Personalised Care Institute (https://www.england.nhs.uk/personalisedcare/supporting-health-and-care-staff-to-deliver-personalised-care/personalised-care-institute/) being established to train social prescribers
- Administrative support

Given that effective long Covid management will span both primary and secondary care, **integrated care pathways** will be essential. Such services are already in development.[21] However, primary care services are already stretched to breaking point and **GPs in particular are unlikely to have the capacity or the appetite** for setting up and running a new service. **New resource, and a new workforce** (perhaps drawn mainly from advanced nurse practitioners, physiotherapists and occupational therapists) is essential.

One potential source of appropriately-trained personnel for community rehabilitation clinics could include **First Contact Practitioners** (https://firstcontactpractitioner.org.uk/how-does-fcp-model-work-with-pcns/) – physiotherapists with general community and rehabilitation training – who are being trained currently to support Primary Care Networks. Those placed to provide non-medical approaches to care, such as **Social Prescribers**, may help some patients to adapt their lifestyles and address their physical and mental health needs. Patients may also benefit from financial advisers, Citizens Advice Bureau, and faith-based support.[1]

In addition to the individual components of the service, clear and efficient lines of referral between the components are crucial. A **'virtual ward' model** may be a useful technological infrastructure, particularly since many patients will have been managed on virtual wards in the acute phase.

What research is being done – and what additional research is needed?
There are three main kinds of research currently happening on long Covid:

a. **Retrospective or prospective collection of routine data** – e.g. respiratory consultants who run rehabilitation clinics for post-acute Covid-19 are analysing 3-month and 6-month follow-up data. This research is mostly unfunded (undertaken by NHS clinicians) and descriptive (i.e. it will

give a useful estimate of case mix and the clinical course of post-acute Covid-19 but was not set up to test particular hypotheses). It's hard to know how much of this kind of research is going on in the NHS, or what the quality of completed studies will be like.

b. **Prospective, independently funded research studies of particular cohorts of patients**. For example,
   o The PHOSP ('post-hospitalisation') study (www.phosp.org), led from the University of Leicester and funded by UK Research and Innovation and National Institute for Health Research (NIHR), is *"a long term research study 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."*
   o COVERSCAN (https://coverscan.com), funded by Innovate UK and EU Horizon 2020, seeks to map organ damage in patients with Covid-19 using serial MRI scanning.
   o University College London is leading the UK arm of an International Observational Study of Outpatients with SARS-CoV-2 Infection in adults who were not hospitalised, to estimate the rate of disease progression for adults who seek testing and test positive for SARS-CoV-2 (https://www.ucl.ac.uk/global-health/research/z-research/international-sars-cov-2-infection-observational-study-icos).

c. **Qualitative and mixed-method research**. A number of smaller studies are using mainly or exclusively qualitative methods to capture the patient experience and understand the challenges for organisation and delivery of services. For example, Remote by Default, a multi-partner study led from the University of Oxford, is exploring service provision for patients with both acute and chronic Covid-19 (https://www.phc.ox.ac.uk/covid-19/projects/remote-by-default-care). We have interviewed over 100 patients with Covid-19 for that study so far.

We have identified the following priority areas for new research:

a. **Studies of risk factors and upstream causes**. The weakest section of this report in terms of published evidence is probably the question of what predisposes a person to develop long Covid (and what could protect people from developing it). Basic science research is needed to understand the underlying causes of Long Covid, how it differs from other post-viral conditions such as Chronic Fatigue Syndrome, and what predisposing factors may predict the likelihood of developing it (eg: genetic or metabolomic studies).

b. **Prospective observational cohort studies of the clinical course of long Covid in non-hospitalised patients**. The PHOSP study has been well-designed but arguably has overly restrictive inclusion criteria, since 90% of patients with Covid-19 were never hospitalised and many (perhaps the majority) never had a positive swab. PHOSP will miss most of the patients in the long Covid support groups, for example. The Society of Rehabilitation Medicine

c. **Intervention studies**. Long Covid rehabilitation clinics are likely to be an ideal setting for clinical trials of different interventions (e.g. different kinds of breathing exercises, different treatments for fatigue and for pain).

d. **Studies of optimising the service model**. Quality improvement and co-design studies could refine and improve the outline model of tiered care described above. The role of virtual services could be explored as part of this work.

e. **Studies of how disadvantage impacts long Covid**. A condition that leads to inability to work is likely to have a disproportionate impact on the poor and disadvantaged (e.g. without full employment benefits, living in poor housing and with low health, digital and system literacy). A major finding in our qualitative research was the amount of work the patient needs to do to secure a diagnosis and a treatment package. The less articulate (including limited English speakers) and less well-connected are likely to be missing out on care. In some cases, long Covid in a family breadwinner will have major impacts (e.g. eviction, repossession).

Conclusion

We welcome the Select Committee's interest in long Covid, which is affecting tens of thousands of people across the country. There is something of a paradox that the services which were established to respond to acute Covid-19 are ill-suited to the assessment and management of this chronic, variable and fluctuating condition which needs ongoing care and support tailored to the patient's particular needs. Whilst the evidence base on this new condition is relatively sparse, we already know enough to improve current services. High on the priority list are interdisciplinary guidelines and a programme of research which incorporates basic science, epidemiology, health services research and the social sciences.

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