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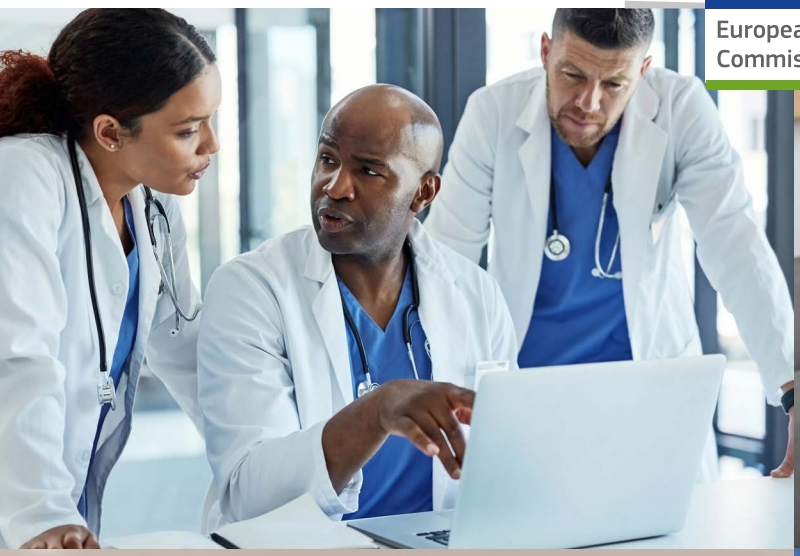

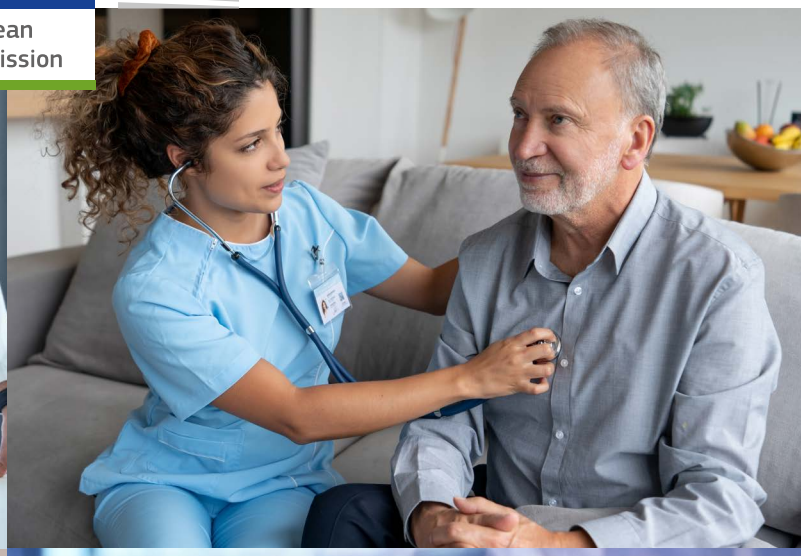

FACING THE IMPACT OF POST-COVID-19 CONDITION (LONG COVID) ON HEALTH SYSTEMS

Opinion of the

Expert Panel on effective ways of investing in health (EXPH)

Health and Food Safety

Further information on the Health and Food Safety Directorate-General is available on the internet at: http://ec.europa.eu/dgs/health_food-safety/index_en.htm

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EXPERT PANEL ON EFFECTIVE WAYS OF INVESTING IN HEALTH

(EXPH)

Opinion on

Facing the impact of post COVID-19 condition (Long COVID) on health systems

The EXPH adopted this Opinion in writing on 12 December 2022
after the public hearing held on 18 October 2022

About the Expert Panel on effective ways of investing in health (EXPH)

Sound and timely scientific advice is an essential requirement for the Commission to pursue modern, responsive and sustainable health systems. To this end, the Commission has set up a multi-disciplinary and independent Expert Panel which provides advice on effective ways of investing in health (Commission Decision 2012/C 198/06).

The core element of the Expert Panel's mission is to provide the Commission with sound and independent advice in the form of opinions in response to questions (mandates) submitted by the Commission on matters related to health care modernisation, responsiveness, and sustainability. The advice does not bind the Commission.

The areas of competence of the Expert Panel include, and are not limited to, primary care, hospital care, pharmaceuticals, research and development, prevention and promotion, links with the social protection sector, cross-border issues, system financing, information systems and patient registers, health inequalities, etc.

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ABSTRACT

This Opinion on the impact of the post-COVID-19 condition also termed long COVID, from the Expert Panel is based on a review of the available evidence (including ongoing work from the ECDC and EMA) and any other relevant ongoing research activities, published before early 2022. There is growing evidence that SARS-CoV-2 can give rise to various post-acute consequences involving several mechanisms with some of them poorly understood. As knowledge is permanently evolving, the Expert Panel decided to highlight some of its key and still unclear issues.

The panel reviewed the existing definition on long COVID and stayed on the WHO clinical case definition. Although the most common symptoms seem to be fatigue, shortness of breath, and cognitive dysfunction, several others, which generally have an impact on everyday functioning, have been reported. A major constraint in recognising an accurate prevalence of long COVID is the lack of surveillance in many places. The prevalence of self-reported long COVID seems to be greatest in groups of the population that partly overlap (people aged 35 to 69 years, females, people living in more deprived areas, hospitalisation during the acute phase, immunoglobulin signature, number of symptoms in the acute phase, those working in social care, those aged 16 years or over whom were not students or retired and who were not in or looking for paid work, and those with another activity-limiting health condition or disability, smoking, vaccination status and SARS-CoV-2 variant). There is also some evidence that the prevalence of long COVID was higher amongst patients recruited in the hospital setting when compared to the community setting. Multiple non-mutually exclusive mechanisms have been implicated in the pathogenesis of long COVID including direct effects of the acute illness resulting in organ damage and tissue injury; persistent viral material reservoirs in certain body tissues; autoimmune and molecular mimicry mechanisms; interactions with host microbiome; dysfunctional coagulation; and impaired neuronal signalling. The panel reviewed also the long COVID in children and adolescents as well as long COVID Stigma. There are several unanswered research questions on long COVID and they have been clearly presented in a Box with 15 items.

Organisational and resource requirements for healthcare systems to design and develop appropriate health services for long COVID have been discussed with a focus on: implications for the health workforce, preventing long COVID among essential workers, supporting health workers with long COVID, preventing patients from getting long COVID, models of care for patients with long COVID, health systems approach to long COVID, service delivery, health workforce, health information systems, access to essential medicines, financing, Leadership and governance.

Finally, the opinion composed 6 recommendations with a focus on research on long COVID and especially on: potential treatments, on health systems that need to embed research on long COVID at all levels of care (including rehabilitation), efforts to reduce transmission (including vaccination), investment on models of care that are co-ordinated in primary care and on establishment of coordinated programmes of surveillance systems.

Keywords: Expert Panel on effective ways of investing in health, public health, long Covid, post-COVID-19 condition

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EXECUTIVE SUMMARY

The high prevalence of COVID-19 in Europe foreshadows a potentially significant burden on national health systems linked to addressing the Post COVID-19 condition (also termed long COVID). This Opinion from the Expert Panel is based on a review of the available evidence to generate analysis and recommendations around three main points.

1. ***Provide an overview of the current best evidence on what post-COVID-19 condition is, its probable causes and symptoms, using the available literature to date, including the work carried out by the ECDC in this area.***

Although different nomenclature exists to describe the condition of symptoms present months after acute COVID-19 infection, the review uses long COVID as per the WHO clinical case definition. Due to the complexity in defining and measuring long COVID it can be difficult to determine prevalence, however the data suggests it affects approximately 3% of the overall population. There are multiple potential mechanisms of long COVID which are non-mutually exclusive. These include persistent viral presence or viral reactivation, fibrosis and organ damage, autoimmune processes, dysbiosis or inflammatory responses including microvascular dysfunction.

Risk factors for developing long COVID seem to include older age, female sex, hospitalisation during acute phase of COVID-19 infection, smoking, presence of co-morbidities and absence of vaccination. Symptoms of long COVID can be difficult to characterise but they are wide-ranging, unpredictable, and there is evidence they cluster into respiratory, cognitive and fatigue clusters. Children and adolescents are also at risk of developing long COVID but may present with different symptoms. Long COVID is associated with health-related stigma, which can have wider impacts for those living with it. There are several research questions that are unanswered that EU-funded research may be well-placed to address with large-scale, multi-disciplinary studies. Specific priorities for EU research include a package of basic science research to further understanding of underlying mechanisms, establishing patient cohorts to better delineate natural history of long COVID, developing candidate therapeutics, researching impact of long COVID at individual and societal level and developing new models of care.

2. ***Provide an analysis of the main knowledge, organisational and resource requirements for healthcare systems to design and develop appropriate health services for post COVID-19 condition.***

The health workforce are at particular risk of developing long COVID and adequate prevention and support of LONG COVID in this group is essential. Health systems will also be affected by caring for patients with long COVID - in this regard both minimising prevalence of long COVID at population level and developing models of care for those with long COVID are essential. Components of long COVID rehabilitation services must include multi-disciplinary rehabilitation teams, continuity and coordination of care, and people-centred care with shared decision-making. The challenges will be implementing these principles whilst incorporating flexibility to allow the health system to respond to the uncertainty surrounding the condition. There is a strong argument for creating dedicated services for patients with long COVID that bring together a range of specialties and expertise, coordinated by primary care. Attention should be paid to the pathways by which patients will enter these services, which will likely differ depending on whether they were managed in the community, hospital or intensive care. The health workforce should be adequately trained with support from specialist expertise underpinning long COVID services. Health systems should also establish mechanisms to collect data on long COVID to ensure there is adequate monitoring of the services, including ensuring issues such as equity of access are considered and to support wider research efforts. The nature of long COVID makes it difficult to predict but healthcare systems should ensure they have adequate financing and governance structures in place to meet the future challenges associated with it.

3. Provide guidance on how public health surveillance should be adapted to measure the impact of the post-COVID-19 condition on the population.

Surveillance systems for long COVID should build on existing systems as far as possible. They should be able to capture the wider impacts of long COVID by incorporating quality of life dimensions, and should include a longitudinal component to allow the disease trajectory to be monitored. The multifaceted presentation of long COVID and the difficulties in accurately diagnosing the condition may pose challenges for passive surveillance mechanisms and active surveillance will be required. The information collected should be standardised across the EU and neighbouring countries as far as possible. Passive surveillance from data collected by health services will help monitor the burden of disease.

Recommendations

Designing services for long COVID can be seen as an opportunity for health systems to address many weaknesses that will help them meet a growing burden of ill health associated with increasing prevalence of chronic conditions and aging populations. Based on the questions posed in the mandate, the recommendations from this report

encompass the knowledge generation required to address long COVID, what health systems can do to meet the burden of long COVID and how effective surveillance systems can be introduced.

Recommendation 1: Research on long COVID should, as far as possible, be explicitly co-produced with people living with the condition, with co-creation of potential therapeutic interventions, as well as a targeted consideration of the pathway along which the findings of the research can achieve impact.

Recommendation 2: Research on long COVID, and especially on potential treatments, needs to be done at sufficient scale to provide definitive answers that take account of any heterogeneity within the population and the contexts in which they are situated.

Recommendation 3: Health systems need to embed research on long COVID at all levels of care including rehabilitation, identifying incentives that can be applied and barriers that can be removed to facilitate the development of health facilities as settings for research and health workers as users of it.

Recommendation 4: As COVID-19 infection is the cause of long COVID, measures to combat it, including vaccination and reducing transmission, must remain a priority.

Recommendation 5: Long COVID is to be recognized as one of many complex chronic conditions that, in many patients, will co-exist with others, calling for models of care that are co-ordinated in primary care, with mechanisms to ensure rapid referral to specialist teams while avoiding placing patients in "long COVID siloes".

Recommendation 6: A coordinated programme of surveillance systems should be established, including data from each member state, using consistent case definitions and methodologies, and encompassing the impact of this condition on health, employment, and the economy.

MANDATE

Preliminary estimates indicate that at least 10% of those infected with COVID-19 will experience debilitating symptoms lasting much longer than expected, leading to impaired quality of life in many cases. The term used by the World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC) is post COVID-19 condition (also referred to as 'long COVID').

The high prevalence of COVID-19 in Europe foreshadows a potentially significant burden on national health systems linked to addressing long COVID in the future.

As the disease burden caused by long COVID on health systems increases, countries strive to define appropriate clinical pathways (diagnosis, symptom management) while waiting for biomedical research to discover potential therapeutic approaches.

The EU strategy on COVID-19 therapeutics specifically mentions long COVID in the framework of research, development and innovation actions, as it requires a different therapeutic approach to COVID-19. Such therapeutics are distinct from specific COVID-19 therapeutics since they will not target the initial viral infection but the wide range of negative health effects that persist long after the infection has been resolved.

One major limitation to defining appropriate clinical pathways is the current uncertainty on the spectrum of presentation, pathophysiology, symptom makeup and expected clinical course of long COVID. While long COVID is still being studied, it is clear that the condition can affect any patient after infection with COVID-19, regardless of hospitalisation status or severity of symptoms in the acute phase.

At the same time, there is an urgent need to understand the resource and organizational implications of long COVID for health systems in the medium to long term, including an assessment of whether current payment systems are fit to meet the care needs of this novel class of patients. Lastly, there is a need to understand the health, social and economic impact of long COVID on patients and their carers.

This Opinion from the Expert Panel is based on a review of the available evidence (including ongoing work from the ECDC and EMA) and any other relevant ongoing research activities, published before early 2022. This includes relevant projects funded by the Horizon 2020 and Horizon Europe Framework programmes, such as those on COVID-19 cohort studies and therapeutics, as well as the upcoming European Partnership on Transforming Health and Care Systems. The recommendations should be practical and provide a solid basis for developing actions to improve the quality and accessibility of care services for long COVID patients.

The target audiences of this Opinion are policymakers, health service purchasers and managers, including those working within health, social and welfare systems and responsible for the planning, organisation, financing and delivery of care and support services at the national, regional or local level.

QUESTIONS FOR THE EXPERT PANEL

The Expert Panel is requested to provide a concise document with analysis and recommendations on the following points:

1. Provide an overview of the current best evidence on what post-COVID-19 condition is, its probable causes and symptoms, using the available literature to date, including the work carried out by the ECDC in this area.
2. Provide an analysis of the main knowledge, organisational and resource requirements for healthcare systems to design and develop appropriate health services for post COVID-19 condition.
3. Provide guidance on how public health surveillance should be adapted to measure the impact of the post-COVID-19 condition on the population.

1. OPINION

1.1. The scope of the opinion

The first step in writing an Opinion on long COVID is to decide what should be included and what not. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is one of several viruses that, while causing an acute self-limiting illness in most of those it infects, can also give rise to enduring consequences. Other examples of such viruses are those causing influenza or polio (Spinney, 2022). Others can cause permanent tissue damage during the acute illness, again as seen with polio, which may kill anterior horn cells in the spinal cord causing flaccid paralysis (Tangermann et al., 2017), while others persist in the body, such as Human Immunodeficiency Virus (HIV), some forms of hepatitis, or Herpes viruses (Boldogh et al., 1996), in some cases causing immune dysfunction. Evidence from follow-up of SARS1 infected individuals points to a relatively high prevalence of long sequelae (Ahmed et al., 2020). There is growing evidence that SARS-CoV-2 can give rise to various post-acute consequences involving all these mechanisms and, probably, others so far poorly understood (as knowledge is permanently evolving). The remainder of this section discusses the considerations that the Expert Panel has taken into account when deciding what to include, combining evidence on mechanisms and signs and symptoms.

Long COVID involves a constellation of symptoms found in people who have had COVID-19, some of whom fail to recover completely, with others developing symptoms after a period of apparent recovery. This condition goes under several names, including Post-COVID-19 condition, the term used in the Mandate given to the Expert Panel. However, other names include the patient-made term Long Covid (Callard and Perego, 2021), Post acute sequelae of COVID-19 (PASC) (National Institutes of Health, 2021), and Post COVID syndrome (National Institute for Health and Care Excellence, 2020). Its symptoms are often episodic and multisystem. The most common include fatigue, cognitive impairment (a manifestation sometimes called "brain fog", memory and concentration problems), difficulty breathing, post-exertional symptom exacerbation (PESE), muscle aches, joint pains, chest pain, palpitations, and dizziness, amongst many other symptoms. Even those whose initial infection was mild or asymptomatic are at risk. Any combination of these symptoms may manifest.

Several conditions may present following COVID-19 that, while important, fall outside a diagnosis of long COVID. Case definitions and epidemiological studies should evolve rapidly to aid distinction between these conditions and long COVID as far as possible, recognising that more than one may be present in a particular patient. Those sufficiently ill to require ventilation may suffer post-intensive care syndrome (PICS) (Rawal et al., 2017). This can include cognitive impairment, psychological manifestations such as depression or anxiety, and physical symptoms, such as muscular weakness, all of which may persist for prolonged

periods. A multisystem inflammatory condition associated with recent COVID-19 in children can cause severe illness or death. (Jiang et al., 2020) These conditions are beyond the scope of this opinion.

Initially viewed as another form of viral pneumonia, the acute COVID-19 infection is now recognized by the medical and scientific community as a complex multi-system disease affecting many body systems (Roberts et al., 2020), with several mechanisms through which long-term damage may occur. One is direct lung damage, especially in those who underwent mechanical ventilation, leading to persistent radiological abnormalities, such as ground glass opacities and reduced diffusion.(McGroder et al., 2021) Another is increased risk of blood clotting, which may lead to permanent ischaemic damage such as infarcts in the brain, heart, or kidneys (Merkler et al., 2020, Modin et al., 2020).

Those who survive COVID-19 infection are at greater risk of other health problems in the subsequent year. One large US study found that those who had had COVID-19 had a 72% increased risk of heart failure compared with controls, a 63% increased risk of heart attack, and a 52% increased risk of stroke (Xie et al., 2022). Future longer-term complications of COVID-19 cannot be excluded.

Thus, some people who have had COVID-19 will have isolated damage to a body system, such as lung scarring, heart damage or a stroke, but they may also have symptoms of long COVID solely due to such specific organ damage or wider pathophysiological changes. Where appropriate in the opinion, these will be included as a manifestation of long COVID if defined as such by the cited evidence.

1.2. Best evidence on post-COVID-19 condition, its probable causes and symptoms

1.2.1. Definition of long COVID

Having set the scope of the Opinion in the previous section, it is necessary to define what is being discussed. The Mandate given to the Expert Panel refers to post-COVID-19 condition, the term used by the World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC), but notes that it is also referred to as 'long Covid'. This terminology requires some unpacking.

Some of the first reports of long-lasting symptoms after acute SARS-CoV-2 infection were provided by people with lived experience of this condition, some of whom coined the term "Long Covid" in Spring 2020 (Callard and Perego, 2021). The language used to name this condition is important (Perego et al., 2020). This is perhaps the first condition to be named by those experiencing it via on social media platforms, and it reflects concern that the

names of previous newly emerging conditions developed by health professionals may exclude, minimize, and delegitimize their experience, particularly if the health condition is poorly understood in terms of underlying mechanisms and effective management. An editorial in the journal Nature said that health authorities "must always give proper consideration to the voices of people with COVID-19 and their representatives, who have done so much to put long COVID on the health-research and policy agenda" (Nature, 2020).

Yet, notwithstanding such concerns, professional bodies have developed their own terminology. In addition to the term post-COVID-19 condition formally used by the WHO (World Health Organization, 2021a), the National Institute for Health and Care Excellence in England proposed the terms "Ongoing symptomatic COVID-19" for those with signs and symptoms lasting 4-12 weeks and "Post-COVID-19 syndrome" where they persisted beyond 12 weeks and are not explained by an alternative diagnosis (National Institute for Health and Care Excellence, 2020). Another term commonly used in the USA is Post acute Sequelae of SARS-CoV-2 Infection or COVID-19 (PASC) (Groff et al., 2021, Tabak, 2022). All these terms can be found in the literature so, throughout this Opinion, the term used in the item of literature being cited will be used for fidelity to it. Readers should, however, note that the terms are, for all practical purposes, interchangeable.

It is not, however, only the condition's name that has generated disagreement. There have been a wide variety of definitions proposed. From the most recent proposals we summarize the main definitions in Table 1.

Table 1 Definitions of post COVID-19 condition

Source	Text
Haute Autorité de santé, France	Three criteria: Having presented with a symptomatic form of COVID-19; presenting with one or more initial symptoms four weeks after the start of the disease and none of these symptoms can be explained by another diagnosis (Haute Autorité de Santé, 2021).
US CDC	Long COVID: While most persons with COVID-19 recover and return to normal health, some patients can have symptoms that can last for weeks or even months after recovery from acute illness. Even people who are not hospitalized and who have mild illness can experience persistent or late symptoms (Centers for Disease Control and Prevention, 2022).
UK National Institute for Health and Care Excellence	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 (National Institute for Health and Care Excellence, 2020).

Royal Society (UK)	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: severe fatigue, reduced exercise capacity, chest pain or heaviness, fever, palpitations, cognitive impairment, anosmia or ageusia, vertigo and tinnitus, headache, peripheral neuropathy, metallic or bitter taste, skin rash joint pain or swelling (Royal Society, 2020). * 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.
Wikipedia	Condition characterized by long-term sequelae – persisting after the typical convalescence period – of coronavirus disease 2019 (COVID-19) (Wikipedia, 2022).
Long COVID (post-COVID-19 condition) in children: research definition	Post-COVID-19 condition occurs in young people with a history of confirmed SARS-CoV-2 infection, with one or more persisting physical symptoms for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis. The symptoms have an impact on everyday functioning, may continue or develop after COVID-19 infection, and may fluctuate or relapse over time (Stephenson et al., 2022).

Source: Adapted in modified form and updated from WHO (2021a)

For the purposes of this Opinion, it is necessary to select one of these and, given its authority in global health and the participatory process described in reaching this case definition (Soriano et al., 2022), we will use the WHO definition (Box 1); the main challenge in the case definition continues to be how to define "persistence", as thresholds set at 4, 8 or 12 weeks massively impact the prevalence and nature of long COVID. There are other limitations of the WHO definition that should be kept in mind. The WHO definition is sensitive but involves a considerable trade-off with specificity. High sensitivity allows more people to be recognized as affected and receive care but, on the other hand, a stricter definition would be required for research purposes. The WHO definition has a focus on respiratory symptoms and fatigue but does not explicitly mention cardiovascular signs and symptoms, which some current research is also pointing as important. Cardiovascular problems (heart failure, arrhythmia and other cardiovascular conditions) may cause shortness of breath and fatigue but lead also to other more specific symptoms (palpitations, chest pain, oedema)

Box 1 WHO clinical case definition of Post COVID-19 condition (long COVID)

Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last for at least two months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children.

Source: WHO (2021a)

1.2.2. How common is long COVID?

There are many issues to be considered in interpreting estimates of the prevalence of long COVID beyond reaching agreement on its nomenclature and definition, although after two years of the pandemic the situation is becoming clearer. First, and most obviously, prevalence is a function of the scale and timing of previous waves of infection, leading to new cases and subsequent recovery or death. If the number of new cases exceed those who recover or die, the prevalence will steadily increase over time. Second, if the definition used requires confirmation of a previous infection, this will be affected by the testing regimes in place at the time of suspected disease onset. Third, when estimating prevalence in research studies rather than routine surveillance, some surveys may seek controls as many of the symptoms are seen with other conditions. However, some conditions may be exacerbated by COVID-19. If this is not considered, prevalence may be underestimated. Fourth, the prevalence will be highly sensitive to the range of symptoms included in the case definition. Fifth, symptoms may fluctuate over time, so a survey that asks about a single time point will give lower figures that one that asks about them over a longer period (Brown and O'Brien, 2021). Finally, some people with COVID-19 or long COVID might not seek help within healthcare systems leading to an underestimate of prevalence.

In practice, the major constraint in establishing prevalence is the lack of surveillance in many places. An early study conducted in the United States among those 14-21 days following a positive test found that 35% had not returned to their previous state of health (Tenforde et al., 2020). Since then, there have been many similar one-off surveys, (Taquet et al., 2021, Søraas et al., 2021) and some brought together in systematic reviews that have concluded that the problems of data quality and comparability are considerable (Domingo et al., 2021, Michelen et al., 2021). One estimate of prevalence of long COVID worldwide concluded that, as per the WHO definition, 3.69% (95% CI 1.38-7.96) of all COVID-19 infections resulted in long COVID (Wulf Hanson et al., 2022).

The most frequently cited data come from the ongoing surveillance conducted by the UK's Office for National Statistics (ONS). This takes data from a household survey, with a sample size of over 350,000 respondents who are asked "Would you describe yourself as having 'long COVID', that is, you are still experiencing symptoms more than four weeks after you first had COVID-19, that are not explained by something else?" It is updated every four weeks.

The most recent data, as of the time of writing (published August 2022) estimate that as of 2nd July 2022 1.79 million people living in private households in the UK (2.8% of the population) were experiencing self-reported Long COVID (Office for National Statistics, 2022c). This figure has been decreasing slightly since it peaked at 1.99 million in April 2022. As this decrease was during a wave of Omicron infections, when 586,000 (33% of the total) of those reporting symptoms first experienced them, the number of people recovering seems to be exceeding new cases, even allowing for some deaths, at least in this period. Of people with self-reported Long COVID, 243,000 (14%) first had (or suspected they had) COVID-19 less than 12 weeks previously, 1.4 million people (81%) at least 12 weeks previously, 761,000 (43%) at least one year previously, and 380,000 (21%) at least two years previously.

The survey questions do not permit an accurate assessment of the need that those reporting symptoms will have on health care. Obviously, those with mild symptoms may need relatively little support beyond advice and symptomatic treatment. However, it can be assumed that those who have more severe symptoms will require more help. The survey estimated, in November 2022, that 2.2 million people, equating to 3.4% of the population, were experiencing self-reported long COVID (symptoms continuing for more than four weeks after the first confirmed or suspected coronavirus (COVID-19) infection that were not explained by something else. Long COVID symptoms adversely affected the day-to-day activities of 1.6 million people (75% of those with self-reported long COVID), with 370,000 (17%) reporting that their ability to undertake their day-to-day activities had been "limited a lot". (Office for National Statistics, 2022b). The most common symptom was fatigue (70% of those with self-reported Long COVID), followed by difficulty concentrating (48%), shortness of breath (46%) and muscle ache (45%).

The prevalence of self-reported long COVID was greatest in people aged 35 to 69 years, females, people living in more deprived areas, those working in social care, those aged 16 years or over who were not students or retired and who were not in or looking for paid work, and those with another activity-limiting health condition or disability.

The ONS supplements these data, used for population-level population estimates, with follow-up of all those with confirmed infection in their survey, asking whether they think

they have Long Covid. 11.7% of all those infected (including those asymptomatic) reported Long Covid symptoms at 12 weeks after infection. Out of those initially symptomatic in the acute phase, the prevalence was 17.7% (Office for National Statistics, 2021). In adults who are triple vaccinated, the ONS survey found a prevalence of 4-5% with no evidence of difference by SARS-CoV-2 variant (Delta, Omicron BA.1 or Omicron BA.2) (Office for National Statistics, 2022d).

As with adults, studies of long COVID in children suffer from problems of comparability. A systematic review published in December 2021 included 14 studies and estimated a prevalence of Long Covid in children to be between 4% and 66% of those infected (Zimmermann et al., 2021). However, studies were of variable quality and some suffered from testing criteria that relied on symptoms found in adults, poor follow-up, and small sample sizes. The latest ONS data, referenced above, from July 2022 estimate that 98,000 children aged 2-16 years in the UK have Long Covid (>4 weeks from onset of illness), with 26,000 estimated to have had Long Covid for at least a year from onset of illness. This latter figure equates to 0.6% of children in the 2–11-year-old group and 1.23% in the 12–16-year-old group (Office for National Statistics, 2022c).

An observational study in the Netherlands, by Ballering et al (2022), using cohort data on people aged 18 or older (mean age 53.7 years), which allows to correct for symptoms present before COVID-19, found 21.4% of COVID-19 positive participants in the study (12.7% of total individuals included in the comparative analysis) to report long term sequelae that were associated with the SARS-Cov-2 infection.

The most recent systematic review on long COVID symptoms available to the Expert Panel is a systematic review and meta-analysis by ECDC (European Centre for Disease Prevention and Control, 2022). It featured 61 retrospective or prospective cohort studies published between January 2020 and mid-February 2022, and included participants with confirmed SARSCoV2 infection with follow-up of at least 12 weeks post infection. Twelve studies were conducted in Italy, 8 in Spain, 7 in France and in the US, 5 in Denmark, 3 each in Germany, Netherlands, Norway, Switzerland and the UK each, 2 each in Australia and Canada, and 1 in Turkey. Some of the findings are as follows (ECDC, 2022).

Box 2 Prevalence estimates of long COVID

A systematic literature review subcontracted by ECDC, assessed the prevalence of symptoms of post COVID-19 condition, stratifying by recruitment setting (community, hospital and intensive care unit (ICU)) as a proxy for disease severity.

Prospective and retrospective cohort studies conducted in Europe, EU/European Economic Area (EEA) countries, United Kingdom, USA, Canada, Australia, and New Zealand were considered. A total of 61 peer-reviewed cohort studies, published up to February 2022, from 15 countries were included in the analysis. These studies included 74,213 post COVID-19 condition cases that had been assessed at least 12 weeks following SARS-CoV-2 infection.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to evaluate the certainty of evidence. An extremely wide range of reported post COVID-19 condition symptoms were supported by evidence scored as high or moderate certainty in both the community and hospital setting. No studies performed in the ICU setting reported symptom prevalence estimates scored as moderate or high certainty.

Considering only estimates supported by evidence of high or moderate certainty, a comparison was made between the estimated prevalence of post COVID-19 condition symptoms reported amongst patients recruited in both the community and hospital recruitment setting. For each of five reported post COVID-19 condition symptoms (fatigue, shortness of breath, depression, headache and dizziness), prevalence was higher amongst patients recruited in the hospital setting when compared to the community setting (Table, box 2).

Table, box 2. Estimated prevalence of post COVID-19 condition symptoms reported amongst patients recruited in both the community and hospital setting.

Post COVID-19 condition symptom	Community setting prevalence	Hospital setting prevalence
Fatigue	**30.8%** 95%CI: 21.0-41.6	**46.1%** 95%CI: 37.5-54.9
Shortness of breath	**21.5%** 95%CI: 12.4-32.2	**45.4%** 95%CI: 31.9-59.2
Depression	**17.3%** 95%CI: 9.0-27.5	**23.3%** 95%CI: 15.0-32.8
Headache	**14.4%** 95%CI: 7.9-22.4	**16.5%** 95%CI: 9.2-25.3
Dizziness	**10.2%** 95%CI: 4.7-17.4	**18.3%** 95%CI: 6.1-35.0

Considering only prevalence estimates supported by evidence scored as high or moderate certainty

There are important limitations to this work. Given the large heterogeneity in study design, as well as the lack of control groups in cohort studies included, several symptom outcomes reported (and not presented here) were deemed to be of low certainty. Absence of non-infected comparator groups in studies may lead to overestimation of those symptoms attributed to prior SARS-CoV-2 infection. Additional large-scale population-based studies with appropriate control groups are required to assess which long term symptoms are specifically attributable to SARS-CoV-2 infection and their association with a wide range of demographic and clinical risk factors.

Due to the time-lag between study design, implementation and publication, results in this systematic review reflect the status quo following the first waves of the pandemic (i.e. pre-omicron period), where historical variants were in circulation and population level immunity was markedly different.

Results presented in this systematic review do not stratify by vaccination or prior infection status, meaning no conclusions can be drawn on the potential protective effect of immunity — which is critical, given current high levels of vaccination and experienced reinfection — on risk for developing post COVID-19 condition symptoms. Furthermore, these data do not objectively quantify the severity or duration of reported symptoms, which future studies will need to address to inform a more global assessment of the burden of disease for individuals as well as healthcare systems.

ECDC intends to periodically update its Latest Evidence item on post COVID-19 condition with a focus on critical and robust peer-reviewed systematic literature review articles as well as through outsourced systematic literature reviews.

Source: ECDC

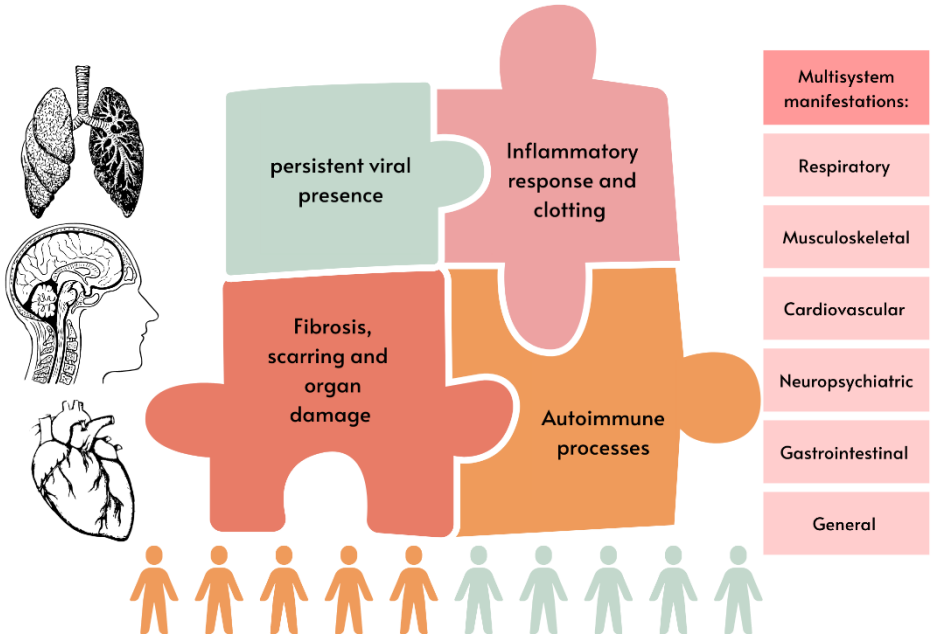
1.2.3. Underlying mechanisms and pathogenesis of long COVID

While much remains uncertain about the causes and underlying mechanisms of long COVID, it can be said with certainty that they are multiple and complex. Post viral illness is not a new phenomenon but it has been severely under-researched in terms of underlying pathological mechanisms in pre-pandemic times. Long COVID shares common features

with other post viral illnesses, however what is specific to COVID-19 in comparison to prolonged illness induced by other viruses is not clear given the pre-existing lack of clarity on the mechanisms and the cellular and extra-cellular processes involved following infections with other viruses such as Q fever (bacteria Coxiella burnetii) or Ebola (Choutka et al., 2022). Some of these post viral illnesses emerge decades after initial infection as such in the case of post-polio syndrome (Li Hi Shing et al., 2019). Viral triggers have been implicated in chronic conditions including myalgic encephalomyelitis (ME), such as influenza, varicella zoster virus, Epstein Barr virus, and enteroviruses (Magnus et al., 2015, Tsai et al., 2014, O'Neal and Hanson, 2021).

In terms of the pathogenetic description, SARS-CoV-2 spike protein often enters cells by binding to angiotensin converting enzyme 2 receptors assisted by Transmembrane serine protease 2 (TMPRSS2), a protein found on the surface of many cells (Beyerstedt et al., 2021, Jackson et al., 2022) (although there may be alternative pathways involved in entry to some cells lacking these receptors, such as neurones (Pepe et al., 2022)). These receptors are distributed widely, so that while the virus enters the body through the respiratory tract, it can infect a wide variety of cells, including those in the respiratory, cardiovascular, gastrointestinal and neurological systems. The following section, which draws extensively from reviews by Crook et al. (2021) and by Mehandru and Merad (2022), summarises some of the proposed non-mutually exclusive mechanisms for the more common manifestations. Several main mechanisms, each related to one another, have been proposed (Figure 1).

Figure 1 Potential pathophysiological mechanisms underlying Post-Covid-19 Condition



The first is persistence of the virus or parts/remnants of the viral material (Pattle and Farrell, 2006), with evidence that it can be found many months after the acute infection in the gastrointestinal tract, central nervous system, and some other issues, as well as evidence that memory B cells may continue to produce antibodies many months after the acute infection. This is seen with other viruses, such as measles, which can give rise to subacute sclerosing panencephalitis, a condition appearing typically seven to ten years after apparent recovery from an acute infection. There is now some evidence of persistent SARS-CoV-2 antigen, nucleocapsid protein or viral RNA especially in tissues that are partially shielded from the immune system, such as the brain, testes, liver, gallbladder, lymph nodes and gut including colon, appendix, and ileum (Chertow et al., 2021, Brooks and Bhatt, 2021, Cheung et al., 2022). Persistent viral antigen presence may generate pathogen-associated molecular patterns (PAMPs) which can in turn engage in host pattern recognition receptors (PRRs) to trigger immune activation, and/or T and B cells. Chronic stimulation of these lymphocytes can cause chronic inflammation (Choutka et al., 2022). Cryptic SARS-CoV-2 tissue reservoirs have also been linked to persistent microvascular endotheliopathy (Ahamed and Laurence, 2022). However, whether the presence of such viral remnants definitely trigger the type of symptoms collectively known as long COVID is still unknown.

The second, and potentially triggered by the first, is persistent inflammation, associated with changes in immune homeostasis, including a reduction in tissue-resident macrophages, persistence of pro-inflammatory cells such as monocytes, altered cytokine production, and increased effector T and B cells (Bergamaschi et al., 2021). When this occurs in the vascular endothelium it can have very widespread effects (Ackermann et al., 2020). Crook and colleagues (2021) discuss how these mechanisms affect different tissues. They propose that lung damage occurs as result of chronic inflammation with the sustained production of pro-inflammatory cytokines and reactive oxygen species. Endothelial damage triggers activation of fibroblasts, leading to pulmonary fibrosis. Endothelial damage, coupled with complement activation, platelet activation, release of pro-inflammatory cytokines, and disruption of normal coagulation pathways may cause a prolonged hyperinflammatory and hypercoagulable state, increasing the risk of thrombosis. The heart can be affected by chronic inflammation of cardiomyocytes (Puntmann et al., 2022), which may lead to myositis and death of affected cells.

The third and potentially linked to the first two is autoimmunity, with proposed mechanisms, including viral mimicry, breakdown of tolerance against self-antigens, and exposure of cryptic antigens during tissue damage. There is strong evidence of acute COVID-19 triggering autoantibodies (Wang et al., 2021, Chang et al., 2021). Autoimmune

activation can also result from the immune system trying to target the pathogen from bystander autoimmune activation unrelated to pathogen structure. B or T cells may become activated if the viral antigens mimic self-antigens (molecular mimicry) (Choutka et al., 2022). Such mechanism has been implicated in the link between EBV and multiple sclerosis (Bjornevik et al., 2022). Dysregulation of the immune system may be in a manner that allows previously harboured pathogens to reactivate and infect new body sites, such as herpes viruses. Cervia et al. (2022) followed up patients who had a COVID-19 infection for a year and identified a distinct SARS-CoV-2 immunoglobulin signature, with reduced IgM and IgG3 titres during the acute infection, possibly related to reduced type I interferons. It is worth noting that autoimmune diseases are generally more common in women than in men, and we find a similar gender pattern in the prevalence of long COVID.

A recent preprint of a study that conducted detailed immunological profiling of 215 long COVID patients found distinct immunological differences to matched controls including in specific circulating myeloid and lymphocyte populations as well as elevated humeral responses. There was also an observation of raised antibody responses against non-SARS-CoV-2 viral pathogens, specifically Epstein-Barr virus. Another striking predictor in long COVID patients was low serum cortisol levels compared to controls (Klein et al., 2022).

Other potential mechanisms, or perhaps manifestations of trigger mechanisms acting as mediators inducing the symptoms of long COVID, include the formation of hyperactivated platelets and microclots (Pretorius et al., 2021). It has been suggested that COVID-19 can give rise to these clots comprised on an anomalous amyloid like form of fibrin that is resistant to fibrinolysis (Kell et al., 2022), possibly contributing to vascular inflammation and hypoperfusion of organs and muscle tissue. There is often dysfunction of the autonomic nervous system. This can lead to postural orthostatic tachycardia syndrome. In the central nervous system, a prolonged immune response can activate glial cells, causing damage to nearby neurons. Again, hyperinflammatory and hypercoagulable states increase the risk of thrombosis. Damage to the blood-brain barrier increases its permeability, allowing toxins, inflammatory substances, and leukocytes to infiltrate the brain parenchyma. Chronic inflammation in the brainstem may cause autonomic dysfunction.

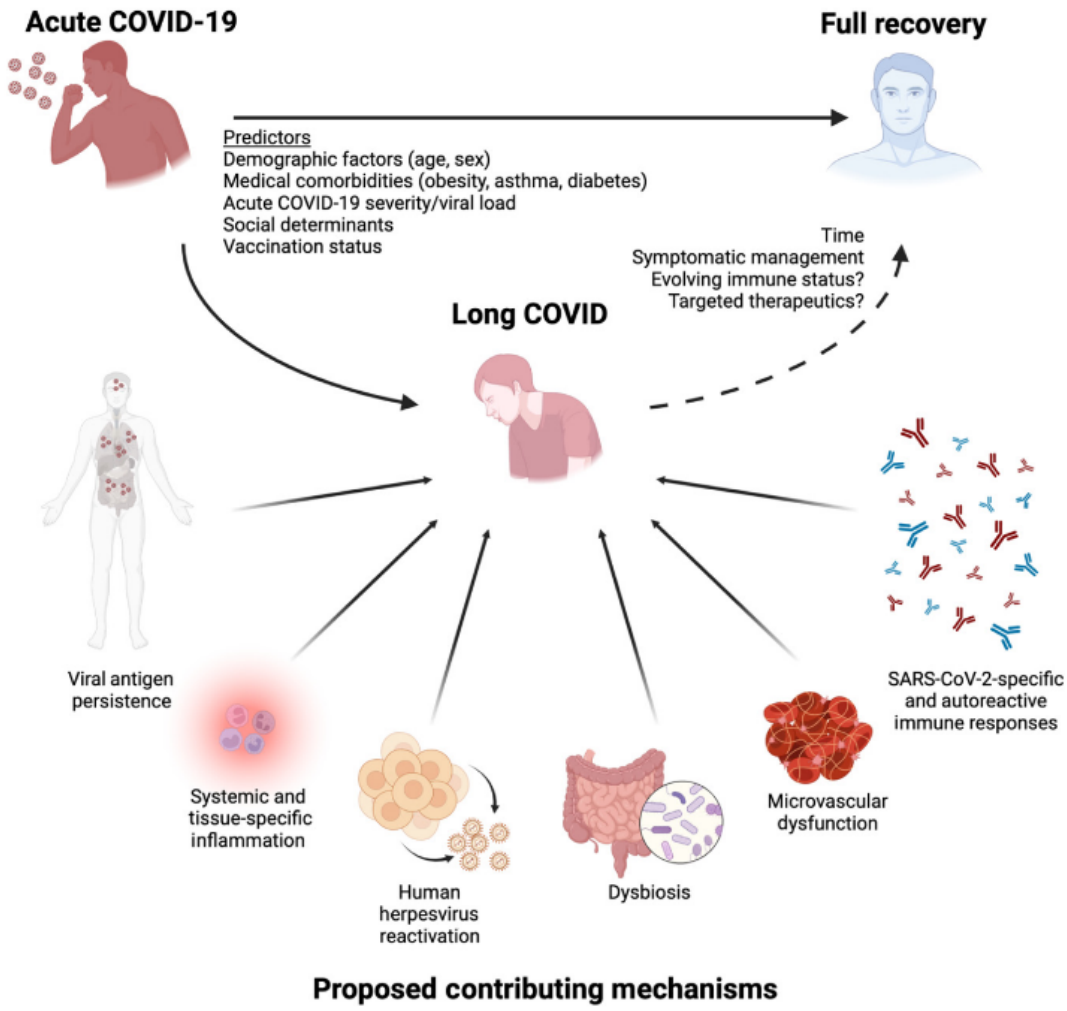
Long COVID symptoms may be a manifestation of acute organ damage and tissue injury (del Rio et al., 2020). This is more likely in those who have suffered severe infection during the first few weeks of the illness.

COVID-19 infection has been linked to microbiome changes (Yeoh et al., 2021), which may in turn be linked to immune function (Manfredo Vieira et al., 2018). A systematic review concluded that changes in faecal and respiratory microbiome were common in patients with COVID-19, with opportunistic pathogen abundance (Yamamoto et al., 2021). One

follow-up of those with post-acute COVID-19 syndrome (PACS) defined as persistent symptoms three weeks after clearance of SARS-CoV-2 found higher levels of *Ruminococcus gnavus*, *Bacteroides vulgatus* and lower levels of *Faecalibacterium prausnitzii* in the gut and various inverse correlations between gut microbiota and symptoms (Liu et al., 2022). It has been suggested that this could allow movement of inflammatory molecules from the gut into the bloodstream.

In summary, multiple non-mutually exclusive mechanisms have been implicated in the pathogenesis of long COVID. These include direct effects of the acute illness resulting in organ damage and tissue injury; persistent viral material reservoirs in certain body tissues; autoimmune and molecular mimicry mechanisms; interactions with host microbiome; dysfunctional coagulation; and impaired neuronal signalling.

Figure 2 Predictors and proposed pathophysiologic mechanisms of Post-Covid-19 Condition



Source: Peluso and Deeks (2022)

1.2.4. Possible risk factors

As with the data on prevalence, clear identification of risk factors is complicated by the plethora of small studies, with different definitions, in different settings, and with different comparators. Some predictors of long COVID reported in the literature include:

- Older age (Westerlind et al., 2021, Jones et al., 2021);
- Female sex (Jones et al., 2021, Huang et al., 2021, Bai et al., 2022)
- Hospitalization during the acute phase (Westerlind et al., 2021)
- Immunoglobulin signature (Cervia et al., 2022)
- Number of symptoms in the acute phase (Sudre et al., 2021, Arjun et al., 2022)
- Smoking (Bai et al., 2022)

- Vaccination status (Arjun et al., 2022, Office for National Statistics, 2022e, Ayoubkhani et al., 2022a)
- SARS-CoV-2 variant (Office for National Statistics, 2022e)

A very large study of almost half a million adults with a positive test result and almost 2 million propensity-matched controls used electronic patient records of primary care use (Subramanian et al., 2022). It identified as risk factors for Long COVID female sex, belonging to an ethnic minority, socioeconomic deprivation, smoking, obesity and a wide range of comorbidities. It also found that the risk of developing Long COVID increased along a gradient with decreasing age.

A crucial question is whether vaccination reduces the risk of long COVID beyond that achieved by reducing COVID-19 infections, in both the adult population and in children. The available evidence suggests that it does, at least in the adult population. An Italian study with 2560 participants, of whom 739 had COVID-19, found that the number of vaccine doses was associated with lower long COVID prevalence, from 41.8% in unvaccinated patients to 30.0% in those with 1 dose, 17.4% in those with 2 doses, and 16.0% in those with 3 doses (Azzolini et al., 2022). Another study, from the United Kingdom, compared just over 3,000 subjects who had COVID-19 after being double vaccinated with those who did so while unvaccinated (Ayoubkhani et al., 2022b). Vaccination was associated with a markedly reduced odds ratio for long COVID, at 0.59 (95% confidence intervals 0.50-0.69). Using data from the US Department of Veterans Affairs, Al-Aly et al. (2022) find that vaccination does offers protection against Long COVID but it is only partial (approximately 15% reduction) and it should not be relied on as the sole mitigation strategy against SARS-CoV-2 infection (Mallapaty, 2022).

1.2.5. The experience of long COVID in adults

The most commonly reported symptoms of long COVID are fatigue, headache, cognitive dysfunction, shortness of breath, muscle aches, palpitations, chest pain/tightness, dizziness, sleep disturbance and joint pain (Ziauddeen et al., 2022, Lopez-Leon et al., 2021). However, a UK analysis of almost half a million patients with a positive test, matched with almost two million others, found 62 symptoms that were significantly more common by 12 weeks post infection (Subramanian et al., 2022). The largest adjusted hazard ratios occur for anosmia (6.49, 95% CI 5.02–8.39), hair loss (3.99, 3.63–4.39), sneezing (2.77, 1.40–5.50), ejaculation difficulty (2.63, 1.61–4.28) and reduced libido (2.36, 1.61–3.47). Importantly, symptoms can fluctuate in severity, can relapse, and can reappear (Brown and O'Brien, 2021). This complicates any attempt to develop characteristic phenotypes.

There is evidence that symptoms cluster into systems. One study identified cardiovascular, pulmonary, and neurocognitive clusters (Nalbandian et al., 2021), with another identifying respiratory, cognitive and fatigue clusters. In those who were initially hospitalized with severe COVID-19, a UK-based study identified four clusters of symptom severity at average follow up of 6 months from hospital discharge. These included very severe (17%), severe (21%), moderate along with cognitive impairment (17%) and mild (35%) (Evans et al., 2021). One study concluded that having more severe and multisystem symptom clusters is associated with being female, worse baseline health, lower income, and inadequate rest in the first two weeks of the illness (Ziauddeen et al., 2022). An additional issue is differentiation according to impairment (say, mild, moderate and severe levels of disability), leading to a matrix classification crossing symptom clusters and disability level, which may help to understand better different kinds of health care needs and thus different health systems responses. Still another distinction can be made according to duration of symptoms (and not just group of symptoms), leading to finer grids of classification.

There is little research defining and characterizing recovery from long COVID. This is complicated by the episodic nature of this condition experienced by most people living with it (Ziauddeen et al., 2022, Davis et al., 2021). In a follow up of patients who had been hospitalized for COVID-19 during their acute illness, only a quarter felt fully recovered after a year. Recovery was defined in this study as patient-perceived recovery – the response of "yes" to the question "Do you feel fully recovered?". The proportion of patients reporting full recovery was unchanged between 5 months and 1 year after discharge from hospital. Factors associated with non-recovery (a "no" or "not sure" response to the self-report question) included being female, obesity and having had invasive mechanical ventilation (Evans et al., 2022). There is evidence that those with milder acute infection had quicker recovery from long COVID than those who were hospitalized (median duration of symptoms 3.99 months compared with 8.84 months respectively) (Wulf Hanson et al., 2022).

Long COVID may affect people's lives in many ways, given its varying manifestations and severity of different symptoms. A structured review on health-related quality of life (HRQoL) associated with Covid-19 found that females, people at older ages, those with more severe disease, and who were from low-income countries experienced greater impact (Poudel et al., 2021). There is growing evidence that those experiencing long COVID are substantially less likely to remain in employment and, if they do, to have reduced their hours (Burns, 2022), with a report by the UK's Institute for Fiscal Studies, published in July 2022, concluding that having long COVID increased the probability of working no hours by six percentage points and reduced overall hours worked by 2.4% (Institute for Fiscal Studies, 2022).

Long COVID in Children and Adolescents

A systematic review of long COVID prevalence in children and adolescents aged 0-18 included 21 studies found an average prevalence of 25% with the most prevalent symptoms being mood symptoms, fatigue and sleep disorders (Lopez-Leon et al., 2022). Compared to controls, children infected with SARS-CoV-2 had a higher risk of shortness of breath and loss of sense of taste and smell.

The potential negative impacts of long COVID in children and adolescents include physical and cognitive disability, isolation, psychological stress, school absenteeism and performance, social activities, further increase in inequities in socioeconomically disadvantaged and parental job loss (Lopez-Leon et al., 2022).

A report by the Swedish Ombudsman for Children on the consequences of the pandemic on children in Sweden, shows that children with post-covid feel stigmatized (Barnombudsmannens, 2021), reflecting a popular misconception that children do not get severe illness.

A CDC analysis using medical claims (under health insurance plans) in the US compared children and adolescents (aged 0–17 years) with and without (confirmed) COVID-19, covering from March 2020 to January 2022, found those that had COVID-19 were associated with higher probability of having potentially serious conditions, such as acute pulmonary embolism, myocarditis and cardiomyopathy, venous thromboembolic event, acute and unspecified renal failure, and type 1 diabetes (Kompaniyets et al., 2022).

Long COVID Stigma

People living with poorly understood health conditions experience health-related stigma, which can get compounded by socio-demographic disadvantage and in turn potentially result in poorer health outcomes (McManimen et al., 2018, Froehlich et al., 2022). Testimonies from people living with long COVID describe experiencing scepticism among professionals when they describe their symptoms, giving rise to difficulty accessing support (Ladds et al., 2020, Kingstone et al., 2020). In a study assessing the extent of perceived stigma in people who report having Long Covid with a sample size of 966 UK participants, 95% experienced stigma at least ‘sometimes’ and 76% experienced stigma ‘often or always’ (Pantelic et al., 2022). Those with a formal clinical diagnosis of Long Covid were most likely to experience stigma. It should also be noted that those with long COVID may experience ‘double stigma’ if they belong to disadvantaged groups such as ethnic minorities, immigrants or economically disadvantaged groups. Their symptoms, especially if they lead to departure from the workforce, may increase the risk of isolation which may compound the experience of stigma, particularly internalized stigma (the expectation of bias or poor treatment by others) (Van de Vyver et al., 2021, Earnshaw et al., 2013).

1.2.6. Future research

Our review of the most up-to-date evidence on long COVID demonstrates the remarkable progress that has been made in a short time, but highlights the many questions that remain unanswered or only partially answered. The Expert Panel has compiled a list but recognises that the situation is constantly changing (Box 3).

Box 3 Some unanswered research questions on long COVID

1. How does the epidemiology of long COVID vary by gender, age group, ethnicity, or socioeconomic status (incidence, recovery)?)
2. How does clinical severity of acute COVID-19 disease (from asymptomatic infections to severe disease) and pre-existing health condition (especially pre-existing comorbidities, medications use, smoking status, obesity) predict long COVID?
3. What are the predictors of recovery from long COVID?
4. What are the pathophysiological mechanisms of long COVID and what are the implications for developing and using biomarkers?
5. Is there a genetic predisposition to long COVID?
6. What are the effective treatments for long COVID in adults and children (pharmacological and non-pharmacological), with particular attention to gender differences?
7. How should treatment effectiveness be defined and which measurement tools can be used for the different components of long COVID syndrome?
8. What are the most effective rehabilitation methods and timing for long COVID?
9. How should care pathways for individuals with long COVID be best organised?
10. What is the interaction of different SARS-CoV-2 variants with the occurrence of long COVID?
11. What is the interaction of the timing and number of COVID-19 vaccine doses with the occurrence of long COVID?
12. What is the relationship of COVID-19 vaccination to the risk of new long COVID and modifying the disease course of existing long COVID and what is the implication of direct active antiviral for SARS-CoV-2 use during acute illness on the risk of developing long COVID?
13. What is the effect of re-infection with the same or different variant of SARS-CoV-2 to the risk of new onset of long COVID and modifying the disease course of existing long COVID?
14. What is the general public's and healthcare professional's knowledge, attitudes and information needs on long COVID and how does this evolve?

15. What is the role of stigma, social identity change and stereotyping in patients with long COVID and how should such negative effects be addressed to maximise positive social mechanisms?
16. What are the wider healthcare, social costs and economic impacts of long COVID?

There are, however, many challenges in conducting research on this topic. For example, case definitions of long COVID vary between studies. This presents difficulties in defining the prevalence overall and in different age and sociodemographic groups. Even the clinical definition of the condition is not unanimously agreed upon; hence researchers use different symptoms as proxies for long COVID. This problem affects both observational and interventional studies. Research needs to be carried out using the same case definition. Access to source data will most likely be needed as opposed to literature based meta-analyses.

Much research has focussed on severe/hospitalised COVID-19 cases, something noted in published systematic reviews. Studies that included non-hospitalised subjects highlight differences in symptoms between the two groups. Those whose initial infection was asymptomatic or mild constitute a neglected group in research.

Causality can be difficult to establish given the temporal separation between infection and long COVID symptoms, presence of multimorbidity, and confusing sequences of symptoms. Related to this, recovery is not consistently defined and is complicated by the fluctuation of symptoms over time and progression of pre-existing conditions. Also, comparison/control groups vary among studies and are not well defined.

The many unanswered questions point to the need for an ambitious research agenda. Many research funders and other organisations have already proposed such agendas and there is no need for us to repeat them in this Opinion (Carson, 2021, NIHR, 2022). As might be expected, they range from basic science through epidemiology and health systems research to social policy. A consistent theme in many of them is the importance of including the voices of patients with various backgrounds and characteristics, There is growing acceptance that they should have their say on study designs and the ways their conditions are labelled and handled (Alwan, 2021). Scientific research faces multiple challenges, including openness to see things from different perspectives and setting both the medical agenda for patients with chronic conditions and the wider social and economic agenda (Alwan, 2022). In December 2020, the "Long-Covid Forum" was organised with the goal of gaining a better understanding of Long-Covid and defining research priorities (Norton et

al., 2021). The question for this Opinion is what might be the added value of EU-funded research?

There are two characteristics of EU-funded research that may be relevant. The first is scale. The clear message from our review of the current state of knowledge is that this is a complex problem that will require input from a wide-range of scientific areas. They include expertise on the function of different body systems, especially but not limited to the respiratory, cardiovascular, neurological systems. They include a range of clinical disciplines, including virology, immunology, pathology, psychology and neuropsychology, psychiatry, pharmacotherapy and rehabilitation (the list is non-exhaustive and it is likely to change as knowledge on Long-Covid evolves). Furthermore, they include those with expertise in health systems research, social, behavioural, and political sciences. There may be insights from potentially related areas, such as research on long-term sequelae of other viruses. These include, in addition to the well-known examples of polio and measles, Ebola, Zika, and Chikungunya viruses (Hickie et al., 2006). While some of the larger member states may be able to cover all these areas, they are the exceptions. Leaving this agenda to national funding bodies risks excluding relevant expertise in the smaller member states.

A related issue, beyond the ability to convene large research teams, is the importance of conducting large-scale studies. This has been recognised in the Horizon 2020-funded ORCHESTRA project, which aims to establish an international large-scale cohort for retrospective and prospective studies, and will be a useful mechanism to study long COVID (ORCHESTRA., 2022). Separately, a number of cohorts of patients with long COVID have already been established (PHOSP-COVID Collaborative Group, 2022), the largest of which has been assembled International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) (Garcia-Gallo et al., 2022). It had enrolled over 700,000 patients in 1,500 centres in 60 countries by September 2021. It will be important that other studies, even if not formally part of this consortium, share methodologies and definitions. For example, there is now a proposed core set of outcomes for use in research on long COVID (and in clinical practice) established by an international Delphi exercise (Munblit et al., 2022).

Similarly, it is important to learn lessons from the issues that plagued therapeutic trials of COVID-19 candidate medicines during the pandemic. A lack of coordination led to large numbers of underpowered trials being conducted. The exception, from the UK, was the RECOVERY trial (Wise and Coombes, 2020). This is an adaptive mono-national platform trial that, despite some methodological limitations such as the open-label design, permits evaluation of different target treatments for the same disease on an ongoing basis, with therapies being allowed to enter or leave the platform based on a decision algorithm (Woodcock and LaVange, 2017). Undertaken in partnership with the NHS, this ensured

that virtually every patient with COVID-19 was given the opportunity to enter a clinical trial. While it will be possible to conduct very large trials in some member states, there is a danger that patients in some of the smaller ones may be excluded from this process. Coordination between clinical trials to ensure that larger studies are conducted must be a priority, given the emerging evidence, from some member states, of the growing use of unevaluated treatments (Davies, 2022). Yet there are major barriers to undertaking such trials at a European level, as described in a paper that collates the experiences of those involved in one such trial (Diallo et al., 2022). This is EU-RESPONSE, funded by Horizon 2020 to enable expansion of the French DisCoVeRy trial to other European and associated countries (Ader, 2020). They also draw on experiences with the EU-SolidAct second-generation pan-European platform trial for COVID-19 treatments, again linked to DisCoVeRy. EU-SolidAct was able to use the Voluntary Harmonization Procedure (VHP) created in 2009 by the Heads of Medicines Agencies, whereby a single application is sent to one reference national competent authority (NCA), coordinating responses of all NCAs, prior to a national phase in each country. This was not possible with EU-RESPONSE because DisCoVeRy had first been authorised in France using a national procedure. While RECOVERY was able to recruit the first patients within 9 days of the first protocol being written, the VHP for EU-SolidAct took 56 days and the subsequent national phases took variable periods from days to months. The expected time frame for any amendments was 50 days. In contrast, the UK system enabled amendments to be made within a few days. There were also many trivial but time-consuming problems such as different requirements for information leaflets. The authors note that the new Clinical Trials Regulation 536/2014 will address some of the problems experienced but make a series of valuable recommendations about how the Regulation might be interpreted. While the issues raised go beyond those of treatments for long COVID, if they are not adequately resolved the conduct of the large-scale European trials that are needed will be compromised. Based on the lesson learned, some initiatives are already ongoing to optimise the EU environment of clinical research; in particular the ACT-EU and the CT-CURE joint action initiatives, which aim to facilitate the conduction of large multinational clinical trials and to provide a harmonized and accelerated assessment for study approval using the Clinical Trial Information System (CTIS).

A second consideration is the ability to take advantage of the natural laboratory that the EU offers. While therapeutic interventions, such as new medicines, can be expected to work in the same way everywhere, this is not true for more complex ones, such as the implementation of multi-disciplinary teams. Their operations will depend on context, such as historical hierarchies within health organisations. As will be discussed in the next section, the evidence that we already have on the management of complex chronic conditions points to a need for much better team working. However, we know that this is

difficult in some countries because of professional boundary disputes. When evaluating and implementing these types of interventions, it will be necessary to find solutions that are consistent with national legislative, regulatory, and cultural contexts.

Further details on early mobilisation of EU funding during the COVID-19 pandemic to support large-scale multi-country trials is described in Box 4.

Box 4. Early mobilisation of EU funding during the COVID 19 pandemic

EU funding was mobilised rapidly, in line with the ERAvsCORONA action plan to support large-scale multi-country trials in the EU, based on previously existing initiatives (REMAP-CAP trial) and supporting new initiatives (EU RESPONSE, VACCELERATE and ECRAID-PRIME). The REMAP-CAP trial is a randomized, embedded, multifactorial, adaptive platform trial, intentionally designed for a pandemic with a pathogen causing severe community-acquired pneumonia (CAP). Funded through the 7th framework programme of the EU, and part of PREPARE preparations started in 2014, the trial is currently funded by the Horizon 2020 RECOVER project. A pandemic stratum was added to the REMAP-CAP protocol and with patient enrolment as early as March 2020. Therefore, in REMAP-CAP they were able to enrol patients at a similar speed as in the RECOVERY trial. The studies made a series of recommendations so that larger, definitive trials for treatment, prevention and diagnostics of infectious diseases are possible to design. The EC response is a high number of actions that already have been taken to address the encountered challenges. The Horizon Europe project ECRAID –PRIME establishes a platform trial for COVID-19 treatment in the primary care population.

While recognising that all knowledge is contingent, so that it is possible that some of the gaps in knowledge that we have identified will be filled shortly after this report is published, we identify some priorities for the EU, taking account of the considerations set out above. This should build on existing work, such as that set out in the 2020 ERAvsCorona Action Plan (European Commission, 2020).

The first priority is a package of research in basic science, building on what is already a large portfolio of studies. It is likely to include further studies on the persistence of the virus in some people, for example, in brain or gastrointestinal tissue. It is also likely to include any impact of the virus on the immune system, and in particular, autoimmunity. This work should also address the need for biomarkers of the various manifestations of long COVID. Here there is some promising news from researchers using machine learning who have identified what appear to be specific patterns of immune markers (Klein et al., 2022). As noted above, further research would usefully involve scientists who have been studying the long-term consequences of infection with other viruses. Already, research on

SARS-CoV-2 and the host response, have increased our knowledge of the mechanisms involved in the role of viruses in disease causation.

The second priority builds on what is already underway in several countries and involves establishing cohorts of patients who can provide information on the natural history of this condition. As noted above, it will be crucial to coordinate these studies and ensure funding support for them. It is neither necessary nor helpful that they all answer the same question, but it would avoid future problems if they could, at a minimum, use shared definitions and methodologies for capturing key variables.

The third priority, which builds on the first, is the development of candidate therapeutics. It is unlikely that there will be a "silver bullet", given the evidence that we already have on the range of manifestations of this condition and the underlying mechanisms. As one report noted, "while a majority of the conditions can be treated using existing therapeutic approaches, some less understood symptoms such as brain fog demand more research to understand the cause and devise an appropriate treatment strategy" (Aitken et al., 2021). There are European mechanisms that could contribute to the development and research of new candidate therapeutics for long COVID, learning from public-private partnerships such as the Innovative Medicines Initiative. The "Innovative Health Initiative" brings forward, within Horizon Europe, some of the lessons of the previous Innovative Medicines Initiative and could be part of the specific research effort on long COVID.

It will also be important to clarify what role, if any, the new health emergency organisation HERA might play (Anderson et al., 2021). In addition to that, it is also important to mention the new reinforced role of the European Medicines Agency (EMA) in providing support to the timely development of medicines during public health emergency, as established by the Regulation (EU) 2022/123. In particular, a Emergency Task Force (ETF) has been set up to provide guidance to industry and academia and facilitate the conduct and approval of clinical trials in close cooperation with HERA, the EC and the Clinical Trial Coordination Group (CTCG). Among other tasks, the ETF can provide clinical trial protocol assistance and accelerated and free of charge scientific advice to ensure the timely development of high-quality, effective, and safe medicines (European Medicines Agency, 2022d). EMA has well-established networks of engagement with EU patient, consumers and healthcare professionals organisations. These platforms allow incorporation of patients', consumers' and healthcare professionals' perspectives on all aspects of medicines and safety monitoring. In addition, reinforcing the patient voice on evidence generation is a key priority for the EU Medicines Regulatory Network, and EMA will be stepping up its work on patient experience data in medicines regulation (European Medicines Agency, 2022c).

A related priority will be to explore the potential for new vaccines in preventing COVID-19 and mitigating risks for long COVID. However, one of the major challenges are the current difficulties in conducting efficacy trials and establishing valid endpoints able to reflect the ability of vaccines to have an impact on long COVID occurrence and/or severity. In the absence of such evidence a valid alternative would be to rely on well-designed observational studies.

The fourth priority is research on the impact of long COVID on those affected and on their families, as well as wider population-level health, social and economic inequalities generated by this condition. As with any impairment, that impact will depend on the extent to which it is possible to make reasonable adjustments within their living and working environments. This research will likely include the development of improved tools to monitor quality of life, both physical and mental, and identify interventions that can support affected people, including in their participation in the labour market and in workplace conditions.

The fifth priority is the development of new models of care. As will be discussed in the next section, this must build on the accumulated body of knowledge on the management of other chronic conditions. For this reason, it can be expected to bring substantial benefits beyond long COVID, offering an opportunity to re-assess how health systems manage the growing burden of multi-morbidity whereby ageing populations accumulate multiple chronic conditions over the course of their life.

1.3. Organisational and resource requirements for healthcare systems to design and develop appropriate health services for long COVID

1.3.1. Implications for the health workforce

The impact of long COVID on health systems will be felt in two areas, the health workforce potentially developing long COVID; and the care of patients with long COVID. For both cases, a comprehensive strategy must include prevention and care. It is evident that one of the best ways to reduce the risk of long COVID is to prevent infection with COVID-19. While it is beyond the scope of this Opinion to address all the things that health systems can do to reduce risks of infection in the population, there are some actions that can be taken within health facilities.

Health workers have been at particular risk of contracting COVID-19 (Gómez-Ochoa et al., 2021) and, consequently, of developing long COVID. Even though most have now been vaccinated, and many will also have had infections during the series of waves of new variants, they remain at risk and each new infection brings with it an additional risk of long

COVID. In some cases, and especially when experiencing a flare-up, their symptoms will be of sufficient severity to prevent them from working. This is occurring at a time when many health systems are struggling to recruit and retain staff as a result of demographic change.

Unfortunately, given the many gaps in surveillance, the scale and nature of the consequences of long COVID for the health workforce in Europe remains unclear but they are likely to be substantial. The UK has one of the very few continuous surveys that can generate estimates of prevalence although even it has limitations (Lawton and Alwan, 2022). As noted above, the UK's ONS estimates that, as of July 2022, about 1.8 million people report symptoms of long COVID, equating to 2.8% of the population or 3.45% of the workforce (Office for National Statistics, 2022c). It also estimates that over 761,000 people have had symptoms of Long COVID for over a year. With healthcare workers at increased risk of COVID 19 infection this is likely to disproportionately affect this group. As noted above, there is increasing evidence of the impact that long COVID has on subsequent employment. For healthcare workers in particular, this presents two priorities for action; reducing the risk of new infections and supporting those who have developed long COVID.

1.3.2. Preventing long COVID among essential workers and, especially, the health workforce

Reducing the risk of new COVID-19 infections in the health workforce means continuation of infection control measures in health facilities as long as the virus is circulating. Measures that are effective have the additional benefit of reducing the risk of other airborne infections, such as seasonal influenza. Thus, organisations with responsibility for health facilities should ensure that they have up-to-date guidance on infection control. Given the airborne nature of transmission, guidance would be expected to prioritise air quality, with high quality ventilation and filtration as appropriate (Conway Morris et al., 2021), mask wearing (with high quality masks of at least FFP2 standard), and monitoring of air quality with CO2 monitors. In the longer term it will be important to ensure that building standards for health facilities are updated to take account of the growing body of evidence from aerosol engineers and others about how to ensure clean indoor air (Morawska et al., 2021). The UK's Royal Academy of Engineering has produced two detailed reports on what is required to create infection resilient buildings (Royal Academy of Engineering, 2022).

1.3.3. Supporting health workers with long COVID

The second imperative is to ensure that there are systems in place to support staff with long COVID. In May 2022 the EU Advisory Committee on Safety and Health at Work (ACSH), representing workers and employers, reached agreement on recognising COVID-

19 as an occupational disease in health and social care and in domiciliary assistance and, in a pandemic context, in sectors where there is an outbreak in activities with proven risk of infection (European Commission, 2022). They also supported an update of the EU list of occupational diseases to include it. This is only a recommendation as designating diseases as occupational is a national competence. In November 2022, the European Commission adopted an updated Recommendation encouraging Member States to recognise COVID-19 as an occupational disease. The Expert Panel considers that this is an important step in recognising the risks that health workers face and encourages accountability for employers to take action to reduce risks. This also links with our previous Opinion on supporting mental health in the health workforce, and specifically emphasizing the need for organisational and managerial support (Expert Panel on Effective Ways of Investing in Health, 2021b). The fluctuating nature of the symptoms may require leave of absences, sometimes at short notice and for initially undetermined periods of time, as well flexible phased return-to-work schemes. This will require adapted human resources structures and processes.

Like all responsible employers, health care managers should seek to address the needs of staff with disabilities, for example by facilitating their access to care and making reasonable adjustments in the workplace. Specifics relate to the episodic nature of long COVID, so the health care managers would need to be flexible to allow staff to start to build up, by inserting some redundancy and flexibility into the organisation of the health workforce. To allow for that, policies may need to be adapted, as well as addressing the culture concerning rehabilitation and return to work. Building up redundancies implies a short-term financial cost, to be compensated for by a larger health workforce in the future, as health professionals with long COVID return to work. Redundancies and work flexibility are also demanding on the culture of organisations and on health systems assessments.

There is an extensive body of evidence derived from experience with other chronic conditions that can be drawn on (Lowenstein, 2022) and there are now several sources of guidance for employers and employees. Most include information specific to the health system concerned (NHS England, 2022, Society of Occupational Medicine, 2022). Best practice suggests that they should contain certain elements, such as opportunities for regular health and wellbeing conversations, including identification of any need for reasonable workplace adjustments, links to occupational health services, and information on support groups, trade unions, and other resources, including financial support.

1.3.4. Preventing patients from getting long COVID

We previously highlighted the need for those responsible for health facilities to ensure that they are designed and operated in ways that minimise the risk to the health workforce.

Many of the measures that were mentioned apply equally to safeguarding patients. While figures will vary over time and place, reflecting different stages in the epidemic curves of successive waves of COVID-19, characteristics of the hospitals involved, and levels of community transmission, it is clear that an appreciable share of COVID-19 infections are acquired in hospitals (Carter et al., 2020, Bhattacharya et al., 2021), with some evidence that official figures substantially underestimate the risk (Lumley et al., 2021).

Several factors have been linked to increased risk of hospital-acquired infection with COVID-19, some of which, like overcrowding, are self-evident. However, it is less clear how they interact. This has been addressed, in part, by a recent study that used machine learning to explore the role of patient characteristics, networks of patient contacts, and hospital characteristics (Myall et al., 2022). The algorithms developed in a group of London hospitals were validated in a Swiss hospital. Background prevalence of infection emerges as especially important and, in particular, patient networks that increase contact with others who are infectious. However, as the authors note, they did not have access to networks of contacts with staff or visitors.

1.3.5. Models of care for patients with long COVID

Although long COVID is a new condition, some of the challenges that it creates are not. It is a chronic disease affecting diverse combinations of body symptoms. Its consequences for the patient's quality of life and ability to function are influenced by many factors. The most obvious is the pattern of clinical manifestations, which will likely change over time but in ways that are not easily predictable. Another is the circumstances of the patient, such as whether their symptoms interfere with their work or leisure activities, and whether this can be addressed by reasonable adjustments, and the resources available to them to obtain support and assistance. These factors are similarly important with any multi-system disease, with diabetes being the classic example. Others, such as various auto-immune disease such as lupus, while less common, provide similar challenges, especially with respect to dealing with unanticipated flare-ups. The large burden of disease caused by these other conditions has generated a large volume of work on how best to manage chronic conditions. However, even though we now know what is needed and, in many cases, what works, it has been far more difficult to implement it. There are many examples of local initiatives, often led by inspirational individuals, that are never scaled up or fail to outlive the employment of their creator.

The latest WHO guidelines on managing COVID-19 set out 3 core components of rehabilitation services – multi-disciplinary rehabilitation teams, continuity and coordination of care and people-centred care and shared decision-making. The basic principles involved in implementing these are simple in theory but difficult in practice (Nolte and McKee, 2008).

The model of care should be centred on the patient, who will often be on a long and complex journey, sharing their story with a diverse array of health workers each with specialised knowledge or skills. Their journey will often be eased if they have the support of someone, typically a contact point in a primary care team, who can offer them at least a tentative map and who can help co-ordinate their many excursions to seek specialist help. Their overall care package will be better if they play a full role in its design. All of this can be assisted by advances in information technology, and especially the sharing and accessibility of electronic health records across levels of care. Allowing patients to access their own electronic health records and share them with health professionals may also help, depending on the level of maturity of information technology within a given health system, although care must be taken to not increase the digital divide.

Beyond these broad principles, there are certain challenges that must be considered. First, recalling that severe COVID-19, including the presence of complications of the acute infection, such as increased clotting, are more common in patients with pre-existing conditions, it will be important to recognize that many (but not all) people with long COVID have several other conditions (Office for National Statistics, 2022a). The burden of multimorbidity increases with age, with the added complication that many older people also suffer from some degree of frailty or diminished cognitive function and impairment of other body systems, such as the musculoskeletal, renal, or cardiovascular. In some cases, the mechanisms giving rise to long COVID will have caused particular problems but in others they will have exacerbated existing ones. Hence, a holistic person-centred approach to managing such patients must encompass all their problems.

Another challenge of long COVID in providing a holistic model of care is that it must take account of the patient's circumstances. Such person-centred and goal-oriented care is an inherent value in rehabilitation medicine. For example, locomotor problems will impact differently on someone who lives on the ground floor near to shops than someone living up several flights of stairs in an isolated area. Similarly, different jobs require different skills and the extent to which a particular impairment becomes a handicap will vary. The impact of long COVID on the person's ability to function and achieve their set goals should be the focus of management, with use of shared decision making to determine appropriate treatments.

A third challenge, which is especially relevant to long COVID, is the high degree of uncertainty about the nature, progression, and management of the condition. Unlike, for example, diabetes, where measuring HbA1c is an established way of monitoring treatment effectiveness, there are no good biomarkers for long COVID now. This uncertainty also means that health workers will struggle to offer advice on prognosis, information that patients need to plan their future. A good approach is to provide simple summaries of the

available evidence to clinicians to help answer common questions about the condition and prognosis (Greenhalgh et al., 2022).

For these reasons, while it is possible to set out certain common pathways to assessment and management of some of the more common manifestations, a health system response must incorporate a high level of flexibility, both within the health system and across sectors.

These challenges were apparent in an exercise that followed best practice by engaging in co-design of a model of care with patients and health workers who engaged in focus groups, narrative interviews, and diaries of symptoms (Ladds et al., 2021). This exercise yielded many important lessons for those developing models of care. Health workers struggled with signs and symptoms that did not fit their pre-existing medical knowledge. They reported doing various tests, some of which generated abnormal results, but did not help them decide what to do next. They made much use of mindlines, internalised and collectively reinforced tacit guidelines that are widely used in clinical practice, to make sense of this uncertainty. This involved informal discussions with patients (many of whom were also professional colleagues) and others to identify what worked or did not in particular circumstances. In some cases this conflicted with official guidance which was, sometimes, seen as detached from the reality that the health workers were experiencing. Support groups of people with long COVID were especially useful, generating tacit knowledge on how to handle long COVID. The exercise generated several suggestions for service development, all of which are intuitive but, as the participants noted, had not, in their experience, been addressed. The most important was a "one stop shop" situated in primary care, but with a multi-disciplinary team that can offer a wide range of skills and expertise. Their role would be to enable rapid identification of conditions requiring rapid treatment, to detect and treat comorbidities and complications, and to provide support for symptomatic management. They should have rapid access to appropriate investigations, both an initial package to evaluate the patient and more specialized ones where necessary.

Unfortunately, even when much is known about the conditions that the patient is suffering from, there are many obstacles to developing, implementing, and sustaining such a model. There are structural barriers, with fragmentation created by administrative borders. There are procedural barriers, caused by differences in operating methods in different organisations. Financial barriers exist where budgets cannot follow the patient or do not rise to meet the new care needs. Professional barriers are common and reflect self-interest, restrictive practices, and inflexibility. These can be overcome, but only with determined leadership. Therefore, while we can broadly describe what health systems must do to respond to the challenge of caring with patients who have long COVID, we are under no illusion that it will be easy. When designing models of care for patients with long COVID,

it will be important to draw on the lessons from successes and failures that have been learned when developing and implementing these models in each country (Nolte et al., 2008). Systematically identifying what works and why, for instance drawing on process evaluation methods and frameworks from the field of implementation science, can help provide valuable insights into the scale and nature of the obstacles listed above and ways in which they might be overcome. We now set out some general principles of how health systems should evolve and adapt to meet the burden of long COVID.

1.3.6. A health systems approach to long COVID

To consider the second question posed in the mandate, "Provide an analysis of the main knowledge, organisational and resource requirements for healthcare systems to design and develop appropriate health services for post COVID-19 condition", we have structured our opinion around the WHO health systems framework and, in particular, the system building blocks on the left in Figure 3.

Figure 3 The WHO Health Systems Framework

Source: World Health Organization (2010)

1.3.7. Service delivery

At least in the short-term, given the high level of uncertainty about this condition and the complexity of managing it, there is a strong argument for creating dedicated services for patients with long COVID that bring together a range of specialties and expertise (World Health Organization, 2022b) with a strong role for coordination in primary care. This has several advantages. First, it offers a means to bring together a range of health professional with appropriate skills (detailed in the next section) in an integrated team, supported by continually revised clinical guidelines and with access to well-functioning referral mechanisms. However, as with all specialised services such as post-myocardial or stroke rehabilitation, there is a risk that those with one or more other conditions, some of which may have predisposed them to COVID-19 and may have manifestations that interact with

those of long COVID, may find that their overall care is fragmented. Consequently, it will be necessary to ensure that there are mechanisms to prevent this happening, as well as supporting both primary and secondary care physicians in managing patients with long COVID (Greenhalgh et al., 2022). The WHO guidelines on rehabilitation services for long COVID highlight core functions that these services should implement including standardised symptom and outcome measurement, and robust referral and follow up systems (World Health Organization, 2022b). They recommend using a hybrid approach of in-person and remote models that is integrated across all levels of health care. Specific training and organisation should be provided to primary care professionals to ensure comprehensive overall care. This will require extra support, financial and organisation transformation, to be effective.

As already noted, this Opinion draws extensively on existing experience with the management of complex chronic diseases. One aspect of this that is often overlooked is the risk that innovative services can widen existing inequalities (Wagenaar and Prainsack, 2021). Consequently, health authorities should undertake exercises during the planning phase that explicitly look for the potential for this to happen. Ideally, they will involve vulnerable groups, such as those from ethnic minorities, migrants, remote areas, and otherwise disadvantaged communities in planning the services. This should include engagement with communities to build trust and understand barriers to accessing healthcare, addressing issues such as interpretation, culturally appropriate messaging, and accessibility, especially for those with disabilities, such as learning disorders (a group that has suffered disproportionately in the pandemic) or visual or hearing impairment. A related issue, sometimes overlooked, is the risk of digital exclusion when innovative services take advantage of the many opportunities provided by, for example, apps on smartphones. This will also include ensuring that health information systems (see later section) are designed in ways that will support monitoring of any potential inequalities. There is an extensive literature on all these topics that can be drawn upon.

There are existing guidelines on the management of long COVID that can be drawn upon in many countries. Examples include those developed by the UK's National Institute for Health and Care Excellence (NICE), published in December 2020 and updated in November 2021 (National Institute for Health and Care Excellence, 2020) or by the UK's Royal College of General Practitioners (Nurek et al., 2021). The WHO's latest guidelines on COVID-19 include up-to-date guidance on the best ways to manage the different symptoms associated with long COVID (World Health Organization, 2022b). It is, however, important to recognize that the evidence base underpinning guidance may change as additional knowledge becomes available. It is particularly important to ensure that guidance is based

on representative groups of patients, covering the full spectrum of long COVID severity and symptom clusters.

As per the guidance prepared by the English NHS and other sources, there are three main routes by which individuals with long COVID may present to the health system. The first comprises those whose acute illness was mild but subsequently develop symptoms suggestive of long COVID. They should be assessed by a trained health professional within primary care, or in a separate designated service to assess physical, cognitive and functional abilities.

Investigations should be based on their signs and symptoms and directed to identify serious conditions that may be related to long COVID, as well as those that can be linked to other conditions that may be present. Inevitably, given the lack of any specific biomarkers for long COVID so far, as well as its myriad manifestations, attribution of any signs or symptoms to long COVID will be complicated, although we can expect that there will be scientific advances that will help in this respect in the future.

Many existing clinical guidelines recommend reviews at four and twelve weeks, with investigations as appropriate for the patient's signs and symptoms. At the twelve week point patients should be advised to seek care from their health care provider if new symptoms arise. However, individuals with long COVID who were hospitalised with COVID-19 may require different services than those who were not. As with all patients in hospital, they should receive a personalised care package upon discharge, shared with their referring provider (if any), who will often be a member of a primary care team. And those who required treatment for COVID-19 in intensive care units (although formally outside the definition of long COVID used in this opinion) are at risk of post-ICU syndrome but also long COVID. Consequently, hospitals should ensure that each patient is assessed by a multi-disciplinary team with expertise in both conditions, and which has easy access to appropriate referral pathways, especially to rehabilitation services.

In all these cases it is important to recognise that symptoms typically fluctuate. Some may resolve and others may appear for the first time. As noted previously, people who have had COVID-19 are at increased risk of certain complications, such as thrombosis, for over a year after the initial illness. Patients should be advised of this and that they should seek further care if needed, with patient initiated follow up if this is available within the health system in question. As with all chronic conditions, self-management is an important part of the overall care package. Patients should be provided with information on appropriate patient organisations, which can provide support and advice on adjusting in daily life, accessing the full range of services they may need, including social and employment support, and generally offering a forum for exchanging information. Some countries have

social prescribing link workers (or similar roles) and can direct patients to other forms of support.

Finally, a major research effort, incorporating co-production with patients and families, is required to understand the impact of long COVID in children and to develop effective services and therapies. It will also be important to create processes to care for children and young people with long COVID. These processes must work closely with education providers and social services. Those providing services must have specialist expertise in paediatric long COVID.

These systems and processes will only come about if healthcare systems commit to addressing long COVID. This is discussed below, under the health workforce (co-ordinating care for individual patients) and leadership and governance (designing systems that reduce fragmentation).

1.3.8. The health workforce

The burden of long COVID in many countries may initiate debates on the need for, or is already giving rise to, new medical and pharmacy specialties. This is not the first time that this has happened, bearing in mind the evolution of health workforce in diabetes care or for Acquired ImmunoDeficiency Syndrome (AIDS).

While services continue, in general, to be led by physicians, clinical management is increasingly a shared process, with the patient taking on an increasing role in their own management, and supported by a team of different health professionals.

Long COVID is, as already noted, a condition with a known cause (COVID-19 infection) that affects many different body systems. The burden of disease is high. As noted previously, in the United Kingdom, one of the few countries with high-quality data on prevalence, as noted previously it affected about 3.4% of the population as at November 2022 (Office for National Statistics, 2022b). This is lower than diabetes, which affects about 6% of the adult population in Europe, but much higher than HIV infection, which has a prevalence of <0.3% in most European countries and a highest prevalence of just under 1% in Estonia.

There are, however, important differences. While future trends in diabetes and HIV can broadly be estimated, the future of long COVID is very uncertain. It is a function of a complex mix of characteristics of the virus, including variants causing unpredictable waves, and to some extent individual-level characteristics, including levels of immunity and underlying health conditions. Hence, it cannot be known with certainty whether the current need for services will persist, increase, or decrease. Given the time it takes to train a new

specialist physician, and the uncertainty about whether there will be a need for that individual's services in the medium and long term, there is a strong case, at least in the immediate future, for creating new teams from existing health professionals with relevant skills. These include history taking, clinical examination and carrying out relevant bedside tests (which are likely to include measurement of oxygen saturations on exertion and cognitive assessment). They should be supported by access to rapid diagnostic tests, likely to include appropriate blood tests (including any biomarkers that may be identified in the future), chest x-rays, 24-hr electrocardiograms, and lung function tests, as well as access to specialist multi-disciplinary teams for organ-specific advice. For example, the commonly described symptom of 'brain fog' may be due to a variety of mechanisms so neurological assessment is likely to be important.

These teams would, ideally, include those with experience in management of disabling chronic conditions, in particular those that present with fatigue or respiratory problems, although other experience may also be relevant, such as physical and neurological rehabilitation. Health authorities must ensure that these professionals have access to the training they need to take up their new roles and to continuing access to information on what can be expected to be a rapidly evolving field.

Drawing on the analogies with other complex conditions, we can identify some broad principles. The first is that health workers caring for patients with long COVID must be organised in multi-disciplinary teams. Given the complexity of this condition, coupled with the rapidly evolving knowledge on its aetiology, there would seem to be a strong argument, at least at present, that these teams should include a health professional with up-to-date understanding of long COVID.

These teams should include, or at least have rapid access to, a wide-range of specialist expertise. There is growing evidence of the value of care coordinators or patient navigators, staff who understand complexity of the journey on which the patient is travelling and who can support their movement along it. This concept draws on the case worker model used in social work, with individuals who can help patients get the care they need from what is often a fragmented system. This should include providing advice to patients about what they can expect in different clinical encounters, recognising these will often be stressful. They can also help to explain things that the patient finds unclear and can liaise with other health professionals as necessary. In some countries, this role may be taken on by specialist nurses who have the additional skills and expertise to arrange and undertake appropriate investigations, and, in some cases, to prescribe medicines for symptomatic management of common complications. Given the impact of long COVID on issues such as employment, it is also useful to have a social worker as part of a trans-disciplinary team (World Health Organization, 2022b).

The diversity of professional expertise is illustrated by the following examples (which are non-exhaustive).

Speech and language therapists can play an important role, supporting rehabilitation of patients with some of the common long COVID symptoms, such as swallowing difficulties, and respiratory and neurological problems.

Occupational therapists can play a crucial role in supporting patients to regain and maintain independence in their daily activities, and in particular supporting vocational rehabilitation and will enable them to re-enter the workforce. The importance of this role is clear from the growing evidence in some countries of how long COVID is depleting the labour force (Lawton and Alwan).

Psychologists can support patients experiencing cognitive dysfunction and common mental disorders, while supporting them as they adjust to constraints on their functional capacity. Dieticians are also important, assisting patients with loss of appetite or swallowing difficulties. Pharmacists can play a role in medicines reviews and provision of advice on the use of over-the-counter preparations.

The roles that each of these groups play, in practice, will vary among health systems. One crucial factor will be the extent to which each health system has embraced modern approaches to task shifting. Unfortunately, as we have noted in a previous Opinion on this topic, this is highly variable and, in many countries, there are significant structural and financial barriers to implementing change (Expert Panel on Effective Ways of Investing in Health, 2019). Arguably, long COVID offers an opportunity to bring about the necessary changes, which would confer benefits not only for this condition but for many other chronic ones.

1.3.9. Health information systems

Access to high-quality data that capture appropriate information on all patients is a prerequisite for the effective and efficient functioning of a health system. Long COVID needs to be systematically and consistently coded, but it can present several challenges (Mayor et al., 2021, Meza-Torres et al., 2022). As noted previously, long COVID can manifest in many ways, presenting to different specialities, and co-existing with other clinical conditions. Thus, operationalising any of the definitions that have been proposed in routine clinical practice will be difficult. How this is done in any particular country will vary according to the organisation of healthcare and the information systems already in place. In this section we have applied well-established principles in developing and implementing health information systems to the challenges created by the advent of long COVID.

However, we stress that these are principles apply more generally, even if long COVID, with its attendant complexities, makes them more important than previously.

We first examine information governance. It seems self-evident that there should be well-functioning systems to ensure that appropriate data are collected, collated, synthesised, and transmitted to those who need them at all levels of the health system. This calls for individuals at all levels with designated responsibility for the timeliness and quality of data. The next paragraphs set out, in broad terms, what such a system might look like, again recognising the need to take account of the specificities of the health system concerned.

At a national, regional, or organisational level (depending on the characteristics of the health system), there should be mechanisms in place for establishing, monitoring, and revising as appropriate the data systems that are in place to ensure that they are fit for the purpose of responding to long COVID. This is likely to draw on individuals with a range of expertise, including informatics, clinicians managing long COVID, and public health specialists who can ensure the inclusion of a population perspective. This structure must have a system to monitor emerging evidence from research and ensuring that it is acted on where appropriate. Such a structure is desirable for management of all common chronic conditions and, where one does not already exist, the advent of long COVID may be seen as an opportunity to create one that can have sub-groups with specialist expertise in a range of these conditions.

Within each major health facility, there is a strong case for having a named clinical lead who can work with informatics experts to ensure that data systems reflect the goals of the service (i.e. 'what are the problems and what are we trying to achieve?'), that appropriate patient-centred outcome measures are being collected (i.e. 'how will we know that our services have been successful?'), and a minimum demographic dataset to inform service development and address health inequalities (i.e. 'how will we know where the gaps are in our services?').

All except the smallest facilities should also have someone responsible for ensuring that data collection systems are in place, rules for coding have been disseminated, and staff have received training in their use, guided by the national principles and rules of sensitive data protection, including valid consent of the patient if applicable. Ideally, the information collected will permit monitoring of the extent to which the facility meets the needs of all groups, necessitating the collection of data on characteristics known to be associated with inequalities in access. Where this is not prohibited by national legislation, this should include data on ethnicity, as well as on contextually appropriate measures of deprivation, which may be based on the characteristics of the area in which the patient resides. There should be mechanisms in place to enable these data to be shared with appropriate higher-

level organisations, which may be organised on a geographical basis, for example, where county councils are responsible for healthcare, or affiliation, as with sickness funds.

Within each higher-level organisation, there should be a designated team who are monitoring the quality and completeness of the data reported by providers and who are tracking, to the extent possible, the quality of the care provided, with a particular focus on equitable access to appropriate care. Thus, for example, an unusually high or low level of referral to certain types of specialists might justify further investigation. This team will also have expertise in information systems and can support smaller health facilities.

The pandemic revealed major shortcomings in the timely access to appropriate health data within the EU. For example, even though excess mortality was soon identified as a critical indicator of the impact of COVID-19 on populations, about one third of member states did not provide data to the EuroMoMo facility (EUROMOMO, 2022). Going forward, and especially given the imperative to monitor the changing burden of long COVID and to learn from the different experiences of member states, it will be essential to have timely and comparable data that are easily available. Governments already report health data to international bodies, including WHO, EUROSTAT, and the OECD. It would be wasteful to duplicate the systems already in place for collating and transmitting health data. It will be important to agree on the content of core datasets for international comparisons. The process to develop them would logically lie with WHO, given the value of comparability beyond the EU.

The second issue to be considered is the type of data that should be collected. Obviously, what is possible will vary depending on the information systems that already exist. Following convention, we divide our comments into those relating to primary, secondary, and community care.

In primary care, health authorities should define a minimum dataset for anyone with a diagnosis of long COVID. This should include the results of any tests for COVID-19, including both antigens and antibodies. It should also include information on when long COVID was diagnosed and the evolution of symptoms over time, with particular attention paid to what are termed "red flag" symptoms, defined as those requiring rapid referral or investigation (World Health Organization, 2022b). Ideally, primary care data should also include regular monitoring of quality-of-life using one of the standard instruments (see later, under surveillance), such as COVID-19 Yorkshire Rehabilitation Scale - C19-YRS (Sivan et al., 2020, Sivan et al., 2021, Sivan et al., 2022).

In many countries, information systems development differs in secondary care and in primary care. Full use should be made of the relevant newly introduced International

Classification of Diseases, Tenth Revision (ICD-10) codes, U08.9 (Personal history of COVID-19, unspecified), U09.9 (Post COVID-19 condition, unspecified), and U10.9 (Multisystem inflammatory syndrome associated with COVID-19, unspecified). National authorities should develop and disseminate guidance on the use of these codes and on other data items relevant to the monitoring of the care of patients with long COVID. This should provide information that can be used to monitor patient trajectories on what will be, for many of them, complex journeys that take in multiple specialties and providers.

Data collection in community care is inevitably more complex, due for example to the multiplicity of providers, some within and some outside formal systems. Again, the precise arrangements will vary from country to country, but where possible health authorities should develop guidance on minimum datasets. This should include details of the services provided.

A final consideration is that health information systems should support research. Given the considerable uncertainty about the progress of long COVID and about its optimal management, health authorities should ensure that their information systems support research. Important elements include the ability to identify patients who can be invited to participate in clinical trials, to be able to follow up cohorts of patients to track the natural history of this condition, and to link data on patient characteristics, treatments and symptoms to undertake non-experimental studies that might shed further light on the nature and management of this condition. In this respect, the United Kingdom's OPENSafely programme is one that could usefully be emulated (though depending on the accuracy and completeness of clinical coding) (EUROMOMO, 2022).

1.3.10. Access to essential medicines

Although one of the WHO building blocks, the Expert Panel has not identified any specific issues for long COVID here, given the current level of evidence regarding effective treatments for long COVID. Current institutions and mechanisms worked as intended. In case of an essential medicine appears in the future, the use of joint procurement by EU countries may avoid tensions inside the EU in differential time access to it, and benefitting from size effects ensuring access of EU patients to essential medicines.

Within the EU, approval of innovative medicines is the responsibility of the European Medicines Agency, which has a dedicated webpage bringing together its work on vaccines and treatments for COVID-19 (European Medicines Agency, 2022b). Moreover, the European Medicines Agency has also a role in monitoring and preventing medicines supply disruptions and actively coordinating the activities at EU level on potential shortages of critical medicinal products during public health crisis (European Medicines Agency, 2022a).

However, it will be important to ensure that the authorities that have the capacity to define the list of essential medicines have access to expert advice, at national or at international level.

It is important that knowledge on effectiveness of current and future pharmaceutical products, resulting from long COVID clinical trials, is shared across countries in a timely manner, both related to reducing infections and re-infections and to secondary prevention (to avoid worsening of symptoms if re-infected).

1.3.11. Financing

Long COVID will inevitably place additional financial strain on health systems, although with current knowledge, and especially given the uncertainty about the future trajectory of disease burden, it is only possible to speculate on the scale of the challenge ahead. In a commentary on the financial implications in the United States, Cutler emphasises that the medical costs will only be part of the financial consequences for society, with lost productivity and payments for disability and social support likely much greater (Cutler, 2022). He also cites a study that estimates the annual cost of managing a patient with chronic fatigue syndrome, which may be similar to long COVID in terms of the consequences of flare-ups, at US$9,000 per year (Jason and Mirin, 2021). However, the given the different nature of the two conditions and the very different price structures in the United States and Europe, this figure should be considered as purely illustrative. In general, as yet another complex chronic disease, long COVID is not likely to require major changes to health care financing structures. The one caveat is that in some systems, typically funded by social insurance with payments on a fee-for-service basis, it may be difficult to construct mechanisms that encourage and sustain the multi-professional teams that will be needed. Another caveat for some health systems is the under-funding of primary care, which may require more funding in order to address the increased responsibilities associated with long COVID diagnosis and management. The experience of implementing initiatives such as the German Disease Management Programmes will be important in this respect (Fuchs et al., 2014, Busse, 2004). Additional funding may become necessary and should be defined under the current financing arrangements of each national health system.

1.3.12. Leadership and governance

As the previous sections have set out, despite gaps in evidence, there is sufficient knowledge on long COVID and on other conditions that have similar characteristics to determine what is needed, at least in the short term. The challenge is how to implement it. Thus, those with responsibility for the operation of health systems must ensure that

there are appropriate governance systems in place to ensure that guidance is adhered to. The precise mechanisms that will be appropriate will depend on the organizational structure of the health system, taking account of issues of ownership and lines of accountability. As far as possible they should be informed by knowledge, ideally from locally undertaken research aligned with larger international studies. This should seek to understand topics such as adherence to such guidance, including facilitators and barriers to uptake and include structural and behavioural interventions and accountability mechanisms that can bring about any necessary changes.

1.3.13. Moving forward

The mandate asked the Expert Panel to advise on the design of health services in the light of long COVID. Our review has highlighted the great uncertainty about the future, scale and nature of the burden that will be imposed by long COVID. While we do have reasonably accurate information on the current prevalence, we cannot know with any certainty what will be the impact of future waves of infection with new variants, some of which may be more or less likely to cause long COVID. Nor can we say with any degree of certainty the impact of recovery from this condition. In these circumstances, health authorities will be taking a risk by investing large sums in stand-alone services for a condition that may not be needed in the future. However, regardless of the future course of the pandemic, the general principles that apply to the management of long COVID are equally applicable to many other conditions, especially in the growing number of patients who have multi-morbidity. Consequently, we believe that the most appropriate response to long COVID is to see it as an opportunity to bring about some of the changes that are needed in those health systems that have yet to respond adequately to the increasing volume of complex chronic diseases. In particular, these involve a shift to a person-centred integrated model of care and the introduction of genuine team working, based on collaboration between professionals who have different skill sets and coming together with the patient to co-produce solutions in non-hierarchical groups. This will, however, require a new approach to governance of health system is in some countries, with an explicit commitment to achieving the core goals of a health system, improved and equitable health outcomes, responsiveness to legitimate public expectations, and fair financing (adequate funds to achieve the objectives of the health system, raised in a fair way).

1.4. How public health surveillance should be adapted to measure the impact of the post-COVID-19 condition

1.4.1. General principles

The principles of disease surveillance are well-established. Surveillance entails the continuous and systematic collection and analysis of data, and the subsequent reporting of any significant findings to effect change (Bennett et al., 2020). Surveillance can be passive or active. Passive surveillance system involves the regular monitoring of reports of disease appearing in existing health information systems, which include laboratory data, administrative systems in health facilities and, increasingly, data from digital technology, including apps and wearables, such as those that monitor heart rhythm. Active surveillance goes beyond this to include proactive case finding by health professionals, for example, in household surveys. The former is obviously much less resource intensive than the latter. Effective surveillance has three main elements:

- Capture and collation of data
- Analysis and interpretation of data (to generate information)
- Dissemination of information

A comprehensive surveillance system will include a fourth element, an action taken when indicated by the data. Often this is represented as a circle, with lessons from the surveillance process feeding back into possible changes in how data are collected and interpreted. This may seem obvious, but it is important to re-state it as, too often, information systems that could contribute to surveillance are created without adequate attention to how the information will be analysed and used. This situation can arise when, for example, software vendors convince health authorities to purchase information systems that collect data, but not necessarily in the form that is needed or are designed in ways that prevent them from being changed when this becomes necessary. This will be especially important with long COVID, given the contingent nature of temporary knowledge about this condition. The challenges inherent in procuring complex information technology systems have been discussed in a previous Opinion by the Expert Panel (Expert Panel on Effective Ways of Investing in Health, 2021a).

In making recommendations for surveillance in light of long COVID, we have adhered to some basic principles. First, given the multifaceted presentation of this complex condition, including many symptoms and signs that are found with other disorders, as far as possible, surveillance systems should build on what already exists for monitoring disease, potentially by extending the currently existing mandates. As will be argued, there are situations in which bespoke solutions are required but, in general, these should be the exception. Second, surveillance should encompass a range of measures that go beyond the presence or absence of the condition. It needs to be able to capture its impact on the life of the affected individual. Third, given the chronic nature of this condition, surveillance should,

as far as possible, include a longitudinal component (following people over time) to allow its trajectory to be ascertained.

1.4.2. The epidemiology of long COVID

Any surveillance system must start by identifying those with the condition in question. The WHO used a Delphi exercise to develop a clinical case definition of post-COVID-19 condition (World Health Organization, 2021a) (see Box 1 above).

This poses some obvious challenges. The first is the capture of acute infection with SARS-CoV-2. Initially, testing data, which then involved polymerase chain reaction (PCR) tests, was limited by laboratory capacity. Once lateral flow tests became available for home use, there was variable reporting of results. A second is that the main symptoms associated with long COVID (fatigue, shortness of breath and cognitive dysfunction) are very common in the general population and may be manifestations of other diseases, some of which will be difficult to exclude in routine surveillance. A third is that symptoms often fluctuate or relapse over time and people, so a definition that is applied at one point in time may miss cases.

The limitations of the WHO case definition for surveillance purposes are, perhaps, inevitable, given the nature of the condition and, crucially, the absence of any biomarkers that can be used at present. Researchers have invested considerable effort in identifying putative biomarkers, ranging from certain findings on imaging of different organs, such as the heart and lungs, persistent viral reservoirs, especially in the intestines, and abnormalities in the blood, in particular micro-clots. It is likely that each of these plays some role in some of the manifestations of this condition, but current knowledge is still far from finding anything that can be used in routine practice.

At this point, it is relevant to note that, given the diverse therapeutic journeys along which people with long COVID travel, it will not be possible to gain a comprehensive picture of the epidemiology of this condition from passive surveillance. Rather, active surveillance with outreach to the population will be required. One pragmatic solution to this problem, albeit with obvious limitations, is to use a case definition based on self-report. This is the approach taken by the UK Office for National Statistics (ONS), whose regular surveys are one of the only high-quality sources of information on prevalence of long COVID at a population level. Participants in the survey are asked: "Would you describe yourself as having 'long COVID', that is, you are still experiencing symptoms more than 4 weeks after you first had COVID-19, that are not explained by something else?" followed by a question on whether it limits their activities. Limitations of this survey have been described previously in this opinion in Section 1.2.2.

The responses to this survey have proven invaluable in tracking the prevalence of long COVID, as well as in providing information on the risks associated with different variants of the virus or following repeated infections. When linked with other socio-demographic data, they have been used to assess the economic and labour force impact of the condition. Thus, given the present state of knowledge, there is a very strong argument that every country should be conducting regular surveys of this type, potentially harmonised at EU level.

If we assume that cases can be tracked in surveys, such as that undertaken by the ONS, the next question is what additional information is required. Logically, this would be standardised across the EU and, ideally, the EEA and in neighbouring countries (Centers for Disease Control, 2022). This can be facilitated by recent changes in the mandate of ECDC that provide for the establishment of an EU Health Task Force to assist local responses to the outbreak of disease, the provision of expertise to EU countries and the European Commission, for instance in the development, examination and updating of preparedness plans. The standardised EEA survey would be run by national statistics offices and EUROSTAT, with advice from ECDC.

1.4.3. Use of health services by patients with long COVID

Although active surveillance will be essential if we are to obtain a comprehensive picture of the epidemiology of this condition, this does not mean that there is no role for passive surveillance. Routine administrative systems in health facilities may provide some valuable insights, while noting that they will exclude those who cannot encounter them. As noted in the previous section, WHO has added codes for SARS-CoV-2-infection on the ICD-10 classification (World Health Organization, 2021b), including for long COVID (U09.9). However, as with all administrative databases, their value is critically dependent on the quality of the data inputted. These databases will provide information on the more serious manifestations of this condition and the treatments required. Administrative data, especially where there is a unique patient identifier, can also be used to look for rarer long-term consequences, as has already been done in research that has identified a greater risk of thrombotic incidents in patients who have had SARS-COV-2 infections (Fanaroff et al., 2021).

In countries where the data quality is good, we can also expect innovations from application of machine learning techniques that may provide important insights on the nature and cause of this condition (Yang et al., 2020). In some countries, it may also be possible to obtain data on the scale and nature of disabilities associated with long COVID from social insurance databases and, in a few, it may be possible to undertake record linkage to

connect the data to that from the health system and other sources and potentially even data from other sectors.

At this specific point in time (August 2022), when results from Randomized Controlled Trials on treatments for long COVID are not in place yet, patients with long COVID may, in desperate desire to seek treatments, resort to expensive and potentially dangerous medical tourism. Appropriately designed research needs to be supported at all levels.

1.4.4. Measuring the impact of long COVID on functioning and quality of life

Most work to date has used well-known and widely used scales, such as the EuroQol's EQ-5D [either with 3 levels (EQ-5D-3L) or with 5 levels (EQ-5D-5L)] (Garrigues et al., 2020, Malik et al., 2022). This has identified decreased mobility, increased pain and discomfort and higher levels of anxiety and/or depression in patients with or attributed to long COVID. Other generic instruments that have been used include the RAND Corporation's Short Form SF-36, Quality of Life Index and the Patient-Reported Outcomes Measurement Information System PROMIS scale (Aiyegbusi et al., 2021, Lopez-Leon et al., 2021, Moreno-Pérez et al., 2021, Chopra et al., 2021, Jacobs et al., 2020, Shah et al., 2021, Taboada et al., 2021, Daher et al., 2020). Several studies report a negative impact on mental health as assessed by the EQ-5D and other measures (Patient Health Questionnaire PHQ-9, General Anxiety Disorder GAD-7, Warwick-Edinburgh mental wellbeing scales) (Arnold et al., 2021, Poyraz et al., 2021, Ma et al., 2020).

The mental health impact of long COVID may be an indirect consequence of an individual's ability to coping with their chronic condition. However, it should not be ruled out that this impact may be a direct consequence of pathophysiological mechanisms. Disentangling these impacts in inherently challenging, yet necessary to appropriately treat all the clinical manifestations of long COVID. Comprehensive longitudinal surveillance within the health system can help in this regard as well. In a 1year follow up, patients who were hospitalised with COVID-19 in the UK experienced a substantial deterioration in median EQ-5D-5L utility index with at most minimal improvements in outcome measures (Evans et al., 2022). A 2-year follow-up of patients hospitalised with COVID-19 in China found that patients who reported symptoms consistent with long COVID at 2 years had lower HRQoL, worse exercise capacity, more mental health problems, and increased use of healthcare than those who did not report symptoms (Huang et al.).

Older people (60 years old and above) seem especially likely to experience problems with mobility, pain/discomfort and ability to perform daily life activities (Walle-Hansen et al., 2021). Patients with pre-existing chronic conditions also seem to experience greater adverse impact on physical health that those without these conditions (there was no

difference in mental health), although the authors noted that it was not possible to assess causality (Shah et al., 2021).

Tabacof has proposed using an instrument comprising questions on demographics, past medical history, acute COVID-19 illness, a symptom checklist, and a battery of patient-reported outcome measures (National Academies of Sciences Engineering Medicine, 2022) including the Fatigue Severity Scale (Hernandez-Ronquillo et al., 2011), MRC Breathlessness Scale (Stenton, 2008), EuroQol EQ-5D-5L (Herdman et al., 2011), Patient Health Questionnaire (PHQ-2) (Arroll et al., 2010), General Anxiety Disorder-7 (GAD-7) (Spitzer et al., 2006), Neuro-QOL Cognitive Function 8-item Short Form (Neuro-QOL) (Iverson et al., 2021), and WHO Disability Assessment Schedule (WHO-DAS) (Üstün et al., 2010).

Others have proposed a new scale, the PAC-19QoL – Post-Acute COVID-19 Quality of Life (Jandhyala, 2021). This measure considers 4 domains, with several elements of interest in each. The domains are psychological, physical, social and work. The details are: (a) psychological domain: Mood, Isolation, Motivation, Anxiety; Cognition, Expression, Mental Exertion; (b) Physical: Exertion, Pain, Travel, Somnolence, Smell/taste, Breathlessness, Fine motor, Libido; (c) Social: Isolation, Relationships, Hobbies; and (d) Work: Ability to work.

This proposal has the merit of including quality-of-life measurement dimensions that are absent from the EQ-5D and SF-36, including more detailed coverage of mental health and the impact on the ability to work (which may affect the ability to earn income, and as such have an indirect effect on mental and physical health). Another proposal of a specific scale is the Post-COVID19 Functional Status scale, which overlaps considerably with the EQ-5D instrument (Klok et al., 2020).

Loss in quality of life can be discussed in terms of depth (how much loss there is) and breadth (which dimensions are most affected). On the breadth of impact, and with reference to the most common measure of quality of life used to assess long COVID, the EQ-5D (either the three-level version, EQ-5D-3L or the five-level version, EQ-5D-5L), the common finding is that all dimensions of the EQ-5D instrument are affected, with mobility, pain/discomfort and anxiety/depression being impacted strongly, while self-care being the less impacted dimension (the remaining dimension, usual activity, lies in between).

Another measurement instrument for long COVID, the COVID-19 Yorkshire Rehabilitation Scale (C19-YRS) was proposed by Sivan et al. (2021). The C19-YRS sets four domains (symptom severity, functional disability, additional symptoms, and overall health). The domains and indicators (questions asked to respondents) result from the joint effort of a

multi-disciplinary team of rehabilitation professionals, together with patients. The set of questions asked include most of the domains and dimensions of other scales.[1] This measure was updated by Sivan et al. (2022), with a re-definition of scales of the domains used in the initial measure, leading to the modified C19-YRSm version.

The new indices that have been proposed in the literature go into further details in several dimensions relevant to patients and to health professionals, compared to pre-COVID-19 QoL widely used measures. The specificities associated with long COVID suggest the importance of using of made-to-purpose measures that are valid across contexts for wide-scale, cross-country surveillance as well. It is likely that further proposals will emerge, although the C19-YRS did collect support for its regular use in the UK.

1.4.5. Moving forward

There is, at present, remarkably little information on the scale and nature of the burden of long COVID in the EU. Given evidence from the UK, where such evidence is collected, that 3.4% of the UK population were affected in November 2022 (Office for National Statistics, 2022b) an appreciable number severely, this situation is untenable (World Health Organization, 2022a). However, it is unsurprising. While there are nationally representative population health surveys in many European countries, there are also many gaps. The European Health Examination Survey, which should have provided the information needed, has been disappointing (European Health Examination Survey, 2022). The programme has struggled to obtain funding and the content, timing, and methods of surveys that have been conducted have varied, precluding meaningful comparisons. Consequently, any recommendation about establishing consistent surveillance systems for long COVID in the EU must start with measures to establish a well-functioning surveillance structure within which it can be incorporated. If this could be done, then the existing survey methods, such as that developed by the ONS, can provide a starting point and important insights into the methods that might be used. The approaches such as EU-SILC, or a regular Eurobarometer might be followed.

1.5. Recommendations

Just as the COVID-19 pandemic has shone a light on many of the weaknesses in society, such as lack of preparedness and weak social safety nets, so the experience with long COVID has highlighted many existing weaknesses in our systems. As with any complex, chronic disease, there are certain principles that should be adhered to. For example, it has long been accepted that patients should be fully involved in the development of care

[1] For example, the 5 dimensions of the EQ-5D and most dimensions of the PAC-19QoL are present in the C19-YRS.

pathways, they should be able to draw on the support of someone who can help them navigate the health system, ideally based on primary care, and they should have easy access to an appropriate range of specialists working as a team. Going beyond the health system, health research should reflect the health needs of the population and, as with the delivery of healthcare, should be designed and implemented with effective public and patient involvement.

This has two implications. The first is that there is a strong argument for seeing long COVID as an opportunity to address many of these weaknesses. While there is still uncertainty about the precise burden of ill health, and the consequences for health and social care and economic growth, we know that it will be substantial. This burden is on top of a growing burden of ill health from traditional non-communicable diseases as a result of ageing populations, conditions which, it is increasingly clear, are exacerbated by infection with SARS-CoV-2. Long COVID is just one of many complex chronic conditions, including both individual diseases that affect many different body systems, such as diabetes or many auto-immune disorders, and the collective burden of multimorbidity (Barnett et al., 2012). While each has distinctive features, they also have similarities, in particular with respect to the organisation of their care. Thus, a more holistic, person-centred model of care should be seen as a goal for those designing responses to long COVID, but also for many other conditions.

The second implication is that these weaknesses have been known about for many years. If they could be fixed easily they would have been. Hence, it is clear that there are many barriers to doing so. These will vary according to context. Often, they reflect organisational characteristics of health systems, with provision of different services located in separate siloes. In other cases, they reflect professional boundaries, often a function of long-established hierarchies that resist change because of the distribution of power within the system. In an earlier Opinion the Expert Panel has drawn attention to the scope for greater task shifting (Expert Panel on Effective Ways of Investing in Health, 2019). Long COVID provides an impetus for renewed action to implement its recommendations.

In formulating our recommendations, we follow the questions posed in the mandate, starting with the latest evidence on long COVID, followed by the implications for health systems, and concluding with the challenges involved in surveillance. The challenge of long COVID is not limited to the delivery of services to patients. As noted in the discussion on research, we have known for some time that, with appropriate investment, it is possible to mount large scale clinical trials rapidly. During the pandemic the United Kingdom's RECOVERY trial confirmed this. However, this requires an acceptance that research should be embedded in the delivery of health care, so that every patient can be confident that

they will be offered the opportunity to participate in a clinical trial. We are still a long way from this in many countries.

Knowledge

A great deal is already being done to extend our knowledge of long COVID, both within members states and at a European level, for example, the ORCHESTRA programme (ORCHESTRA., 2022), as well as other cohort studies being done under Horizon Europe funding from the EC (projects VERDI, EU-CARE and END-VOC, for example), and coordinated by a "cohort coordination board". Given the rapidly evolving state of knowledge, it would be inappropriate for the Expert Panel to make specific recommendations, although we have provided a list of currently unanswered or incompletely answered questions in Box 3. We do, however, make one exception, reflecting a concern that it may otherwise be relatively neglected. This is that research on the wider impact of long COVID, including on the labour force and on the economic and social circumstances of those affected and the wide range of health, social and other services necessary to support them should be prioritised. The reason we are concerned about possible neglect is that it will require studies that transcend sectors and disciplines, a type of research that has often struggled to attract funding. Beyond this, our recommendations address principles that we believe should underpin research on long COVID but, echoing our argument above that the advent of long COVID should be seen as an opportunity to fix weaknesses that have persisted for too long across health research. Several EC funded HORIZON projects starting in 2022 might, by design, tackle some of the issues outlined in the recommendations.

Recommendation 1: Research on long COVID should, as far as possible, be explicitly co-produced with people living with the condition, with co-creation of potential therapeutic interventions, as well as a targeted consideration of the pathway along which the findings of the research can achieve impact.

As noted previously, long COVID was the first medical condition to be named and delineated by those affected by it using social media. Those with lived experience were the first to characterise the condition through patient-led research and have described the struggle they have often experienced in having their problem recognised and in obtaining care. This has sometimes left a legacy of distrust. We believe that a dialogue based on mutual respect that involves those with long COVID, the health professionals from whom they seek care, the health system directors and managers who are tasked with organising and financing such care, and the research community will benefit all parties.

Recommendation 2: Research on long COVID, and especially on potential treatments, needs to be done at sufficient scale to provide definitive answers that

take account of any heterogeneity within the population and the contexts in which they are situated.

Much of the research on therapy for COVID-19 undertaken during the pandemic is comprised of underpowered studies on often unrepresentative samples of the population. This is wasteful and, although small studies can be combined in meta-analyses, these often struggle with differences in case definitions, specifics of treatment, and duration of follow-up, among other problems. As with almost all health research, certain groups tend to be systematically excluded, such as children, older people, and those from ethnic minorities, and gender differences might not be addressed appropriately. These problems are especially acute where the treatment packages involve behavioural components or are dependent on characteristics of the health system, such as the extent of multi-disciplinary working. Thus, research on interventions should answer not just the question of what works, but what works in what circumstances? Aiming to a harmonization of definitions, establishing valid measurement tools and definition of outcomes, and ensuring coordination within different research projects are also essential points to be considered. The field of implementation science may provide frameworks, study designs, and other guidance to assist in this regard.

Recommendation 3: Health systems need to embed research on long COVID at all levels of care including rehabilitation, identifying incentives that can be applied and barriers that can be removed to facilitate the development of health facilities as settings for research and health workers as users of it.

While there is still considerable uncertainty about the long-term burden of long COVID, at least in the short and medium term it will be substantial. There is an urgent need to understand it better. This will only happen if those responsible for health systems prioritize the generation and uptake of knowledge. As long as there is uncertainty about the most appropriate way to manage long COVID and treatment options exist, all patients should be given the opportunity to participate in clinical trials, both of specific therapeutic agents and packages of care, such as different forms of rehabilitation. Obviously, it is also important to ensure that new findings are shared, validated, and acted upon. The mechanisms for disseminating new knowledge from research vary greatly, often reflecting different roles of universities, research bodies, and professional associations. Thus, it is not appropriate to make specific recommendations here beyond arguing that the relevant stakeholders in each member state should ensure that contextually appropriate systems are in place.

Health systems

The first consideration in developing recommendations for health systems is the adage that "prevention is better than cure". The second consideration is that long COVID, in its various manifestations, is a complex chronic condition.

Recommendation 4: As SARS-CoV-2 infection is the cause of long COVID, measures to combat it, including vaccination and reducing transmission, must remain a priority.

While there may be continuing uncertainty about the precise mechanisms involved, one thing can be said with certainty. Long COVID can only arise in people who have been infected by SARS-CoV-2. While this now includes most of the population in many countries, it does not include everyone. Also, there is growing evidence that avoiding long COVID after an initial infection does not exclude you from developing it after subsequent infections. Despite evidence that initial and booster vaccination reduces the risk of long COVID in adults, there remains substantial numbers of people who have not yet been vaccinated. While COVID-19 continues to be transmitted and to cause appreciable numbers of deaths, it is important to continue measures known to reduce transmission, while recognizing that the intensity of restrictions at the height of the pandemic will be difficult given changing public perceptions. However, some of those measures, such as improved ventilation and installation of air filtration, are effective in reducing other airborne respiratory viruses. This could be a positive legacy of the pandemic. Similarly, it will be important to maintain momentum in vaccination campaigns, extending coverage to those who remain unvaccinated and emphasizing the importance of boosters. Related to all these aspects, the importance of public awareness and ability to identify long COVID symptoms should not be neglected.

Recommendation 5: Long COVID is to be recognized as one of many complex chronic conditions that, in many patients, will co-exist with others, calling for models of care that are co-ordinated in primary care, with mechanisms to ensure rapid referral to specialist teams while avoiding placing patients in "long COVID siloes".

Health systems have been struggling to develop responses to complex chronic conditions for several decades, with limited success. While some progress has been made in developing care pathways for patients with a single condition, such as diabetes, the lived reality for many patients is that they have multiple conditions. This creates major challenges. First, it can be difficult to determine which of their symptoms is attributable to which condition, something that may have implications for treatment. This problem is exacerbated by the difficulty in distinguishing a pathological process from the physiological process of ageing. Second, the treatments required may interact in unexpected ways with

each other or be influenced by factors such as impaired renal disease or frailty. Third, those affected need support to manage a complex pathway that can involve interaction with multiple specialists and health professionals. Fourth, being a woman brings one of the highest risks for long COVID, so gender differences need to be appropriately considered.

We already know that long COVID is also more common in people who are older and have co-morbidities, so the starting point to develop a health systems response must be to situate it in the context of probable multimorbidity (including conditions such as new onset diabetes that may be a direct consequence of infection with SARS-CoV-2) and to centre it around the needs of the patient. This has two implications. First, it emphasizes the importance of adopting the principles of person-centred care. Second, it argues against the creation of a specific vertical system for the management of long COVID. Given that many patients with long COVID will have other health disorders, an effective response should be coordinated by a team with oversight of the patient's care. This will logically be situated in primary care. However, that team will require specialist support from time to time. This is already the case in the best functioning models of care for other multi-system conditions such as diabetes or auto-immune disorders, although it is by no means universal. Thus, it will be important to develop centres of expertise in long COVID, the pathological processes involved, and the therapeutic options. These will inevitably require multi-disciplinary teams including physiotherapists, occupational therapists, nurses, psychologists, speech and language therapists, physicians and social workers (World Health Organization, 2022b). However, it is equally important to have robust assessment criteria to ensure that patients that have problems better managed elsewhere, for example by primary care or medical specialists, are appropriately referred.

Surveillance

In writing this Opinion we have been limited by the lack of high-quality data on the prevalence and natural history of long COVID. We have relied disproportionately on evidence from a few countries, in particular the United Kingdom, that has established an on-going surveillance study. Consequently, while we would have liked to have produced estimates for the future burden, in health and economic terms, attributable to long COVID for each member state, it has not been possible.

Recommendation 6: A coordinated programme of surveillance systems should be established, including data from each member state, using consistent case definitions and methodologies, and encompassing the impact of this condition on health, employment, and the economy.

The record of the European Union in health surveillance has been mixed. The responsibility lies, primarily, with member states, although with some coordination by EUROSTAT. This means that, while there are some commonalities, there may be differences in survey methods and questions. There may also be problems with comparability of responses to some questions in different languages. There are several different surveys, including the European Health Examination Survey (EHES), which is a collaboration between organizers of national health examination surveys in Europe, and the European Health Interview Survey (EHIS) which collects data on health status, health care use, health determinants and socio-economic background variables across all member states. However each has inherent limitations – EHES only includes 14 member states and the UK, whereas EHIS is only undertaken every 5 years (European Health Examination Survey, 2022, EUROSTAT, 2022). The European Social Survey includes 32 countries does not focus solely on health and is conducted every 2 years, but does address self-reported health and general well-being. It includes monitoring of national contexts and specific modules are developed in response to important issues, such as COVID-19 (European Social Survey, 2022). Given the challenges that have been faced in establishing these surveys, it will be difficult to achieve a stand-alone survey that can monitor continuously the prevalence and impact of long COVID in all member states. Nonetheless, we call for, at least, a series of surveys with waves repeated at relatively short intervals for at least the next three years. These should be of adequate size in each member state to be powered to identify inequalities within the population, something that may require sample boosts to increase the numbers from certain groups, such as ethnic minorities. While, if this was to be an on-going survey, it would logically reside with EUROSTAT, due to the short-term nature of it might logically reside initially with another part of the commission, such as DG SANTE. An important pre-requisite will be to ensure that those involved in undertaking the survey use a set of diagnostic criteria consistent with those being used more widely. This would logically follow the WHO's lead. These surveys should not be confused with active cohort follow-up for research purposes to explore multiple possible symptom and pathophysiological facets of a syndrome.

In a broader sense, publishing long COVID statistics more regularly alongside the infection and recovery statistics, ideally on non-scientific web sites that are accessible to a non-specialist is desirable. Such information, easily available to citizens and journalists, will keep awareness that long COVID exists and requires attention from everyone.

LIST OF ABBREVIATIONS

ACSH	EU Advisory Committee on Safety and Health at Work
AIDS	Acquired ImmunoDeficiency Syndrome (AIDS)
C19-YRS	The COVID-19 Yorkshire Rehabilitation Scale
CTCG	Clinical Trial Coordination Group
CTIS	Clinical Trial Information System
ECDC	European Centre for Disease Prevention and Control
EEA	EU/European Economic Area
EHES	European Health Examination Survey
EHIS	European Health Interview Survey
EMA	The European Medicines Agency
ETF	Emergency Task Force
EXPH	Expert Panel on effective ways of investing in health\
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
HIV	Human Immunodeficiency Virus
HRQoL	Health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
ICU	Intensive care unit
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
ME	Myalgic encephalomyelitis
NCA	National competent authority
NEURO-QOL	Neuro-QOL Cognitive Function 8-item Short Form
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
PAC-19QoL	Post-Acute COVID-19 Quality of Life
PACS	Post-acute COVID-19 syndrome
PAMPS	Pathogen-associated molecular patterns
PASC	Post acute sequelae of COVID-19
PCR	Polymerase Chain Reaction
PESE	Post-exertional symptom exacerbation
PHQ-2	Patient Health Questionnaire
PICS	Post-intensive care syndrome
PRRs	Pattern recognition receptors
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TMPRSS2	Transmembrane serine protease 2
VHP	Voluntary Harmonization Procedure
WHO	World Health Organization

WHO-DAS	WHO Disability Assessment Schedule

REFERENCES

ACKERMANN, M., VERLEDEN, S. E., KUEHNEL, M., HAVERICH, A., WELTE, T., LAENGER, F., VANSTAPEL, A., WERLEIN, C., STARK, H., TZANKOV, A., LI, W. W., LI, V. W., MENTZER, S. J. & JONIGK, D. 2020. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med,* 383**,** 120-128.

ADER, F. 2020. Protocol for the DisCoVeRy trial: multicentre, adaptive, randomised trial of the safety and efficacy of treatments for COVID-19 in hospitalised adults. *BMJ Open,* 10**,** e041437.

AHAMED, J. & LAURENCE, J. 2022. Long COVID endotheliopathy: hypothesized mechanisms and potential therapeutic approaches. *The Journal of Clinical Investigation,* 132.

AHMED, H., PATEL, K., GREENWOOD, D. C., HALPIN, S., LEWTHWAITE, P., SALAWU, A., EYRE, L., BREEN, A., O'CONNOR, R., JONES, A. & SIVAN, M. 2020. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis. *J Rehabil Med,* 52**,** jrm00063.

AITKEN, M., PHADKE, C., PRASAD, R., PURI, K. & TEWAERY, V. 2021. *Assessing the Global Burden of Post-COVID-19 Conditions* [Online]. IQVIA Institute for Human Data Science. Available: https://www.iqvia.com/insights/the-iqvia-institute/reports/assessing-the-global-burden-of-post-covid-19-conditions [Accessed 13th May 2022].

AIYEGBUSI, O. L., HUGHES, S. E., TURNER, G., RIVERA, S. C., MCMULLAN, C., CHANDAN, J. S., HAROON, S., PRICE, G., DAVIES, E. H., NIRANTHARAKUMAR, K., SAPEY, E. & CALVERT, M. J. 2021. Symptoms, complications and management of long COVID: a review. *J R Soc Med,* 114**,** 428-442.

AL-ALY, Z., BOWE, B. & XIE, Y. 2022. Long COVID after breakthrough SARS-CoV-2 infection. *Nat Med,* 28**,** 1461-1467.

ALWAN, N. A. 2021. The road to addressing Long Covid. *Science,* 373**,** 491-493.

ALWAN, N. A. 2022. Lessons from Long COVID: working with patients to design better research. *Nat Rev Immunol,* 22**,** 201-202.

ANDERSON, M., FORMAN, R. & MOSSIALOS, E. 2021. Navigating the role of the EU Health Emergency Preparedness and Response Authority (HERA) in Europe and beyond. *Lancet Reg Health Eur,* 9**,** 100203.

ARJUN, M. C., SINGH, A. K., PAL, D., DAS, K., GAJJALA, A., VENKATESHAN, M., MISHRA, B., PATRO, B. K., MOHAPATRA, P. R. & SUBBA, S. H. 2022. Prevalence, characteristics, and predictors of Long COVID among diagnosed cases of COVID-19. *medRxiv***,** 2022.01.04.21268536.

ARNOLD, D. T., HAMILTON, F. W., MILNE, A., MORLEY, A. J., VINER, J., ATTWOOD, M., NOEL, A., GUNNING, S., HATRICK, J., HAMILTON, S., ELVERS, K. T., HYAMS, C., BIBBY, A., MORAN, E., ADAMALI, H. I., DODD, J. W., MASKELL, N. A. & BARRATT, S. L. 2021. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax,* 76**,** 399-401.

ARROLL, B., GOODYEAR-SMITH, F., CRENGLE, S., GUNN, J., KERSE, N., FISHMAN, T., FALLOON, K. & HATCHER, S. 2010. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. *Annals of Family Medicine,* 8**,** 348-353.

AYOUBKHANI, D., BOSWORTH, M. L., KING, S., POUWELS, K. B., GLICKMAN, M., NAFILYAN, V., ZACCARDI, F., KHUNTI, K., ALWAN, N. A. & WALKER, A. S. 2022a. Risk of Long Covid in people infected with SARS-CoV-2 after two doses of a COVID-19 vaccine: community-based, matched cohort study. *medRxiv***,** 2022.02.23.22271388.

AYOUBKHANI, D., BOSWORTH, M. L., KING, S., POUWELS, K. B., GLICKMAN, M., NAFILYAN, V., ZACCARDI, F., KHUNTI, K., ALWAN, N. A. & WALKER, A. S. 2022b. Risk of Long Covid in people infected with SARS-CoV-2 after two doses of a COVID-19 vaccine: community-based, matched cohort study. *Open Forum Infectious Diseases*.

AZZOLINI, E., LEVI, R., SARTI, R., POZZI, C., MOLLURA, M., MANTOVANI, A. & RESCIGNO, M. 2022. Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers. *JAMA,* 328**,** 676-678.

BAI, F., TOMASONI, D., FALCINELLA, C., BARBANOTTI, D., CASTOLDI, R., MULÈ, G., AUGELLO, M., MONDATORE, D., ALLEGRINI, M., CONA, A., TESORO, D., TAGLIAFERRI, G., VIGANÒ, O., SUARDI, E., TINCATI, C., BERINGHELI, T., VARISCO, B., BATTISTINI, C. L., PISCOPO, K., VEGNI, E., TAVELLI, A., TERZONI, S., MARCHETTI, G. & MONFORTE, A. D. A. 2022. Female gender is associated with long COVID syndrome: a prospective cohort study. *Clinical Microbiology and Infection,* 28**,** 611.e9-611.e16.

BALLERING, A. V., VAN ZON, S. K. R., OLDE HARTMAN, T. C. & ROSMALEN, J. G. M. 2022. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet,* 400**,** 452-461.

BARNETT, K., MERCER, S. W., NORBURY, M., WATT, G., WYKE, S. & GUTHRIE, B. 2012. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet,* 380**,** 37-43.

BARNOMBUDSMANNENS. 2021. *COVID-19-pandemins konsekvenser för barn,* [Online]. Stockholm. Available: https://www.barnombudsmannen.se/globalassets/dokument/publikationer/barnombudsmannens-rapport---covid-19-pandemins-konsekvenser-for-barn-slutredovisning-av-regeringsuppdrag_.pdf [Accessed 28th November 2022].

BENNETT, J. E., DOLIN, R. & BLASER, M. J. 2020. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, Elsevier Health Sciences.

BERGAMASCHI, L., MESCIA, F., TURNER, L., HANSON, A. L., KOTAGIRI, P., DUNMORE, B. J., RUFFIEUX, H., DE SA, A., HUHN, O., MORGAN, M. D., GERBER, P. P., WILLS, M. R., BAKER, S., CALERO-NIETO, F. J., DOFFINGER, R., DOUGAN, G., ELMER, A., GOODFELLOW, I. G., GUPTA, R. K., HOSMILLO, M., HUNTER, K., KINGSTON, N., LEHNER, P. J., MATHESON, N. J., NICHOLSON, J. K., PETRUNKINA, A. M., RICHARDSON, S., SAUNDERS, C., THAVENTHIRAN, J. E. D., TOONEN, E. J. M., WEEKES, M. P., GÖTTGENS, B., TOSHNER, M., HESS, C., BRADLEY, J. R., LYONS, P. A. & SMITH, K. G. C. 2021. Longitudinal analysis reveals that delayed bystander CD8+ T cell activation and early immune pathology distinguish severe COVID-19 from mild disease. *Immunity,* 54**,** 1257-1275.e8.

BEYERSTEDT, S., CASARO, E. B. & RANGEL É, B. 2021. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur J Clin Microbiol Infect Dis,* 40**,** 905-919.

BHATTACHARYA, A., COLLIN, S. M., STIMSON, J., THELWALL, S., NSONWU, O., GERVER, S., ROBOTHAM, J., WILCOX, M., HOPKINS, S. & HOPE, R. 2021. Healthcare-associated COVID-19 in England: A national data linkage study. *Journal of Infection,* 83**,** 565-572.

BJORNEVIK, K., CORTESE, M., HEALY, B. C., KUHLE, J., MINA, M. J., LENG, Y., ELLEDGE, S. J., NIEBUHR, D. W., SCHER, A. I., MUNGER, K. L. & ASCHERIO, A. 2022. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science,* 375**,** 296-301.

BOLDOGH, I., ALBRECHT, T. & PORTER, D. D. 1996. Persistent Viral Infections. *In:* BARON, S. (ed.) *Medical Microbiology.* Galveston (TX): University of Texas Medical Branch at Galveston

Copyright © 1996, The University of Texas Medical Branch at Galveston.

BROOKS, E. F. & BHATT, A. S. 2021. The gut microbiome: a missing link in understanding the gastrointestinal manifestations of COVID-19? *Cold Spring Harb Mol Case Stud,* 7.

BROWN, D. A. & O'BRIEN, K. K. 2021. Conceptualising Long COVID as an episodic health condition. *BMJ Global Health,* 6**,** e007004.

BURNS, A. 2022. *What are the Implications of Long COVID for Employment and Health Coverage?* [Online]. Kaiser Family Foundation. Available: https://www.kff.org/policy-watch/what-are-the-implications-of-long-covid-for-employment-and-health-coverage/ [Accessed 8th September 2022].

BUSSE, R. 2004. Disease management programs in Germany's statutory health insurance system. *Health affairs,* 23**,** 56-67.
CALLARD, F. & PEREGO, E. 2021. How and why patients made Long Covid. *Soc Sci Med,* 268**,** 113426.
CARSON, G. 2021. Research priorities for Long Covid: refined through an international multi-stakeholder forum. *BMC Med,* 19**,** 84.
CARTER, B., COLLINS, J. T., BARLOW-PAY, F., RICKARD, F., BRUCE, E., VERDURI, A., QUINN, T. J., MITCHELL, E., PRICE, A., VILCHES-MORAGA, A., STECHMAN, M. J., SHORT, R., EINARSSON, A., BRAUDE, P., MOUG, S., MYINT, P. K., HEWITT, J., PEARCE, L. & MCCARTHY, K. 2020. Nosocomial COVID-19 infection: examining the risk of mortality. The COPE-Nosocomial Study (COVID in Older PEople). *J Hosp Infect,* 106**,** 376-384.
CENTERS FOR DISEASE CONTROL. 2022. *Event-based Surveillance* [Online]. Available: https://www.cdc.gov/globalhealth/healthprotection/gddopscenter/how.html [Accessed 4th April 2022].
CENTERS FOR DISEASE CONTROL AND PREVENTION. 2022. *Long COVID or Post-COVID Conditions* [Online]. Available: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html#:~:text=behind%20Long%20COVID-,Symptoms,away%20or%20come%20back%20again. [Accessed 13th May 2022].
CERVIA, C., ZURBUCHEN, Y., TAESCHLER, P., BALLOUZ, T., MENGES, D., HASLER, S., ADAMO, S., RAEBER, M. E., BÄCHLI, E., RUDIGER, A., STÜSSI-HELBLING, M., HUBER, L. C., NILSSON, J., HELD, U., PUHAN, M. A. & BOYMAN, O. 2022. Immunoglobulin signature predicts risk of post-acute COVID-19 syndrome. *Nature Communications,* 13**,** 446.
CHANG, S. E., FENG, A., MENG, W., APOSTOLIDIS, S. A., MACK, E., ARTANDI, M., BARMAN, L., BENNETT, K., CHAKRABORTY, S., CHANG, I., CHEUNG, P., CHINTHRAJAH, S., DHINGRA, S., DO, E., FINCK, A., GAANO, A., GEßNER, R., GIANNINI, H. M., GONZALEZ, J., GREIB, S., GÜNDISCH, M., HSU, A. R., KUO, A., MANOHAR, M., MAO, R., NEELI, I., NEUBAUER, A., ONIYIDE, O., POWELL, A. E., PURI, R., RENZ, H., SCHAPIRO, J., WEIDENBACHER, P. A., WITTMAN, R., AHUJA, N., CHUNG, H. R., JAGANNATHAN, P., JAMES, J. A., KIM, P. S., MEYER, N. J., NADEAU, K. C., RADIC, M., ROBINSON, W. H., SINGH, U., WANG, T. T., WHERRY, E. J., SKEVAKI, C., LUNING PRAK, E. T. & UTZ, P. J. 2021. New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat Commun,* 12**,** 5417.
CHERTOW, D., STEIN, S., RAMELLI, S., GRAZIOLI, A., CHUNG, J.-Y., SINGH, M., YINDA, C. K., WINKLER, C., DICKEY, J. & YLAYA, K. 2021. SARS-CoV-2 infection and persistence throughout the human body and brain. *ResearchSquare***,** DOI: 10.21203/rs.3.rs-1139035/v1.
CHEUNG, C. C. L., GOH, D., LIM, X., TIEN, T. Z., LIM, J. C. T., LEE, J. N., TAN, B., TAY, Z. E. A., WAN, W. Y., CHEN, E. X., NERURKAR, S. N., LOONG, S., CHEOW, P. C., CHAN, C. Y., KOH, Y. X., TAN, T. T., KALIMUDDIN, S., TAI, W. M. D., NG, J. L., LOW, J. G., YEONG, J. & LIM, K. H. 2022. Residual SARS-CoV-2 viral antigens detected in GI and hepatic tissues from five recovered patients with COVID-19. *Gut,* 71**,** 226-229.
CHOPRA, V., FLANDERS, S. A., O'MALLEY, M., MALANI, A. N. & PRESCOTT, H. C. 2021. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. *Ann Intern Med,* 174**,** 576-578.
CHOUTKA, J., JANSARI, V., HORNIG, M. & IWASAKI, A. 2022. Unexplained post-acute infection syndromes. *Nature Medicine,* 28**,** 911-923.
CONWAY MORRIS, A., SHARROCKS, K., BOUSFIELD, R., KERMACK, L., MAES, M., HIGGINSON, E., FORREST, S., PEREIRA-DIAS, J., CORMIE, C., OLD, T., BROOKS, S., HAMED, I., KOENIG, A., TURNER, A., WHITE, P., FLOTO, R. A., DOUGAN, G., GKRANIA-KLOTSAS, E., GOULIOURIS, T., BAKER, S. & NAVAPURKAR, V. 2021. The removal of airborne SARS-CoV-2 and other microbial bioaerosols by air filtration on COVID-19 surge units. *Clin Infect Dis*.
CROOK, H., RAZA, S., NOWELL, J., YOUNG, M. & EDISON, P. 2021. Long covid—mechanisms, risk factors, and management. *BMJ,* 374**,** n1648.

CUTLER, D. M. 2022. The Costs of Long COVID. *JAMA Health Forum,* 3**,** e221809-e221809.

DAHER, A., BALFANZ, P., CORNELISSEN, C., MÜLLER, A., BERGS, I., MARX, N., MÜLLER-WIELAND, D., HARTMANN, B., DREHER, M. & MÜLLER, T. 2020. Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. *Respir Med,* 174**,** 106197.

DAVIES, M. 2022. Long covid patients travel abroad for expensive and experimental "blood washing". *BMJ,* 378**,** o1671.

DAVIS, H. E., ASSAF, G. S., MCCORKELL, L., WEI, H., LOW, R. J., RE'EM, Y., REDFIELD, S., AUSTIN, J. P. & AKRAMI, A. 2021. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine,* 38**,** 101019.

DEL RIO, C., COLLINS, L. F. & MALANI, P. 2020. Long-term Health Consequences of COVID-19. *JAMA,* 324**,** 1723-1724.

DIALLO, A., TRØSEID, M., SIMENSEN, V. C., BOSTON, A., DEMOTES, J., OLSEN, I. C., CHUNG, F., PAIVA, J. A., HITES, M., ADER, F., ARRIBAS, J. R., BARATT-DUE, A., MELIEN, Ø., TACCONELLI, E., STAUB, T., GREIL, R., TSIODRAS, S., BRIEL, M., ESPEROU, H., MENTRÉ, F., EUSTACE, J., SAILLARD, J., DELMAS, C., LEMESTRE, S., DUMOUSSEAUX, M., COSTAGLIOLA, D., RØTTINGEN, J. A. & YAZDANPANAH, Y. 2022. Accelerating clinical trial implementation in the context of the COVID-19 pandemic: challenges, lessons learned and recommendations from DisCoVeRy and the EU-SolidAct EU response group. *Clin Microbiol Infect,* 28**,** 1-5.

DOMINGO, F. R., WADDELL, L. A., CHEUNG, A. M., COOPER, C. L., BELCOURT, V. J., ZUCKERMANN, A. M. E., CORRIN, T., AHMAD, R., BOLAND, L., LAPRISE, C., IDZERDA, L., KHAN, A., MORISSETTE, K. & GARCIA, A. J. 2021. Prevalence of long-term effects in individuals diagnosed with COVID-19: an updated living systematic review. *medRxiv***,** 2021.06.03.21258317.

EARNSHAW, V. A., SMITH, L. R., CHAUDOIR, S. R., AMICO, K. R. & COPENHAVER, M. M. 2013. HIV stigma mechanisms and well-being among PLWH: a test of the HIV stigma framework. *AIDS Behav,* 17**,** 1785-95.

EUROMOMO. 2022. Available: https://www.euromomo.eu/ [Accessed 2nd August 2022].

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL. 2022. *Prevalence of post COVID-19 condition symptoms: a systematic review and meta-analysis of cohort study data, stratified by recruitment setting, Technical report,* [Online]. Available: https://www.ecdc.europa.eu/sites/default/files/documents/Prevalence-post-COVID-19-condition-symptoms.pdf [Accessed 28th November 2022].

EUROPEAN COMMISSION. 2020. *First "ERAvsCorona" action plan: short-term coordinated research and innovation actions* [Online]. Available: https://ec.europa.eu/info/files/first-eravscorona-action-plan-short-term-coordinated-research-and-innovation-actions_en [Accessed 2nd August 2022].

EUROPEAN COMMISSION. 2022. *Member States, workers and employers agree on the need to recognise COVID-19 as an occupational disease* [Online]. Available: https://ec.europa.eu/commission/presscorner/detail/en/IP_22_3117 [Accessed 29th July 2022].

EUROPEAN HEALTH EXAMINATION SURVEY. 2022. *National health examination surveys in Europe* [Online]. Available: https://ehes.info/national_hes.htm# [Accessed 27th September 2022].

EUROPEAN MEDICINES AGENCY. 2022a. *Availability of medicines during COVID-19 pandemic* [Online]. Available: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/availability-medicines-during-covid-19-pandemic#critical-medicines-for-covid-19-(new)-section [Accessed 28th November 2022].

EUROPEAN MEDICINES AGENCY. 2022b. *COVID-19: latest updates* [Online]. Available: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/covid-19-latest-updates [Accessed 1st August 2022].

EUROPEAN MEDICINES AGENCY. 2022c. *Patient experience data in EU medicines development and regulatory decision-making.* [Online]. Available:

https://www.ema.europa.eu/en/documents/other/executive-summary-patient-experience-data-eu-medicines-development-regulatory-decision-making_en.pdf [Accessed 28th November 2022].

EUROPEAN MEDICINES AGENCY. 2022d. *Scientific advice and protocol assistance* [Online]. Available: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance [Accessed 28th November 2022].

EUROPEAN SOCIAL SURVEY. 2022. Available: https://www.europeansocialsurvey.org/ [Accessed 27th September 2022].

EUROSTAT. 2022. *EUROPEAN HEALTH INTERVIEW SURVEY (EHIS)* [Online]. Available: https://ec.europa.eu/eurostat/web/microdata/european-health-interview-survey [Accessed 27th September 2022].

EVANS, R. A., LEAVY, O. C., RICHARDSON, M., ELNEIMA, O., MCCAULEY, H. J. C., SHIKOTRA, A., SINGAPURI, A., SERENO, M., SAUNDERS, R. M., HARRIS, V. C., HOUCHEN-WOLLOFF, L., AUL, R., BEIRNE, P., BOLTON, C. E., BROWN, J. S., CHOUDHURY, G., DIAR-BAKERLY, N., EASOM, N., ECHEVARRIA, C., FULD, J., HART, N., HURST, J., JONES, M. G., PAREKH, D., PFEFFER, P., RAHMAN, N. M., ROWLAND-JONES, S. L., SHAH, A. M., WOOTTON, D. G., CHALDER, T., DAVIES, M. J., DE SOYZA, A., GEDDES, J. R., GREENHALF, W., GREENING, N. J., HEANEY, L. G., HELLER, S., HOWARD, L. S., JACOB, J., JENKINS, R. G., LORD, J. M., MAN, W. D. C., MCCANN, G. P., NEUBAUER, S., OPENSHAW, P. J. M., PORTER, J. C., ROWLAND, M. J., SCOTT, J. T., SEMPLE, M. G., SINGH, S. J., THOMAS, D. C., TOSHNER, M., LEWIS, K. E., THWAITES, R. S., BRIGGS, A., DOCHERTY, A. B., KERR, S., LONE, N. I., QUINT, J., SHEIKH, A., THORPE, M., ZHENG, B., CHALMERS, J. D., HO, L. P., HORSLEY, A., MARKS, M., POINASAMY, K., RAMAN, B., HARRISON, E. M., WAIN, L. V., BRIGHTLING, C. E., ABEL, K., ADAMALI, H., ADELOYE, D., ADEYEMI, O., ADREGO, R., AGUILAR JIMENEZ, L. A., AHMAD, S., AHMAD HAIDER, N., AHMED, R., AHWIRENG, N., AINSWORTH, M., AL-SHEKLLY, B., ALAMOUDI, A., ALI, M., ALJAROOF, M., ALL, A. M., ALLAN, L., ALLEN, R. J., ALLERTON, L., ALLSOP, L., ALMEIDA, P., ALTMANN, D., ALVAREZ CORRAL, M., AMOILS, S., ANDERSON, D., ANTONIADES, C., ARBANE, G., ARIAS, A., ARMOUR, C., et al. 2022. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *The Lancet Respiratory Medicine*.

EVANS, R. A., MCAULEY, H., HARRISON, E. M., SHIKOTRA, A., SINGAPURI, A., SERENO, M., ELNEIMA, O., DOCHERTY, A. B., LONE, N. I., LEAVY, O. C., DAINES, L., BAILLIE, J. K., BROWN, J. S., CHALDER, T., DE SOYZA, A., DIAR BAKERLY, N., EASOM, N., GEDDES, J. R., GREENING, N. J., HART, N., HEANEY, L. G., HELLER, S., HOWARD, L., HURST, J. R., JACOB, J., JENKINS, R. G., JOLLEY, C., KERR, S., KON, O. M., LEWIS, K., LORD, J. M., MCCANN, G. P., NEUBAUER, S., OPENSHAW, P. J. M., PAREKH, D., PFEFFER, P., RAHMAN, N. M., RAMAN, B., RICHARDSON, M., ROWLAND, M., SEMPLE, M. G., SHAH, A. M., SINGH, S. J., SHEIKH, A., THOMAS, D., TOSHNER, M., CHALMERS, J. D., HO, L.-P., HORSLEY, A., MARKS, M., POINASAMY, K., WAIN, L. V., BRIGHTLING, C. E., ABEL, K., ADAMALI, H., ADELOYE, D., ADEYEMI, O., ADEYEMI, F., AHMAD, S., AHMED, R., AINSWORTH, M., ALAMOUDI, A., ALJAROOF, M., ALLAN, L., ALLEN, R., ALLI, A., AL-SHEKLLY, B., ALTMANN, D., ANDERSON, D., ANDREWS, M., ANGYAL, A., ANTONIADES, C., ARBANE, G., ARMOUR, C., ARMSTRONG, N., ARMSTRONG, L., ARNOLD, H., ARNOLD, D., ASHWORTH, M., ASHWORTH, A., ASSEFA-KEBEDE, H., ATKIN, P., ATKINS, H., ATKINS, A., AUL, R., AVRAM, C., BAGGOTT, R., BAGULEY, D., BAILLIE, J. K., BAIN, S., BAKALI, M., BAKAU, M., BALDRY, E., BALDWIN, D., BALLARD, C., BAMBROUGH, J., BARKER, R. E., BARRATT, S., BARRETT, F., BASU, N., et al. 2021. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *The Lancet Respiratory Medicine,* 9**,** 1275-1287.

EXPERT PANEL ON EFFECTIVE WAYS OF INVESTING IN HEALTH. 2019. *Task shifting and health system design* [Online]. Brussels: European Commission. Available:

https://health.ec.europa.eu/publications/task-shifting-and-health-system-design_en [Accessed 29th July 2022].
EXPERT PANEL ON EFFECTIVE WAYS OF INVESTING IN HEALTH. 2021a. *Public procurement in healthcare systems* [Online]. Brussels: European Commission. Available: https://health.ec.europa.eu/publications/public-procurement-healthcare-systems-0_en [Accessed 29th July 2022].
EXPERT PANEL ON EFFECTIVE WAYS OF INVESTING IN HEALTH. 2021b. *Supporting mental health of health workforce and other essential workers* [Online]. Brussels: European Commission. Available: https://health.ec.europa.eu/publications/supporting-mental-health-health-workforce-and-other-essential-workers-0_en [Accessed 29th July 2022].
FANAROFF, A. C., GARCIA, S. & GIRI, J. 2021. Myocardial Infarction During the COVID-19 Pandemic. *Jama,* 326**,** 1916-1918.
FROEHLICH, L., HATTESOHL, D. B., COTLER, J., JASON, L. A., SCHEIBENBOGEN, C. & BEHRENDS, U. 2022. Causal attributions and perceived stigma for myalgic encephalomyelitis/chronic fatigue syndrome. *J Health Psychol,* 27**,** 2291-2304.
FUCHS, S., HENSCHKE, C., BLÜMEL, M. & BUSSE, R. 2014. Disease management programs for type 2 diabetes in Germany: a systematic literature review evaluating effectiveness. *Dtsch Arztebl Int,* 111**,** 453-63.
GARCIA-GALLO, E., MERSON, L., KENNON, K., KELLY, S., CITARELLA, B. W., FRYER, D. V., SHRAPNEL, S., LEE, J., DUQUE, S., FUENTES, Y. V., BALAN, V., SMITH, S., WEI, J., GONÇALVES, B. P., RUSSELL, C. D., SIGFRID, L., DAGENS, A., OLLIARO, P. L., BARUCH, J., KARTSONAKI, C., DUNNING, J., ROJEK, A., RASHAN, A., BEANE, A., MURTHY, S. & REYES, L. F. 2022. ISARIC-COVID-19 dataset: A Prospective, Standardized, Global Dataset of Patients Hospitalized with COVID-19. *Sci Data,* 9**,** 454.
GARRIGUES, E., JANVIER, P., KHERABI, Y., LE BOT, A., HAMON, A., GOUZE, H., DOUCET, L., BERKANI, S., OLIOSI, E., MALLART, E., CORRE, F., ZARROUK, V., MOYER, J. D., GALY, A., HONSEL, V., FANTIN, B. & NGUYEN, Y. 2020. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect,* 81**,** e4-e6.
GÓMEZ-OCHOA, S. A., FRANCO, O. H., ROJAS, L. Z., RAGUINDIN, P. F., ROA-DÍAZ, Z. M., WYSSMANN, B. M., GUEVARA, S. L. R., ECHEVERRÍA, L. E., GLISIC, M. & MUKA, T. 2021. COVID-19 in Health-Care Workers: A Living Systematic Review and Meta-Analysis of Prevalence, Risk Factors, Clinical Characteristics, and Outcomes. *Am J Epidemiol,* 190**,** 161-175.
GREENHALGH, T., SIVAN, M., DELANEY, B., EVANS, R. & MILNE, R. 2022. Long covid—an update for primary care. *BMJ,* 378**,** e072117.
GROFF, D., SUN, A., SSENTONGO, A. E., BA, D. M., PARSONS, N., POUDEL, G. R., LEKOUBOU, A., OH, J. S., ERICSON, J. E., SSENTONGO, P. & CHINCHILLI, V. M. 2021. Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection: A Systematic Review. *JAMA Network Open,* 4**,** e2128568-e2128568.
HAUTE AUTORITÉ DE SANTÉ. 2021. *Covid long : les recommandations de la Haute Autorité de santé. Service-Public.fr. 16* [Online]. Available: https://www.service-public.fr/particuliers/actualites/A14678 [Accessed 13th May 2022].
HERDMAN, M., GUDEX, C., LLOYD, A., JANSSEN, M., KIND, P., PARKIN, D., BONSEL, G. & BADIA, X. 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res,* 20**,** 1727-36.
HERNANDEZ-RONQUILLO, L., MOIEN-AFSHARI, F., KNOX, K., BRITZ, J. & TELLEZ-ZENTENO, J. F. 2011. How to measure fatigue in epilepsy? The validation of three scales for clinical use. *Epilepsy Res,* 95**,** 119-29.
HICKIE, I., DAVENPORT, T., WAKEFIELD, D., VOLLMER-CONNA, U., CAMERON, B., VERNON, S. D., REEVES, W. C. & LLOYD, A. 2006. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *Bmj,* 333**,** 575.
HUANG, L., LI, X., GU, X., ZHANG, H., REN, L., GUO, L., LIU, M., WANG, Y., CUI, D., WANG, Y., ZHANG, X., SHANG, L., ZHONG, J., WANG, X., WANG, J. & CAO, B. 2022. Health outcomes in people 2 years after surviving hospitalisation with

COVID-19: a longitudinal cohort study. *The Lancet Respiratory Medicine,* 10**,** 863-876.

HUANG, Y., PINTO, M. D., BORELLI, J. L., MEHRABADI, M. A., ABRIHIM, H., DUTT, N., LAMBERT, N., NURMI, E. L., CHAKRABORTY, R., RAHMANI, A. M. & DOWNS, C. A. 2021. COVID Symptoms, Symptom Clusters, and Predictors for Becoming a Long-Hauler: Looking for Clarity in the Haze of the Pandemic. *medRxiv*.

INSTITUTE FOR FISCAL STUDIES. 2022. *Long COVID and the labour market* [Online]. Available: https://ifs.org.uk/uploads/BN346-Long-COVID-and-the-labour-market.pdf [Accessed 29th July 2022].

IVERSON, G. L., CONNORS, E. J., MARSH, J. & TERRY, D. P. 2021. Examining Normative Reference Values and Item-Level Symptom Endorsement for the Quality of Life in Neurological Disorders (Neuro-QoL™) v2.0 Cognitive Function-Short Form. *Archives of Clinical Neuropsychology,* 36**,** 126-134.

JACKSON, C. B., FARZAN, M., CHEN, B. & CHOE, H. 2022. Mechanisms of SARS-CoV-2 entry into cells. *Nature Reviews Molecular Cell Biology,* 23**,** 3-20.

JACOBS, L. G., GOURNA PALEOUDIS, E., LESKY-DI BARI, D., NYIRENDA, T., FRIEDMAN, T., GUPTA, A., RASOULI, L., ZETKULIC, M., BALANI, B., OGEDEGBE, C., BAWA, H., BERROL, L., QURESHI, N. & ASCHNER, J. L. 2020. Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. *PLoS One,* 15**,** e0243882.

JANDHYALA, R. 2021. Design, validation and implementation of the post-acute (long) COVID-19 quality of life (PAC-19QoL) instrument. *Health Qual Life Outcomes,* 19**,** 229.

JASON, L. & MIRIN, A. 2021. Updating the National Academy of Medicine ME/CFS prevalence and economic impact figures to account for population growth and inflation. *Fatigue: Biomedicine, Health & Behavior,* 9**,** 9-13.

JIANG, L., TANG, K., LEVIN, M., IRFAN, O., MORRIS, S. K., WILSON, K., KLEIN, J. D. & BHUTTA, Z. A. 2020. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis,* 20**,** e276-e288.

JONES, R., DAVIS, A., STANLEY, B., JULIOUS, S., RYAN, D., JACKSON, D. J., HALPIN, D. M. G., HICKMAN, K., PINNOCK, H., QUINT, J. K., KHUNTI, K., HEANEY, L. G., OLIVER, P., SIDDIQUI, S., PAVORD, I., JONES, D. H. M., HYLAND, M., RITCHIE, L., YOUNG, P., MEGAW, T., DAVIS, S., WALKER, S., HOLGATE, S., BEECROFT, S., KEMPPINEN, A., APPIAGYEI, F., ROBERTS, E.-J., PRESTON, M., HARDJOJO, A., CARTER, V., VAN MELLE, M. & PRICE, D. 2021. Risk Predictors and Symptom Features of Long COVID Within a Broad Primary Care Patient Population Including Both Tested and Untested Patients. *Pragmatic and observational research,* 12**,** 93-104.

KELL, D. B., LAUBSCHER, G. J. & PRETORIUS, E. 2022. A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications. *Biochem J,* 479**,** 537-559.

KINGSTONE, T., TAYLOR, A. K., O'DONNELL, C. A., ATHERTON, H., BLANE, D. N. & CHEW-GRAHAM, C. A. 2020. Finding the 'right' GP: a qualitative study of the experiences of people with long-COVID. *BJGP Open,* 4.

KLEIN, J., WOOD, J., JAYCOX, J., LU, P., DHODAPKAR, R. M., GEHLHAUSEN, J. R., TABACHNIKOVA, A., TABACOF, L., MALIK, A. A., KAMATH, K., GREENE, K., MONTEIRO, V. S., PEÑA-HERNANDEZ, M., MAO, T., BHATTACHARJEE, B., TAKAHASHI, T., LUCAS, C., SILVA, J., MCCARTHY, D., BREYMAN, E., TOSTO-MANCUSO, J., DAI, Y., PEROTTI, E., AKDUMAN, K., TZENG, T. J., XU, L., YILDIRIM, I., KRUMHOLZ, H. M., SHON, J., MEDZHITOV, R., OMER, S. B., VAN DIJK, D., RING, A. M., PUTRINO, D. & IWASAKI, A. 2022. Distinguishing features of Long COVID identified through immune profiling. *medRxiv***,** 2022.08.09.22278592.

KLOK, F. A., BOON, G., BARCO, S., ENDRES, M., GEELHOED, J. J. M., KNAUSS, S., REZEK, S. A., SPRUIT, M. A., VEHRESCHILD, J. & SIEGERINK, B. 2020. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. *Eur Respir J,* 56.

KOMPANIYETS, L., BULL-OTTERSON, L., BOEHMER, T. K., BACA, S., ALVAREZ, P., HONG, K., HSU, J., HARRIS, A. M., GUNDLAPALLI, A. V. & SAYDAH, S. 2022. Post-COVID-19 Symptoms and Conditions Among Children and Adolescents - United States, March 1, 2020-January 31, 2022. *MMWR Morb Mortal Wkly Rep,* 71**,** 993-999.

LADDS, E., RUSHFORTH, A., WIERINGA, S., TAYLOR, S., RAYNER, C., HUSAIN, L. & GREENHALGH, T. 2020. Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft quality principles for services. *BMC Health Services Research,* 20**,** 1144.

LADDS, E., RUSHFORTH, A., WIERINGA, S., TAYLOR, S., RAYNER, C., HUSAIN, L. & GREENHALGH, T. 2021. Developing services for long COVID: lessons from a study of wounded healers. *Clinical Medicine,* 21**,** 59.

LAWTON, T. & ALWAN, N. A. 2022. The UK COVID-19 Inquiry must examine the foundations of pandemic decision making. *The Lancet,* 400**,** 1087-1089.

LI HI SHING, S., CHIPIKA, R. H., FINEGAN, E., MURRAY, D., HARDIMAN, O. & BEDE, P. 2019. Post-polio Syndrome: More Than Just a Lower Motor Neuron Disease. *Frontiers in neurology,* 10**,** 773-773.

LIU, Q., MAK, J. W. Y., SU, Q., YEOH, Y. K., LUI, G. C.-Y., NG, S. S. S., ZHANG, F., LI, A. Y. L., LU, W., HUI, D. S.-C., CHAN, P. K. S., CHAN, F. K. L. & NG, S. C. 2022. Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. *Gut,* 71**,** 544.

LOPEZ-LEON, S., WEGMAN-OSTROSKY, T., DEL VALLE, C. A., PERELMAN, C., SEPULVEDA, R., REBOLLEDO, P. A., CUAPIO, A. & VILLAPOL, S. 2022. Long COVID in Children and Adolescents: A Systematic Review and Meta-analyses. *medRxiv***,** 2022.03.10.22272237.

LOPEZ-LEON, S., WEGMAN-OSTROSKY, T., PERELMAN, C., SEPULVEDA, R., REBOLLEDO, P. A., CUAPIO, A. & VILLAPOL, S. 2021. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Scientific Reports,* 11**,** 16144.

LOWENSTEIN, F. 2022. *How Managers Can Support Employees With Long COVID* [Online]. Available: https://sloanreview.mit.edu/article/how-managers-can-support-employees-with-long-covid/ [Accessed 27th July 2022].

LUMLEY, S. F., CONSTANTINIDES, B., SANDERSON, N., RODGER, G., STREET, T. L., SWANN, J., CHAU, K. K., O'DONNELL, D., WARREN, F., HOOSDALLY, S., O'DONNELL, A.-M., WALKER, T. M., STOESSER, N. E., BUTCHER, L., PETO, T. E. A., CROOK, D. W., JEFFERY, K., MATTHEWS, P. C. & EYRE, D. W. 2021. Epidemiological data and genome sequencing reveals that nosocomial transmission of SARS-CoV-2 is underestimated and mostly mediated by a small number of highly infectious individuals. *Journal of Infection,* 83**,** 473-482.

MA, Y. F., LI, W., DENG, H. B., WANG, L., WANG, Y., WANG, P. H., BO, H. X., CAO, J., WANG, Y., ZHU, L. Y., YANG, Y., CHEUNG, T., NG, C. H., WU, X. & XIANG, Y. T. 2020. Prevalence of depression and its association with quality of life in clinically stable patients with COVID-19. *J Affect Disord,* 275**,** 145-148.

MAGNUS, P., GUNNES, N., TVEITO, K., BAKKEN, I. J., GHADERI, S., STOLTENBERG, C., HORNIG, M., LIPKIN, W. I., TROGSTAD, L. & HÅBERG, S. E. 2015. Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine. *Vaccine,* 33**,** 6173-7.

MALIK, P., PATEL, K., PINTO, C., JAISWAL, R., TIRUPATHI, R., PILLAI, S. & PATEL, U. 2022. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol,* 94**,** 253-262.

MALLAPATY, S. 2022. COVID jabs for kids: they're safe and they work - so why is uptake so patchy? *Nature,* 610**,** 246-248.

MANFREDO VIEIRA, S., HILTENSPERGER, M., KUMAR, V., ZEGARRA-RUIZ, D., DEHNER, C., KHAN, N., COSTA, F. R. C., TINIAKOU, E., GREILING, T., RUFF, W., BARBIERI, A., KRIEGEL, C., MEHTA, S. S., KNIGHT, J. R., JAIN, D., GOODMAN, A. L. & KRIEGEL, M. A. 2018. Translocation of a gut pathobiont drives autoimmunity in mice and humans. *Science,* 359**,** 1156-1161.

MAYOR, N., TSANG, R., JOY, M., HOBBS, F. D. R. & DE LUSIGNAN, S. 2021. Long covid: coding is caring. *BMJ,* 373**,** n1262.
MCGRODER, C. F., ZHANG, D., CHOUDHURY, M. A., SALVATORE, M. M., SOUZA, B. M., HOFFMAN, E. A., WEI, Y., BALDWIN, M. R. & GARCIA, C. K. 2021. Pulmonary fibrosis 4 months after COVID-19 is associated with severity of illness and blood leucocyte telomere length. *Thorax,* 76**,** 1242.
MCMANIMEN, S. L., MCCLELLAN, D., STOOTHOFF, J. & JASON, L. A. 2018. Effects of unsupportive social interactions, stigma, and symptoms on patients with myalgic encephalomyelitis and chronic fatigue syndrome. *Journal of Community Psychology,* 46**,** 959-971.
MEHANDRU, S. & MERAD, M. 2022. Pathological sequelae of long-haul COVID. *Nat Immunol,* 23**,** 194-202.
MERKLER, A. E., PARIKH, N. S., MIR, S., GUPTA, A., KAMEL, H., LIN, E., LANTOS, J., SCHENCK, E. J., GOYAL, P., BRUCE, S. S., KAHAN, J., LANSDALE, K. N., LEMOSS, N. M., MURTHY, S. B., STIEG, P. E., FINK, M. E., IADECOLA, C., SEGAL, A. Z., CUSICK, M., CAMPION, T. R., JR., DIAZ, I., ZHANG, C. & NAVI, B. B. 2020. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza. *JAMA Neurol,* 77**,** 1-7.
MEZA-TORRES, B., DELANEROLLE, G., OKUSI, C., MAYOR, N., ANAND, S., MACARTNEY, J., GATENBY, P., GLAMPSON, B., CHAPMAN, M., CURCIN, V., MAYER, E., JOY, M., GREENHALGH, T., DELANEY, B. & DE LUSIGNAN, S. 2022. Differences in Clinical Presentation With Long COVID After Community and Hospital Infection and Associations With All-Cause Mortality: English Sentinel Network Database Study. *JMIR public health and surveillance* [Online], 8. Available: http://europepmc.org/abstract/MED/35605170
https://doi.org/10.2196/37668
https://europepmc.org/articles/PMC9384859 [Accessed 2022/08//].
MICHELEN, M., MANOHARAN, L., ELKHEIR, N., CHENG, V., DAGENS, A., HASTIE, C., O'HARA, M., SUETT, J., DAHMASH, D., BUGAEVA, P., RIGBY, I., MUNBLIT, D., HARRISS, E., BURLS, A., FOOTE, C., SCOTT, J., CARSON, G., OLLIARO, P., SIGFRID, L. & STAVROPOULOU, C. 2021. Characterising long COVID: a living systematic review. *BMJ Glob Health,* 6.
MODIN, D., CLAGGETT, B., SINDET-PEDERSEN, C., LASSEN, M. C. H., SKAARUP, K. G., JENSEN, J. U. S., FRALICK, M., SCHOU, M., LAMBERTS, M., GERDS, T., FOSBØL, E. L., PHELPS, M., KRAGHOLM, K. H., ANDERSEN, M. P., KØBER, L., TORP-PEDERSEN, C., SOLOMON, S. D., GISLASON, G. & BIERING-SØRENSEN, T. 2020. Acute COVID-19 and the Incidence of Ischemic Stroke and Acute Myocardial Infarction. *Circulation,* 142**,** 2080-2082.
MORAWSKA, L., ALLEN, J., BAHNFLETH, W., BLUYSSEN, P. M., BOERSTRA, A., BUONANNO, G., CAO, J., DANCER, S. J., FLOTO, A., FRANCHIMON, F., GREENHALGH, T., HAWORTH, C., HOGELING, J., ISAXON, C., JIMENEZ, J. L., KURNITSKI, J., LI, Y., LOOMANS, M., MARKS, G., MARR, L. C., MAZZARELLA, L., MELIKOV, A. K., MILLER, S., MILTON, D. K., NAZAROFF, W., NIELSEN, P. V., NOAKES, C., PECCIA, J., PRATHER, K., QUEROL, X., SEKHAR, C., SEPPÄNEN, O., TANABE, S. I., TANG, J. W., TELLIER, R., THAM, K. W., WARGOCKI, P., WIERZBICKA, A. & YAO, M. 2021. A paradigm shift to combat indoor respiratory infection. *Science,* 372**,** 689-691.
MORENO-PÉREZ, O., MERINO, E., LEON-RAMIREZ, J. M., ANDRES, M., RAMOS, J. M., ARENAS-JIMÉNEZ, J., ASENSIO, S., SANCHEZ, R., RUIZ-TORREGROSA, P., GALAN, I., SCHOLZ, A., AMO, A., GONZÁLEZ-DELAALEJA, P., BOIX, V. & GIL, J. 2021. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *J Infect,* 82**,** 378-383.
MUNBLIT, D., NICHOLSON, T., AKRAMI, A., APFELBACHER, C., CHEN, J., DE GROOTE, W., DIAZ, J. V., GORST, S. L., HARMAN, N., KOKORINA, A., OLLIARO, P., PARR, C., PRELLER, J., SCHIESS, N., SCHMITT, J., SEYLANOVA, N., SIMPSON, F., TONG, A., NEEDHAM, D. M. & WILLIAMSON, P. R. 2022. A core outcome set for post-COVID-19 condition in adults for use in clinical practice and research: an international Delphi consensus study. *Lancet Respir Med,* 10**,** 715-724.

MYALL, A., PRICE, J. R., PEACH, R. L., ABBAS, M., MOOKERJEE, S., ZHU, N., AHMAD, I., MING, D., RAMZAN, F., TEIXEIRA, D., GRAF, C., WEIßE, A. Y., HARBARTH, S., HOLMES, A. & BARAHONA, M. 2022. Prediction of hospital-onset COVID-19 infections using dynamic networks of patient contact: an international retrospective cohort study. *The Lancet Digital Health,* 4**,** e573-e583.

NALBANDIAN, A., SEHGAL, K., GUPTA, A., MADHAVAN, M. V., MCGRODER, C., STEVENS, J. S., COOK, J. R., NORDVIG, A. S., SHALEV, D., SEHRAWAT, T. S., AHLUWALIA, N., BIKDELI, B., DIETZ, D., DER-NIGOGHOSSIAN, C., LIYANAGE-DON, N., ROSNER, G. F., BERNSTEIN, E. J., MOHAN, S., BECKLEY, A. A., SERES, D. S., CHOUEIRI, T. K., URIEL, N., AUSIELLO, J. C., ACCILI, D., FREEDBERG, D. E., BALDWIN, M., SCHWARTZ, A., BRODIE, D., GARCIA, C. K., ELKIND, M. S. V., CONNORS, J. M., BILEZIKIAN, J. P., LANDRY, D. W. & WAN, E. Y. 2021. Post-acute COVID-19 syndrome. *Nature Medicine,* 27**,** 601-615.

NATIONAL ACADEMIES OF SCIENCES ENGINEERING MEDICINE 2022. *Long COVID: Examining Long-Term Health Effects of COVID-19 and Implications for the Social Security Administration: Proceedings of a Workshop,* Washington DC, National Academies Press.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2020. *COVID-19 rapid guideline: managing the long-term effects of COVID-19* [Online]. Available: https://www.nice.org.uk/guidance/ng188 [Accessed 13th May 2022].

NATIONAL INSTITUTES OF HEALTH. 2021. *NIH launches new initiative to study "Long COVID"* [Online]. Available: https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-launches-new-initiative-study-long-covid [Accessed 22nd June 2022].

NATURE 2020. Long COVID: let patients help define long-lasting COVID symptoms. *Nature,* 586**,** 170.

NHS ENGLAND. 2022. *Guidelines for supporting our NHS people affected by Long COVID* [Online]. Available: https://www.england.nhs.uk/wp-content/uploads/2022/02/C1672_Guidelines-for-supporting-our-NHS-people-affected-by-Long-COVID_July-2022.pdf [Accessed 29th July 2022].

NIHR. 2022. *Researching long COVID: addressing a new global health challenge* [Online]. Available: https://evidence.nihr.ac.uk/themedreview/researching-long-covid-addressing-a-new-global-health-challenge/ [Accessed 2nd August 2022].

NOLTE, E., KNAI, C. & MCKEE, M. 2008. *Managing chronic conditions: experience in eight countries,* Copenhagen, WHO Regional Office Europe.

NOLTE, E. & MCKEE, M. 2008. *Caring for People With Chronic Conditions: A Health System Perspective,* Buckingham, McGraw-Hill Education (UK).

NORTON, A., OLLIARO, P., SIGFRID, L., CARSON, G., PAPARELLA, G., HASTIE, C., KAUSHIC, C., BOILY-LAROUCHE, G., SUETT, J. C. & O'HARA, M. 2021. Long COVID: tackling a multifaceted condition requires a multidisciplinary approach. *Lancet Infect Dis,* 21**,** 601-602.

NUREK, M., RAYNER, C., FREYER, A., TAYLOR, S., JÄRTE, L., MACDERMOTT, N. & DELANEY, B. C. 2021. Recommendations for the recognition, diagnosis, and management of long COVID: a Delphi study. *Br J Gen Pract,* 71**,** e815-e825.

O'NEAL, A. J. & HANSON, M. R. 2021. The Enterovirus Theory of Disease Etiology in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Critical Review. *Front Med (Lausanne),* 8**,** 688486.

OFFICE FOR NATIONAL STATISTICS. 2021. *Technical article: Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK: 26 April 2020 to 1 August 2021* [Online]. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/technicalarticleupdatedestimatesoftheprevalenceofpostacutesymptomsamongpeoplewithcoronaviruscovid19intheuk/26april2020to1august2021 [Accessed 22nd June 2022].

OFFICE FOR NATIONAL STATISTICS. 2022a. *Additional data relating to 'Prevalence of ongoing Symptoms following coronavirus (COVID-19) infection in the UK: 1 September 2022'* [Online]. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/con

ditionsanddiseases/datasets/additionaldatarelatingtoprevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk1september2022 [Accessed 3rd September 2022].

OFFICE FOR NATIONAL STATISTICS. 2022b. *Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1st December 2022* [Online]. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1december2022 [Accessed 17th May 2022].

OFFICE FOR NATIONAL STATISTICS. 2022c. *Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 4 August 2022* [Online]. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/4august2022 [Accessed 3rd September 2022].

OFFICE FOR NATIONAL STATISTICS. 2022d. *Self-reported long COVID after infection with the Omicron variant in the UK: 18 July 2022* [Online]. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/selfreportedlongcovidafterinfectionwiththeomicronvariant/18july2022 [Accessed 3rd September 2022].

OFFICE FOR NATIONAL STATISTICS. 2022e. *Self-reported long COVID after two doses of a coronavirus (COVID-19) vaccine in the UK: 26 January 2022* [Online]. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/selfreportedlongcovidaftertwodosesofacoronaviruscovid19vaccineintheuk/26january2022 [Accessed 17th May 2022].

ORCHESTRA. 2022. Available: https://orchestra-cohort.eu/ [Accessed 27th September 2022].

PANTELIC, M., ZIAUDDEEN, N., BOYES, M., O'HARA, M. E., HASTIE, C. & ALWAN, N. A. 2022. Long Covid stigma: estimating burden and validating scale in a UK-based sample. *medRxiv*, 2022.05.26.22275585.

PATTLE, S. B. & FARRELL, P. J. 2006. The role of Epstein-Barr virus in cancer. *Expert Opin Biol Ther,* 6**,** 1193-205.

PELUSO, M. J. & DEEKS, S. G. 2022. Early clues regarding the pathogenesis of long-COVID. *Trends in Immunology,* 43**,** 268-270.

PEPE, A., PIETROPAOLI, S., VOS, M., BARBA-SPAETH, G. & ZURZOLO, C. 2022. Tunneling nanotubes provide a route for SARS-CoV-2 spreading. *Sci Adv,* 8**,** eabo0171.

PEREGO, E., CALLARD, F., STRAS, L., MELVILLE-JÓHANNESSON, B., POPE, R. & ALWAN, N. 2020. Why the Patient-Made Term 'Long Covid' is needed [version 1; peer review: 1 approved with reservations, 1 not approved]. *Wellcome Open Research,* 5.

PHOSP-COVID COLLABORATIVE GROUP 2022. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med,* 10**,** 761-775.

POUDEL, A. N., ZHU, S., COOPER, N., RODERICK, P., ALWAN, N., TARRANT, C., ZIAUDDEEN, N. & YAO, G. L. 2021. Impact of Covid-19 on health-related quality of life of patients: A structured review. *PLoS One,* 16**,** e0259164.

POYRAZ, B., POYRAZ, C. A., OLGUN, Y., GÜREL, Ö., ALKAN, S., ÖZDEMIR, Y. E., BALKAN, İ. & KARAALI, R. 2021. Psychiatric morbidity and protracted symptoms after COVID-19. *Psychiatry Res,* 295**,** 113604.

PRETORIUS, E., VLOK, M., VENTER, C., BEZUIDENHOUT, J. A., LAUBSCHER, G. J., STEENKAMP, J. & KELL, D. B. 2021. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. *Cardiovasc Diabetol,* 20**,** 172.

PUNTMANN, V. O., MARTIN, S., SHCHENDRYGINA, A., HOFFMANN, J., KA, M. M., GIOKOGLU, E., VANCHIN, B., HOLM, N., KARYOU, A., LAUX, G. S., ARENDT, C., DE LEUW, P., ZACHAROWSKI, K., KHODAMORADI, Y., VEHRESCHILD, M. J. G. T., ROHDE, G., ZEIHER, A. M., VOGL, T. J., SCHWENKE, C. & NAGEL, E. 2022. Long-

term cardiac pathology in individuals with mild initial COVID-19 illness. *Nature Medicine*.
RAWAL, G., YADAV, S. & KUMAR, R. 2017. Post-intensive Care Syndrome: an Overview. *Journal of translational internal medicine,* 5**,** 90-92.
ROBERTS, C. M., LEVI, M., MCKEE, M., SCHILLING, R., LIM, W. S. & GROCOTT, M. P. W. 2020. COVID-19: a complex multisystem disorder. *Br J Anaesth,* 125**,** 238-242.
ROYAL ACADEMY OF ENGINEERING. 2022. *Infection resilient environments* [Online]. Available: https://raeng.org.uk/infection-resilient-environments [Accessed 29th July 2022].
ROYAL SOCIETY. 2020. *Long Covid: what is it, and what is needed?* [Online]. Available: https://royalsociety.org/-/media/policy/projects/set-c/set-c-long-covid.pdf [Accessed 13th May 2022].
SHAH, R., ALI, F. M., NIXON, S. J., INGRAM, J. R., SALEK, S. M. & FINLAY, A. Y. 2021. Measuring the impact of COVID-19 on the quality of life of the survivors, partners and family members: a cross-sectional international online survey. *BMJ Open,* 11**,** e047680.
SIVAN, M., HALPIN, S., GEE, J., MAKOWER, S., PARKIN, A., ROSS, D., HORTON, M. & O'CONNOR, R. 2021. The self-report version and digital format of the COVID-19 Yorkshire rehabilitation scale (C19-YRS) for long Covid or Post-COVID syndrome assessment and monitoring. *Advances in CLinical Neuroscience and Rehabilitation,* 20.
SIVAN, M., HALPIN, S., HOLLINGWORTH, L., SNOOK, N., HICKMAN, K. & CLIFTON, I. J. 2020. Development of an integrated rehabilitation pathway for individuals recovering from COVID-19 in the community. *J Rehabil Med,* 52**,** jrm00089.
SIVAN, M., PRESTON, N., PARKIN, A., MAKOWER, S., GEE, J., ROSS, D., TARRANT, R., DAVISON, J., HALPIN, S., O'CONNOR, R. J. & HORTON, M. 2022. The modified COVID-19 Yorkshire Rehabilitation Scale (C19-YRSm) patient-reported outcome measure for Long Covid or Post-COVID-19 syndrome. *J Med Virol,* 94**,** 4253-4264.
SOCIETY OF OCCUPATIONAL MEDICINE. 2022. *COVID-19 return to work guide for recovering workers* [Online]. Available: https://www.som.org.uk/COVID-19_return_to_work_guide_for_recovering_workers.pdf [Accessed 27th July 2022].
SØRAAS, A., KALLEBERG, K. T., DAHL, J. A., SØRAAS, C. L., MYKLEBUST, T., AXELSEN, E., LIND, A., BÆVRE-JENSEN, R., JØRGENSEN, S. B., ISTRE, M. S., KJETLAND, E. F. & URSIN, G. 2021. Persisting symptoms three to eight months after non-hospitalized COVID-19, a prospective cohort study. *PLoS One,* 16**,** e0256142.
SORIANO, J. B., MURTHY, S., MARSHALL, J. C., RELAN, P. & DIAZ, J. V. 2022. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *The Lancet Infectious Diseases,* 22**,** e102-e107.
SPINNEY, L. 2022. Pandemics disable people - the history lesson that policymakers ignore. *Nature,* 602**,** 383-385.
SPITZER, R. L., KROENKE, K., WILLIAMS, J. B. & LÖWE, B. 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med,* 166**,** 1092-7.
STENTON, C. 2008. The MRC breathlessness scale. *Occup Med (Lond),* 58**,** 226-7.
STEPHENSON, T., ALLIN, B., NUGAWELA, M. D., ROJAS, N., DALRYMPLE, E., PINTO PEREIRA, S., SONI, M., KNIGHT, M., CHEUNG, E. Y., HEYMAN, I., CONSORTIUM, C. L. & SHAFRAN, R. 2022. Long COVID (post-COVID-19 condition) in children: a modified Delphi process. *Archives of Disease in Childhood,* 107**,** 674.
SUBRAMANIAN, A., NIRANTHARAKUMAR, K., HUGHES, S., MYLES, P., WILLIAMS, T., GOKHALE, K. M., TAVERNER, T., CHANDAN, J. S., BROWN, K., SIMMS-WILLIAMS, N., SHAH, A. D., SINGH, M., KIDY, F., OKOTH, K., HOTHAM, R., BASHIR, N., COCKBURN, N., LEE, S. I., TURNER, G. M., GKOUTOS, G. V., AIYEGBUSI, O. L., MCMULLAN, C., DENNISTON, A. K., SAPEY, E., LORD, J. M., WRAITH, D. C., LEGGETT, E., ILES, C., MARSHALL, T., PRICE, M. J., MARWAHA, S., DAVIES, E. H., JACKSON, L. J., MATTHEWS, K. L., CAMARADOU, J., CALVERT, M. & HAROON, S. 2022. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nature Medicine*.
SUDRE, C. H., MURRAY, B., VARSAVSKY, T., GRAHAM, M. S., PENFOLD, R. S., BOWYER, R. C., PUJOL, J. C., KLASER, K., ANTONELLI, M., CANAS, L. S., MOLTENI, E.,

MODAT, M., JORGE CARDOSO, M., MAY, A., GANESH, S., DAVIES, R., NGUYEN, L. H., DREW, D. A., ASTLEY, C. M., JOSHI, A. D., MERINO, J., TSERETELI, N., FALL, T., GOMEZ, M. F., DUNCAN, E. L., MENNI, C., WILLIAMS, F. M. K., FRANKS, P. W., CHAN, A. T., WOLF, J., OURSELIN, S., SPECTOR, T. & STEVES, C. J. 2021. Attributes and predictors of long COVID. *Nature Medicine,* 27**,** 626-631.

TABAK, L. 2022. *Using AI to Advance Understanding of Long COVID Syndrome* [Online]. Available: https://directorsblog.nih.gov/tag/post-acute-sequelae-of-covid-19/ [Accessed 22nd June 2022].

TABOADA, M., RODRÍGUEZ, N., DIAZ-VIEITO, M., DOMÍNGUEZ, M. J., CASAL, A., RIVEIRO, V., CARIÑENA, A., MORENO, E., POSE, A., VALDÉS, L., ALVAREZ, J. & SEOANE-PILLADO, T. 2021. [Quality of life and persistent symptoms after hospitalization for COVID-19. A prospective observational study comparing ICU with non-ICU Patients]. *Rev Esp Anestesiol Reanim (Engl Ed)*.

TANGERMANN, R. H., LAMOUREUX, C., TALLIS, G. & GOEL, A. 2017. The critical role of acute flaccid paralysis surveillance in the Global Polio Eradication Initiative. *Int Health,* 9**,** 156-163.

TAQUET, M., DERCON, Q., LUCIANO, S., GEDDES, J. R., HUSAIN, M. & HARRISON, P. J. 2021. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med,* 18**,** e1003773.

TENFORDE, M. W., KIM, S. S., LINDSELL, C. J., BILLIG ROSE, E., SHAPIRO, N. I., FILES, D. C., GIBBS, K. W., ERICKSON, H. L., STEINGRUB, J. S., SMITHLINE, H. A., GONG, M. N., ABOODI, M. S., EXLINE, M. C., HENNING, D. J., WILSON, J. G., KHAN, A., QADIR, N., BROWN, S. M., PELTAN, I. D., RICE, T. W., HAGER, D. N., GINDE, A. A., STUBBLEFIELD, W. B., PATEL, M. M., SELF, W. H. & FELDSTEIN, L. R. 2020. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep,* 69**,** 993-998.

TSAI, S. Y., YANG, T. Y., CHEN, H. J., CHEN, C. S., LIN, W. M., SHEN, W. C., KUO, C. N. & KAO, C. H. 2014. Increased risk of chronic fatigue syndrome following herpes zoster: a population-based study. *Eur J Clin Microbiol Infect Dis,* 33**,** 1653-9.

ÜSTÜN, T. B., KOSTANJSEK, N., CHATTERJI, S. & REHM, J. 2010. *Measuring health and disability: Manual for WHO disability assessment schedule WHODAS 2.0*, World Health Organization.

VAN DE VYVER, J., LEITE, A. C. & ALWAN, N. A. 2021. Navigating the social identity of long covid. *BMJ,* 375**,** n2933.

WAGENAAR, H. & PRAINSACK, B. 2021. *The Pandemic Within: Policy Making for a Better World*, Policy Press.

WALLE-HANSEN, M. M., RANHOFF, A. H., MELLINGSÆTER, M., WANG-HANSEN, M. S. & MYRSTAD, M. 2021. Health-related quality of life, functional decline, and long-term mortality in older patients following hospitalisation due to COVID-19. *BMC Geriatr,* 21**,** 199.

WANG, E. Y., MAO, T., KLEIN, J., DAI, Y., HUCK, J. D., JAYCOX, J. R., LIU, F., ZHOU, T., ISRAELOW, B., WONG, P., COPPI, A., LUCAS, C., SILVA, J., OH, J. E., SONG, E., PEROTTI, E. S., ZHENG, N. S., FISCHER, S., CAMPBELL, M., FOURNIER, J. B., WYLLIE, A. L., VOGELS, C. B. F., OTT, I. M., KALINICH, C. C., PETRONE, M. E., WATKINS, A. E., DELA CRUZ, C., FARHADIAN, S. F., SCHULZ, W. L., MA, S., GRUBAUGH, N. D., KO, A. I., IWASAKI, A. & RING, A. M. 2021. Diverse functional autoantibodies in patients with COVID-19. *Nature,* 595**,** 283-288.

WESTERLIND, E., PALSTAM, A., SUNNERHAGEN, K. S. & PERSSON, H. C. 2021. Patterns and predictors of sick leave after Covid-19 and long Covid in a national Swedish cohort. *BMC Public Health,* 21**,** 1023.

WIKIPEDIA. 2022. *Long COVID* [Online]. Available: https://en.wikipedia.org/wiki/Long_COVID [Accessed 13th May 2022].

WISE, J. & COOMBES, R. 2020. Covid-19: The inside story of the RECOVERY trial. *BMJ,* 370**,** m2670.

WOODCOCK, J. & LAVANGE, L. M. 2017. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *N Engl J Med,* 377**,** 62-70.

WORLD HEALTH ORGANIZATION 2010. *Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies,* Geneva, World Health Organization.

WORLD HEALTH ORGANIZATION. 2021a. *A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021* [Online]. Available: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 [Accessed 4th April 2022].

WORLD HEALTH ORGANIZATION. 2021b. *International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10): U07.1 COVID-19* [Online]. Available: https://icd.who.int/browse10/2019/en#/U07.1 [Accessed 4th April 2022].

WORLD HEALTH ORGANIZATION. 2022a. *At least 17 million people in the WHO European Region experienced long COVID in the first two years of the pandemic; millions may have to live with it for years to come* [Online]. Available: https://www.who.int/europe/news/item/13-09-2022-at-least-17-million-people-in-the-who-european-region-experienced-long-covid-in-the-first-two-years-of-the-pandemic--millions-may-have-to-live-with-it-for-years-to-come [Accessed 28th November 2022].

WORLD HEALTH ORGANIZATION 2022b. *Clinical management of COVID-19: living guideline, 15 September 2022 (WHO/2019-nCoV/Clinical/2022.2),* Geneva, World Health Organization.

WULF HANSON, S., ABBAFATI, C., AERTS, J. G., AL-ALY, Z., ASHBAUGH, C., BALLOUZ, T., BLYUSS, O., BOBKOVA, P., BONSEL, G., BORZAKOVA, S., BUONSENSO, D., BUTNARU, D., CARTER, A., CHU, H., DE ROSE, C., DIAB, M. M., EKBOM, E., EL TANTAWI, M., FOMIN, V., FRITHIOF, R., GAMIROVA, A., GLYBOCHKO, P. V., HAAGSMA, J. A., JAVANMARD, S. H., HAMILTON, E. B., HARRIS, G., HEIJENBROK-KAL, M. H., HELBOK, R., HELLEMONS, M. E., HILLUS, D., HUIJTS, S. M., HULTSTRÖM, M., JASSAT, W., KURTH, F., LARSSON, I. M., LIPCSEY, M., LIU, C., LOFLIN, C. D., MALINOVSCHI, A., MAO, W., MAZANKOVA, L., MCCULLOCH, D., MENGES, D., MOHAMMADIFARD, N., MUNBLIT, D., NEKLIUDOV, N. A., OGBUOJI, O., OSMANOV, I. M., PEÑALVO, J. L., PETERSEN, M. S., PUHAN, M. A., RAHMAN, M., RASS, V., REINIG, N., RIBBERS, G. M., RICCHIUTO, A., RUBERTSSON, S., SAMITOVA, E., SARRAFZADEGAN, N., SHIKHALEVA, A., SIMPSON, K. E., SINATTI, D., SORIANO, J. B., SPIRIDONOVA, E., STEINBEIS, F., SVISTUNOV, A. A., VALENTINI, P., VAN DE WATER, B. J., VAN DEN BERG-EMONS, R., WALLIN, E., WITZENRATH, M., WU, Y., XU, H., ZOLLER, T., ADOLPH, C., ALBRIGHT, J., AMLAG, J. O., ARAVKIN, A. Y., BANG-JENSEN, B. L., BISIGNANO, C., CASTELLANO, R., CASTRO, E., CHAKRABARTI, S., COLLINS, J. K., DAI, X., DAOUD, F., DAPPER, C., DEEN, A., DUNCAN, B. B., ERICKSON, M., EWALD, S. B., FERRARI, A. J., FLAXMAN, A. D., FULLMAN, N., GAMKRELIDZE, A., GILES, J. R., GUO, G., HAY, S. I., HE, J., HELAK, M., et al. 2022. A global systematic analysis of the occurrence, severity, and recovery pattern of long COVID in 2020 and 2021. *medRxiv*.

XIE, Y., XU, E., BOWE, B. & AL-ALY, Z. 2022. Long-term cardiovascular outcomes of COVID-19. *Nat Med*.

YAMAMOTO, S., SAITO, M., TAMURA, A., PRAWISUDA, D., MIZUTANI, T. & YOTSUYANAGI, H. 2021. The human microbiome and COVID-19: A systematic review. *PLoS One,* 16**,** e0253293.

YANG, J., LI, Y., LIU, Q., LI, L., FENG, A., WANG, T., ZHENG, S., XU, A. & LYU, J. 2020. Brief introduction of medical database and data mining technology in big data era. *J Evid Based Med,* 13**,** 57-69.

YEOH, Y. K., ZUO, T., LUI, G. C.-Y., ZHANG, F., LIU, Q., LI, A. Y. L., CHUNG, A. C. K., CHEUNG, C. P., TSO, E. Y. K., FUNG, K. S. C., CHAN, V., LING, L., JOYNT, G., HUI, D. S.-C., CHOW, K. M., NG, S. S. S., LI, T. C.-M., NG, R. W. Y., YIP, T. C. F., WONG, G. L.-H., CHAN, F. K. L., WONG, C. K., CHAN, P. K. S. & NG, S. C. 2021. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut,* 70**,** 698.

ZIAUDDEEN, N., GURDASANI, D., O'HARA, M. E., HASTIE, C., RODERICK, P., YAO, G. & ALWAN, N. A. 2022. Characteristics and impact of Long Covid: Findings from an online survey. *PLoS One,* 17**,** e0264331.

ZIMMERMANN, P., PITTET, L. F. & CURTIS, N. 2021. How Common is Long COVID in Children and Adolescents? *Pediatr Infect Dis J,* 40**,** e482-e487.

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