

HEALTH SYSTEMS AND POLICY ANALYSIS

POLICY BRIEF 39

# In the wake of the pandemic

## Preparing for Long COVID

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This policy brief is one of a new series to meet the needs of policy-makers and health system managers. The aim is to develop key messages to support evidence-informed policy-making and the editors will continue to strengthen the series by working with authors to improve the consideration given to policy options and implementation.

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- Tailor the way evidence is identified and synthesised to reflect the nature of the policy question and the evidence available
- Are underpinned by a formal and rigorous open peer review process to ensure the independence of the evidence presented.

Each brief has a one page key messages section; a two page executive summary giving a succinct overview of the findings; and a 20 page review setting out the evidence. The idea is to provide instant access to key information and additional detail for those involved in drafting, informing or advising on the policy issue.

Policy briefs provide evidence for policy-makers not policy advice. They do not seek to explain or advocate a policy position but to set out clearly what is known about it. They may outline the evidence on different prospective policy options and on implementation issues, but they do not promote a particular option or act as a manual for implementation.

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## Foreword

Over the past year the world has tracked the progress of the COVID-19 pandemic using data on cases and deaths. Yet we now know that these provide only a partial picture. Many people struggle to recover from the acute infection, suffering often disabling symptoms that last weeks or months and, in some cases, with disabilities that are likely to be very long lasting. Our understanding of this new condition, now termed Long COVID, is growing rapidly. For this, we owe a great deal to many people, but especially to those affected who have come together to document, analyse and report on the complex nature of this condition and its impact on their lives, as well as the health professionals, in some cases themselves suffering from Long COVID, who have initiated important research projects.

This policy brief seeks to raise awareness of Long COVID and to provide a resource for those in decision-making roles, setting out in basic terms what we know about this condition and what the policy options are for developing a response that leaves no one behind.

This is rapidly changing field and one where we have much to learn from the many initiatives being taken across Europe, some of which are described in this policy brief. We now need to implement and evaluate new models of care, building on the key messages from the 2018 Tallinn Conference that called on us to include, invest, and innovate and from the European Programme of Work 2020–25 United Action for Better Health. The legacy of COVID-19 will, sadly, be with us for a long time.

*Hans Kluge*

Regional Director

WHO Regional Office for Europe

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## Key messages

- COVID-19 can cause persistent ill-health. Around a quarter of people who have had the virus experience symptoms that continue for at least a month but one in 10 are still unwell after 12 weeks. This has been described by patient groups as “Long COVID”.
- Our understanding of how to diagnose and manage Long COVID is still evolving but the condition can be very debilitating. It is associated with a range of overlapping symptoms including generalized chest and muscle pain, fatigue, shortness of breath, and cognitive dysfunction, and the mechanisms involved affect multiple system and include persisting inflammation, thrombosis, and autoimmunity. It can affect anyone, but women and health care workers seem to be at greater risk.
- Long COVID has a serious impact on people’s ability to go back to work or have a social life. It affects their mental health and may have significant economic consequences for them, their families and for society.
- Policy responses need to take account of the complexity of Long COVID and how what is known about it is evolving rapidly. Areas to address include:
  - The need for multidisciplinary, multispecialty approaches to assessment and management;
  - Development, in association with patients and their families, of new care pathways and contextually appropriate guidelines for health professionals, especially in primary care to enable case management to be tailored to the manifestations of disease and involvement of different organ systems;
  - The creation of appropriate services, including rehabilitation and online support tools;
  - Action to tackle the wider consequences of Long COVID, including attention to employment rights, sick pay policies, and access to benefit and disability benefit packages;
  - Involving patients both to foster self-care and self-help and in shaping awareness of Long COVID and the service (and research) needs it generates; and
  - Implementing well-functioning patient registers and other surveillance systems; creating cohorts of patients; and following up those affected as a means to support the research which is so critical to understanding and treating Long COVID.





## Executive summary

### **Long COVID is an emerging condition that is not yet well understood but that can be severely disabling**

A proportion of people experience persisting ill health following the acute manifestations of COVID-19. There may be several reasons for this, but among them is the condition that is now termed Long COVID. The mechanisms by which the infection leads to Long COVID are also not yet fully understood. There is growing evidence that the virus can cause direct organ damage but also give rise to an abnormal response, increasing blood clotting and release of inflammatory substances. This can affect many different body systems, in particular the heart, lungs and brain.

Long COVID can be severely disabling, and those suffering from it report functional disabilities. Although there is no simple symptom or test for diagnosing it, many people experience severe fatigue and a range of troubling physical symptoms that make it difficult for those who are employed to return to work. This has obvious economic consequences.

### **A significant number of adults with COVID-19 suffer from Long COVID but exact numbers are currently difficult to estimate**

Estimates vary as to how common Long COVID is, but about a quarter of those with COVID-19 have continuing symptoms 4–5 weeks after testing positive, with about one in 10 experiencing symptoms after 12 weeks. The reasons why some people get Long COVID and others do not remain unknown, although it is associated with increasing age, the number of symptoms in the acute phase, and being female, among other characteristics. Children can also, rarely, be affected by a separate multisystem condition. Existing surveillance systems developed to track the course of the pandemic have, so far, generally not recorded data on this condition, in part because of the lack of an agreed case definition.

### **An emerging consensus on best practice points to the importance of multidisciplinary and multi-specialty approach to assessment and management**

Existing guidelines propose that the initial management of Long COVID should be in primary care and should include a series of investigations both to characterize how the individual is affected and to exclude other conditions that may coexist. This should be universally accessible. Management should then be tailored to the manifestations of disease, including investigation and referral for signs of involvement of different organ systems. Particular attention must be paid to actions aimed at narrowing inequalities in Long COVID, including employment rights and sick pay policies, particularly for health care workers who are more at risk. At present very few countries have specific employment benefit packages to support patients to access disability benefits.

### **Different European countries have been responding to the emergence of this new condition via organized health systems responses**

This policy brief lists a number of responses that have been adopted in different European countries. These include development of new guidelines for assessing and managing Long COVID, development of new care pathways, as well as creation of post-COVID clinics and online support tools. There are also examples of initiatives undertaken by local service providers and professional bodies that other countries can learn from.

### **Patients suffering from Long COVID have been instrumental in shaping awareness, research and service provision**

There is a growing recognition of the importance of engagement with those affected, with a number of patient communities operating online, as well as groups that bring together health workers who have been affected and who have played an important role in generating and exchanging knowledge. Self-help groups have been created in many countries and have helped to articulate the patient voice and provide support.

### **Further research remains a high priority**

Given the many unanswered questions about this condition, research is a high priority. The policy brief describes some of the ongoing studies being undertaken in Europe, following up those affected and conducting detailed clinical assessments. Some of these are creating cohorts of patients, something that will be of great value for the evaluation of potential treatments.



## POLICY BRIEF

### 1. Introduction

At least 1 in 5 people infected with COVID-19 experience persisting ill health following the acute phase of infection (Office for National Statistics, 2020). There may be several reasons for this, but among them is the condition that is now termed Long COVID. As the scale of disease burden attributable to Long COVID becomes recognized, health systems in many countries are seeking to understand the implications in the medium and long term and are asking how they should respond. This policy brief, written for decision-makers, is in two parts. First, it summarizes what is known about this condition, reviewing evidence on the mechanisms involved, who and what proportion of those infected get it, how it affects them, and what is known about diagnosis and treatment. Second, it brings together examples of how European countries are responding to this new condition.

This policy brief is not a substitute for either the detailed guidelines for clinicians or the resources for patients that have been developed in several countries, some of which are referred to later in this brief. As this is a rapidly developing topic, this brief offers a primer for those audiences who are involved in planning a policy response to this emerging condition.

### 2. What do we know about Long COVID?

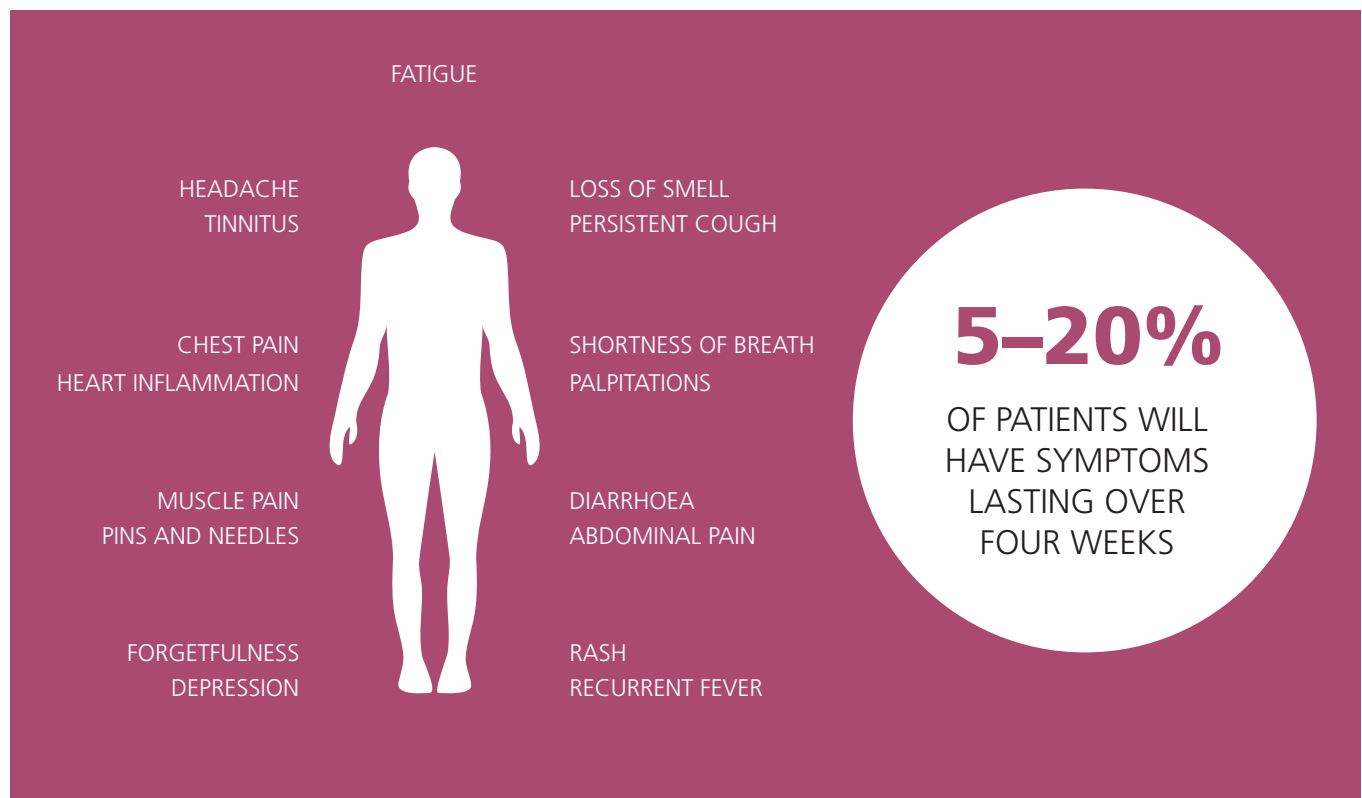
#### 2.1. Causes and definition

*Mechanisms by which Long COVID develops have not yet been fully understood but some of their harmful consequences are recognized*

There is mounting evidence that Long COVID is both common and debilitating (as outlined in sections 2.3 and 2.4 and summarized in Fig. 1). Its development and severity do not seem to correlate with the extent and nature of symptoms during the acute phase of the infection (Greenhalgh et al., 2020), although it is more common in hospitalized patients (Sudre et al., 2020). The exact mechanisms by which Long COVID develops remain unknown (see Box 1).

Symptoms include generalized pain, fatigue, shortness of breath, chest pain, muscle aches, palpitations, persisting high temperature and cognitive dysfunction, among others (Davis et al., 2020; Greenhalgh et al., 2020; Office for National Statistics, 2020), clustering and overlapping, often changing over time, and with evidence of involvement of almost any system within the body. The unpredictable and debilitating nature of this clinical picture can also lead to mood disorders. The worrying aspects of Long COVID include the multisystem pathology (National Institute for

Fig. 1 The long-term effects of COVID-19



Source: Reproduced with permission from SIMPLECOVID (2020)

Health and Clinical Excellence, 2020) that is associated with a variety of harmful consequences including scarring in multiple organs (especially the lungs, heart, kidneys, liver, adrenal glands and gastrointestinal tract) (Dennis et al., 2020), development of autoimmunity (British Society for Immunology, 2020) and blood clots causing strokes or other tissue damage (Libby & Lüscher, 2020).

#### Box 1: What causes Long COVID?

Available evidence shows that SARS-CoV-2 can trigger a hypercoagulable state and endothelial dysfunction (Libby & Lüscher, 2020), resulting in widespread formation of thrombi, and dysregulation of the immune response leading to a so-called cytokine storm in hospitalized patients and dysregulated inflammation in milder cases (British Society for Immunology, 2020; Gupta et al., 2020). In essence, the body produces pro-inflammatory cytokines, which are designed to kill the virus but are also unintentionally harmful, especially when not counter-balanced by the production of anti-inflammatory cytokines. There are many precedents of acute viral infections leading to long-term sequelae through immune and inflammatory responses, such as measles and subacute sclerosing panencephalitis (Bellini et al., 2005). Others include Ebola virus, Chikungunya virus and Epstein–Barr virus, which itself has been proposed as a potential trigger for an autoimmune reaction that leads to multiple sclerosis (Altmann & Boyton, 2020). However, the consequences of infection with SARS-CoV-2 are especially widespread, with many, and particularly the cardiovascular complications, seeming to relate to the widespread presence of angiotensin-converting enzyme 2 (ACE-2) receptors, which are highly expressed in the heart and lungs and act as the binding site for coronaviruses, including SARS-CoV and SARS-CoV-2, increasing the risk of endothelial damage and thrombo-inflammation (British Society for Immunology, 2020; Gupta et al., 2020).

#### *There is no internationally agreed definition of Long COVID*

In early literature a variety of terms are used, including “post-COVID syndrome”. The National Institute for Health and Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network, and the Royal College of General Practitioners include two conditions within the umbrella of Long COVID (Ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4 to 12 weeks; and Post-COVID-19 syndrome: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis). The French Haute Autorité de Santé specifies three criteria to identify patients suffering from “*sympômes prolongés de la Covid-19*”: having presented with a symptomatic form of Covid-19; presenting with one or more initial symptoms 4 weeks after the start of the disease; and none of these symptoms can be explained by another diagnosis (Haute Autorité de Santé, 2021). However, there is no internationally agreed definition and this syndrome, however it is termed, is commonly associated with the persistence of a range of heterogeneous symptoms, some of which may be due to other problems, and the choice of 12 weeks is arbitrary (Alwan & Johnson, 2020).

## 2.2. Who is more susceptible to Long COVID?

*Susceptibility in adults appears to increase with age, the number of symptoms in the acute phase, body mass index and being female*

Developing symptomatic Long COVID is not dependent on the severity of the initial COVID-19 infection or the duration of symptoms associated with it. A **German** study found that 78% of people known to have had COVID-19 had evidence of myocardial involvement based on a detailed assessment, and two thirds of these had not required hospital admission. There was no correlation with the severity of the initial infection (Puntmann et al., 2020). However, not everyone seems to be equally susceptible. The COVID Symptom Study, based at King’s College London, which has recruited 4 million people who report COVID-19 symptoms and test results on an app, found that the strongest predictors of persistent symptoms were increasing age, followed by the number of symptoms in the acute phase and, particularly, hoarseness of voice, greater body mass index, shortness of breath and being female (although men are more likely to die in the acute illness). Individuals with asthma were also reported to be at greater risk of developing Long COVID compared with those without. Among those over 70, the leading risk factors were loss of smell, early fever, hoarseness of voice and comorbidities, particularly those involving the heart and lung (Sudre et al., 2020). A study from the **United States**, based on telephone interviews with 292 people who had tested positive for COVID-19 but who were never admitted to hospital, found that 35% had not returned to their usual state of health after a median of 16 days from their original test. This increased steadily from 26% among those aged 18–34 years, to 32% among those aged 35–49 years, and 47% among those aged  $\geq 50$  years (Tenforde et al., 2020). Other surveys also suggest that increasing age, previous health status, presence of comorbidities and the number of symptoms during the acute phase, are all associated with the number of Long COVID symptoms an individual may subsequently develop (Goërtz et al., 2020).

## 2.3. How common is Long COVID?

*Estimating prevalence of Long COVID is not easy due to differences in methods used in surveys*

There are large variations in the symptoms and reported prevalence in studies of Long COVID because a common definition is still lacking (see section 2.1) and because surveys include people recruited in different ways, and record different sets of symptoms reported at different follow-up periods, undergoing different types of investigation, with many reports based on small samples that may not be particularly representative of those affected. Some survey participants have undergone especially detailed phenotyping including biomarker and radiological analyses, and it may be difficult to know whether any abnormalities detected are chance findings or are associated with their symptoms and whether these will resolve with time or persist.

A living systematic review of 28 studies, 61% of which were from Europe and including 9 442 adults with COVID-19, noted that while Long COVID seemed to affect both previously hospitalized and nonhospitalized populations, the quality of evidence was low, with a high risk of bias, with many studies lacking control subjects and prevalence varying between studies (Michelen et al., 2020). Differences in populations and methods make it difficult to generalize the findings across settings, particularly given the paucity of evidence from low- and middle-income countries, from primary care, and in children. Below, we describe results from some of the key studies published to date, with summaries presented in Tables 1 and 2.

***A significant number of nonhospitalized patients experience persistent symptoms but estimates vary greatly among studies***

The largest set of data with the right denominator to calculate prevalence for the **United Kingdom** comes from the Office for National Statistics (ONS) Coronavirus (COVID-19) Infection Survey, UK (Office for National Statistics, 2021), which has performed weekly tests for COVID-19 since April in a nationally representative sample. Simultaneously, the investigators asked a subset of 9 063 respondents who ever tested positive for COVID-19 (including those without symptoms) whether they had experienced persistent fatigue, cough, headache, loss of

taste, loss of smell, myalgia, sore throat, fever, shortness of breath, nausea/vomiting, diarrhoea or abdominal pain within 5 weeks of infection. Up until 14 December 2020, approximately 1 in 5 exhibited symptoms 5 weeks after the initial infection. Among those aged 25–69 this was 1 in 4, with similar proportions in men and women. Of these, the most common symptoms were fatigue, cough and headache, each of which were present in approximately 10% of those with symptoms at 5 weeks; 1 in 7 children aged 2–10 also reported symptoms at 5 weeks, demonstrating that this condition is not limited to adults alone. However, the ONS symptom list was limited and may have not captured those who experienced symptoms that were not listed in the questionnaire. In addition, these surveys lack control groups as some of these symptoms may occur in those who have not had COVID-19.

The second largest study in the **United Kingdom** is led by researchers at King's College London who developed the COVID Symptom Study app, together with health data science company ZOE Global, which is now used by several million people (Sudre et al., 2020). They identified 4 182 people who had laboratory-confirmed COVID and continued to log symptoms comparing them to matched negative testing controls. Of cases, 1 in 8 had symptoms lasting over 28 days compared with just 1 in 50 of controls, with 1 in 20 cases continuing to experience symptoms for over 8 weeks and 1 in 50 for over 12 weeks. Those with symptoms lasting

**Table 1 Summary of selected studies on the prevalence of Long COVID in nonhospitalized patients<sup>a</sup>**

COUNTRY	STUDY	SAMPLE	NUMBER OF CASES INCLUDED	RESULTS
United Kingdom	Office for National Statistics (2020)	Population representative	8 193	<ul style="list-style-type: none"> <li>• <b>21%</b> had symptoms <b>5 weeks</b> after infection</li> <li>• <b>10%</b> had symptoms <b>12 weeks</b> after infection</li> </ul>
	Sudre et al. (2020)	COVID Symptom App users (out of which 14% were hospitalized)	4 182	<ul style="list-style-type: none"> <li>• <b>13%</b> of cases had symptoms lasting <b>28 days</b> after symptom onset</li> <li>• <b>5%</b> of cases had symptoms for over <b>8 weeks</b> and <b>2%</b> for over <b>12 weeks</b> after symptom onset</li> </ul>
	Townsend et al. (2020)	Hospital outpatients (out of which 56% were hospitalized)	127	<ul style="list-style-type: none"> <li>• <b>52%</b> reported persistent fatigue at <b>10 weeks</b> after symptom onset</li> </ul>
USA	Tenforde et al. (2020)	Hospital outpatients (out of which 7% were hospitalized)	292	<ul style="list-style-type: none"> <li>• <b>35%</b> had symptoms after a median of <b>16 days</b> after testing positively for SARS-CoV-2 infection</li> </ul>
Switzerland	Nehme et al. (2020)	Hospital outpatients	669	<ul style="list-style-type: none"> <li>• About <b>33%</b> of cases had symptoms <b>30–45 days</b> after diagnosis</li> </ul>
The Netherlands and Belgium	Goërtz et al. (2020) <sup>b</sup>	Facebook group for coronavirus patients with persistent complaints (out of which 5% were hospitalized)	2 113	<ul style="list-style-type: none"> <li>• Over <b>99%</b> infected individuals did not fully recover within <b>12 weeks</b> after symptom onset</li> </ul>

<sup>a</sup>Some of the studies reported in this table included hospitalized patients

<sup>b</sup>Included suspected cases

Source: Authors

longer than 4 weeks were also more susceptible to symptom relapses (16%) than those whose symptoms resolved within 10 days (8.4%). The researchers did point out that those using their app were not necessarily representative of everyone getting COVID-19. They had more women, fewer people over 70, and fewer people from ethnic minorities than in the general population but they were able to adjust for this. However, they could not take account of the possibility that those who did experience persisting symptoms would be more or less likely to continue to report symptoms than those whose symptoms resolved.

Another study of 127 people in the **United Kingdom** (over half of whom were admitted to hospital), used a validated fatigue questionnaire and found that 52% reported persistent fatigue at 10 weeks after initial COVID symptoms (Townsend et al., 2020). There was no association with COVID-19 severity or laboratory markers of inflammation or cell turnover but females and those with a pre-existing diagnosis of depression/anxiety had higher prevalence.

In **Switzerland**, around a third of ambulatory patients had persistent symptoms of COVID-19 between 30 and 45 days after diagnosis with COVID-19, with cough and loss of taste

or smell being most common early in the disease course, and fatigue, dyspnoea and loss of taste or smell being more persistent (Nehme et al., 2020).

#### *Many people admitted to hospital for COVID-19 experience persisting symptoms for at least 60 days after discharge*

Although more patients are surviving severe COVID-19, there are limited data on outcomes after initial hospitalization. Initial studies were limited to 60 day follow-ups, but there is now data demonstrating that symptoms can last for 12 weeks and longer, and these are also reported below.

A study of hospitalized patients from the **United Kingdom** found that 68% reported persistent fatigue, 57% sleep disturbance and 32% breathlessness after an average of 60 days after discharge (Cruz et al., 2020). However, it was not possible to compare these findings with the individuals' conditions before getting COVID. Another **French** study reported persisting fatigue in 40% of hospitalized patients, also 60 days after symptom onset, with breathlessness in 30% (Carvalho-Schneider et al., 2020). Similarly,

**Table 2 Summary of selected studies on the prevalence of Long COVID in hospitalized patients postdischarge**

COUNTRY	STUDY	NUMBER OF CASES INCLUDED	RESULTS
<b>Canada</b>	Wong et al. (2020)	78	<ul style="list-style-type: none"> <li>• <b>51%</b> had persistently reduced quality of life and <b>50%</b> had shortness of breath at <b>12 weeks</b> after symptom onset</li> </ul>
<b>France</b>	Carvalho-Schneider et al. (2020)	130	<ul style="list-style-type: none"> <li>• <b>40%</b> reported persistent fatigue and <b>30%</b> breathlessness at <b>60 days</b> after symptom onset</li> </ul>
<b>Italy</b>	Carfi, Bernabei & Landi (2020)	143	<ul style="list-style-type: none"> <li>• <b>87%</b> had symptoms, <b>55%</b> had three or more symptoms at <b>60 days</b> after discharge</li> </ul>
<b>United Kingdom</b>	Cruz et al. (2020)	119	<ul style="list-style-type: none"> <li>• <b>68%</b> reported persistent fatigue, <b>57%</b> sleep disturbance and <b>32%</b> breathlessness at <b>60 days</b> after discharge</li> </ul>
	Arnold et al. (2020)	110	<ul style="list-style-type: none"> <li>• <b>74%</b> had persistent symptoms, typically breathlessness and fatigue and <b>10%</b> had persistent anomalies on chest X-ray or respiratory function testing at <b>12 weeks</b> after discharge</li> </ul>
<b>USA</b>	Donnelly et al. (2020)	2 179	<ul style="list-style-type: none"> <li>• <b>19.9%</b> were readmitted, <b>9.1%</b> died and <b>27%</b> were readmitted or died within <b>60 days</b> after discharge</li> </ul>
<b>China</b>	Huang et al. (2021)	1 733	<ul style="list-style-type: none"> <li>• <b>76%</b> reported persistent symptoms, and <b>50%</b> had residual anomalies on chest imaging <b>6 months</b> after discharge</li> </ul>

Source: Authors



143 hospitalized Italian patients, examined at a mean of 60 days since the onset of symptoms, found that only 13% were symptom-free 55% had three or more symptoms (Carfi, Bernabei & Landi, 2020).

The largest study to look at clinical outcomes among hospital patients is from the **United Kingdom** and compared clinical outcomes in 47 780 patients discharged alive with COVID-19 compared with matched controls. After a mean follow-up of 140 days, readmission rates in COVID-19 patients were 3 times higher than controls, as were new onset cardiovascular (3 times), respiratory (27 times) and diabetic (1.5 times) events, with the greatest risks observed among those over the age of 70 and in ethnic minorities (Ayoubkhani et al., 2021). Readmission rates, reasons for readmission and mortality rates were measured after hospital discharge among patients with COVID-19 in the nationwide Veterans Affairs (VA) in the **USA**. Within 60 days of discharge, 354 patients (19.9%) who survived COVID-19 hospitalization were readmitted, 162 (9.1%) died, and 479 (27.0%) were readmitted or died. Of those readmitted, the most common readmission diagnoses were COVID-19 (30.2%), sepsis (8.5%), pneumonia (3.1%), and heart failure (3.1%). During readmission, 22.6% were treated in intensive care, 7.1% were mechanically ventilated, and 7.9% received vasopressors (Donnelly et al., 2020).

### *Symptoms may last longer than 12 weeks*

While a high proportion of COVID-19 patients have persistent symptoms in the short term, the ONS Infection survey and the COVID Symptom App study show that many can suffer with symptoms for as long as 12 weeks. Earlier data from the ONS survey found that among 8 193 COVID-19 cases, 1 in 10 cases were still symptomatic 12 weeks post-infection, with symptoms lasting a median of 40 days (Office for National Statistics, 2020). In addition, data collected from 2 113 (16%) members of two Facebook groups for coronavirus in the **Netherlands and Belgium** found that fewer than 1% of infected individuals fully recover within 12 weeks (Goërtz et al., 2020).

Among those who were hospitalized, an even greater proportion report symptoms at 12 weeks. In one **British** study of 110 patients, 74% reported persisting symptoms, typically breathlessness and fatigue, and about 10% had persisting anomalies on chest X-ray or respiratory function (Arnold et al., 2020). Similarly, a **Canadian** study of previously hospitalized patients, found that 51% had persistently reduced quality of life and 50% had shortness of breath 12 weeks after discharge (Wong et al., 2020). Symptoms can persist for up to 6 months, as seen in one study of 1 733 hospitalized patients in **China** in which many reported fatigue or muscle weakness (63%), sleep difficulties (26%) and anxiety or depression (23%). Patients who were more unwell during admission were more likely to have ongoing pulmonary complications observed in both their pulmonary diffusion capacities and abnormal chest imaging (Huang et al., 2021).

The persistence of symptoms in some patients has implications for health services and according to a survey of GPs in the **United Kingdom** in 2020, 67% were looking

after patients with COVID-19 symptoms lasting longer than 12 weeks but only 23% had access to a Long COVID clinic that they could refer into (Royal College of General Practitioners, 2020).

For now the natural history on Long COVID is unknown but, on the basis of what is known about the pathology, it seems likely that it will vary considerably, with some effects, for example a consequence of thrombosis, causing organ damage permanent, others due to persisting viral infection uncertain, and some other effects likely to resolve in weeks or months.

### *Young children seem to be less susceptible to disease with COVID-19 but the number of children with Long COVID is uncertain*

Young children (under 11 years of age) are much less likely to develop severe illness, perhaps due to their lower levels of expression of the receptors to which the virus binds. Yet there have been reports from Europe and North America of children and adolescents with COVID-19 requiring acute admission to intensive care units with a multisystem inflammatory condition with some features of Kawasaki disease and toxic shock syndrome (Moreira, 2020). These children present with acute illness accompanied by a hyperinflammatory syndrome, leading to multiorgan failure and shock. This seems to be distinct from Long COVID, although some of the mechanisms involved may be similar.

Both the ONS survey described in section 2.3 and other informal surveys among patient groups suggest that children can experience persisting fatigue, nonspecific gastrointestinal problems, sore throats, headaches, and muscle pain and weakness. Other symptoms included fevers, nausea, mood changes, rashes, dizziness, breathing difficulties and cognitive blunting.

One Swedish case series describes five children, with a median age of 12 years, who had symptoms persisting for 6–8 months (Ludvigsson, 2020). One large **United Kingdom** study of 651 children admitted to hospital with confirmed COVID-19 found that the median age was 4.6 years, 56% were male and 43% were non-White (Swann et al., 2020). Overall, 11% of children had a systematic mucocutaneous-enteric cluster of symptoms. However, data on long-term outcomes in these populations have not been reported.

Evidence is, however, fragmentary and there is an urgent need for collection of standardized data on epidemiology, including clinical presentations, severity, and outcomes (Simpson & Lokugamage, 2020). WHO has developed a preliminary case definition and case report form for multisystem inflammatory disorder in children and adolescents (WHO, 2020b).

## **2.4. What are the symptoms of Long COVID?**

Evidence on the clinical sequelae of Long COVID is emerging and indicates a number of particular features, reflecting the increased risk of damage to multiple body systems tissues. There is still little data on the social impacts of Long COVID but available evidence points to reduced ability or even

inability to work, which has implications for labour force productivity and the cost of long-term sickness absence. Data on Long COVID in health care workers and the associated social impact are so far lacking.

*People suffering from Long COVID experience symptoms affecting many body systems including fatigue, breathing difficulty and fever*

The investigators of the **United Kingdom**-based COVID Symptom Study identified two clusters of symptoms. People with the first cluster of symptoms suffered only fatigue, headache and upper respiratory symptoms, such as shortness of breath, sore throat, persistent cough and loss of smell (Sudre et al., 2020). The second group also had symptoms affecting other body systems, including ongoing fever and gut problems. In general, fatigue was present all the time while headaches came and went. They also found that cardiac symptoms (palpitations and tachycardia) and neurological symptoms (concentration issues, tinnitus and peripheral neuropathy) were more common among those whose symptoms persisted beyond 28 days compared with those whose symptoms resolved within 10 days.

Another study, which is a rare example of research initiated, led and reported by people affected with the condition being described, recruited 3 762 patients from **56 countries** via support groups and social media although as the authors note, this approach to recruitment makes it difficult to know how representative the results are (Davis et al., 2020). The mean number of body systems affected was 9, with the most common symptoms being fatigue (77%), post-exertional malaise (72%) and cognitive dysfunction and brain fog (85%). Of those who recovered within 90 days, symptoms peaked at Week 2. Gastrointestinal and skin symptoms were especially common. In this study, 86% experienced relapses following exercise, physical or mental activity. Investigators reported a third cluster of late-onset symptoms, including cardiac changes such as palpitations, neurological (including tinnitus) and skin changes.

Other studies have reported patients describing experiencing insomnia, dizziness, anxiety and depression, chills and sweats, persistent fever, body aches, and skin rashes (Patient led research for COVID-19, 2020). Patients report that their symptoms often fluctuate in intensity and frequency, with approximately 16% in the ZOE study in the **United Kingdom** reporting relapse, with new symptoms appearing at different stages of their illness.

*Long COVID can also affect specific body systems including heart, lungs and brain*

Turning to individual body systems, myocardial injury has attracted much attention (Puntmann et al., 2020) in part because it has been found in previously fit athletes, a group whose cardiovascular system had been examined prior to being infected with COVID-19, thus enabling comparison pre- and post-illness (Rajpal et al., 2020). Most recently, provisional data has emerged from the COVERSCAN study in the **United Kingdom** (Dennis et al., 2020), which performed serial MRI scans on a self-selected sample of 201

middle-aged, generally healthy individuals with COVID-19, of whom 70% were female, 32% were health care workers and only 18% were initially hospitalized. The investigators found evidence of mild organ impairment in heart (32%), lungs (33%), kidneys (12%), liver (10%), pancreas (17%) and spleen (6%) and reported that almost 70% of individuals have impairments in one or more organs 4 months after initial symptoms of SARS-CoV-2 infection, which was higher than age-matched healthy controls. Of note, 23% had mild systolic dysfunction and 11% had evidence of myocarditis (Dennis et al., 2020), which was associated with more severe disease.

The Hradec Králové study on Long COVID (Czech Pneumological and Phthiseological Society, ČLS JEP, 2020) in **Czechia**, examined 79 adults 3 months after their initial infection with COVID-19. The mean age was 45 and 82% were never admitted to hospital. Almost half (49%) reported having respiratory symptoms, which were most often difficulty breathing (21%), then cough (10%), fatigue (17%) or chest pain (9%). In addition, 28% of them still had a poor sense of smell after 3 months. In this study, 37% of participants had an impaired lung function (specifically, a reduced oxygen carrying capacity), while 20% had signs of residual lung damage on imaging of the chest.

There have also been case reports of new onset Type 1 diabetes, an association that is plausible as the islet cells in the pancreas have ACE-2 receptors (Rubino et al., 2020). This is currently being studied in the COVIDIAB international study (King's College London & Monash University, 2020). However, those with pre-existing cardiometabolic diseases are also at greater risk of severe COVID-19 disease and mortality (Singh et al., 2020). A recent systematic review and meta-analysis reported the proportion of new onset diabetes of 14.4% (Sathish et al., 2020) and it will be essential to ensure long-term follow-up of these patients to track the evolution of this manifestation of Long COVID.

Neurological complications of acute COVID-19 have also been documented, with the most common neurological symptoms being headaches and altered smell and taste (Padda et al., 2020). In addition, the international patient-led study of Long COVID symptoms described above recorded self-reported brain fog or cognitive dysfunction in 85% of respondents (Davis et al., 2020). The most common symptoms were poor concentration (75%) and difficulty thinking (65%). Cognitive dysfunction increased over the first 3 months and was present in all age groups. Approximately 73% experienced memory impairments. A study of 509 hospitalized patients in Chicago in the USA, found that the most frequent neurologic manifestations were myalgias (44.8%), headaches (37.7%), encephalopathy (31.8%), dizziness (29.7%), altered smell (11.4%) and taste (15.9%) (Liotta et al., 2020) with between 0.2 and 1.4% of hospitalized patients suffering from strokes, movement disorders, motor and sensory deficits, ataxia and seizures. Neurological complications were more common in those who were younger and had severe COVID-19, while those with encephalopathy were slower to regain their functional capacity and had a higher mortality than those



without. There is also some evidence of SARS-COV-2 invasion leading to persisting inflammation of the olfactory mucosa in those with continuing loss of the sense of smell (De Melo et al., 2020). However, methodological differences between different studies make it difficult to determine how common these manifestations actually are among the overall population who have COVID-19 (Pezzini & Padovani, 2020).

As with diabetes, the association with psychiatric disorders is likely bidirectional. Of GPs surveyed by the Royal College of General Practitioners in the **United Kingdom**, 76% described patients reporting sleep disorders or mood changes (Royal College of General Practitioners, 2020). Electronic health record data from 69 million individuals in the United Kingdom also showed that a diagnosis of COVID-19 was associated with an increased incidence of a first psychiatric diagnosis between 14 and 90 days after diagnosis (Taquet et al., 2020), with the greatest risk observed for anxiety disorders, insomnia and dementia. Similarly, those with a psychiatric diagnosis in the previous year were reported to be at a 65% greater risk of being diagnosed with COVID-19, suggesting that mental ill health could be both a risk factor and a complication of COVID-19, although this did not account for crucial differences in socioeconomic status.

#### *Long COVID can be severely disabling with implications for people's ability to work and social lives*

There is still little data on the social impacts of Long COVID, but evidence from 150 patients with non-critical COVID-19 who were discharged from hospital in France between March and June 2020 showed that 11% were still on sick leave at Day 60 (Yelin et al., 2020). Half of the cohort were health care workers, posing a reminder of the risks that Long COVID presents to health systems. Similarly, the international patient-led survey described above found that 45% of Long COVID sufferers had reduced their workload and 22% were not working due to their illness (Davis et al., 2020). Similar findings were observed in Canada when SARS took hold and researchers at the University of Toronto described 22 people with SARS who were unable to work for up to 36 months after initial infection (Moldofsky & Patcai, 2011). Previous experience with chronic fatigue syndrome (CFS) has also taught us a great deal about the potential costs of long-term sickness absence (Reynolds et al., 2004). In one study from the USA, household productivity declined by 37% and labour force productivity by 54% among people with CFS. The annual lost productivity in the USA was US\$ 9.1 billion, representing about US\$ 20 000 per person with CFS. This accounts for around half of the household and labour force productivity of the average person with this syndrome. Data on Long COVID in health care workers and social impacts are lacking although a group of health care workers have documented their experiences of COVID-19 and persistence of symptoms and have made recommendations about potential methods of follow-up and Long COVID surveillance (Alwan et al., 2020). A UK Doctors Long COVID group has also been set

up and has reported on symptoms they experience, including myocarditis or pericarditis, microvascular angina, cardiac arrhythmias including atrial flutter and atrial fibrillation, dysautonomia including postural orthostatic tachycardia syndrome, mast cell activation syndrome, interstitial lung disease, thromboembolic disease (pulmonary emboli or cerebral venous thrombosis), myelopathy, neuropathy and neurocognitive disorders, renal impairment, new onset diabetes and thyroiditis, hepatitis and abnormal liver enzymes, new onset allergies and anaphylaxis and dysphonia, all of which impact on their ability to continue working (Gorna et al., 2020).

## 2.5. Diagnosis and treatment

### *There is no simple symptom or test for diagnosing Long COVID*

Long COVID is a clinical diagnosis, based on a history of COVID-19 and a failure to fully recover, with development of some of the symptoms listed in section 2.4. Although a positive swab or antibody test for COVID-19 is helpful, it is not a prerequisite for diagnosis. This is because availability of testing was very limited for to most people in Europe in the early stages of the pandemic. Moreover, PCR testing is not 100% sensitive and both it and antibody testing may miss those with residual symptoms from older infections, as antibodies often decline substantially by about 4 months (Gudbjartsson et al., 2020).

Long COVID is different from the well-recognized postintensive care syndrome, which is marked by chronically impaired pulmonary function, neuromuscular weakness, long-term psychological impacts and reduced quality of life (Ahmed et al., 2020; Society of Critical Care Medicine, 2020), a pattern that was also observed in SARS survivors (Ahmed et al., 2020). The syndrome is common among people with severe acute infections who have spent long periods on ventilators (Desai, Law & Needham, 2011) and may coexist with Long COVID in some cases.

While the symptoms of Long COVID do bear some semblance to the postviral symptoms observed in those with CFS (Institute of Medicine, 2015), Long COVID seems to manifest as a broader spectrum of symptoms and may potentially be more common, although further study is required to confirm this (Perego et al., 2020).

Emerging evidence points to Long COVID having a number of particular features, at least some of which seem to be related to the increased risk of damage to the certain tissues, in particular cardiac, vascular, lung, kidney involvement with evidence implicating both infection by the virus and the resulting inflammatory response (see Box 1).

In the United Kingdom, the National Institute for Clinical Excellence (NICE) have produced guidelines, in which they define some criteria for classifying these ongoing symptoms, which are presented in Box 2.

**Box 2: NICE guidelines on diagnosing Long COVID**

Guidelines developed by NICE in England (National Institute for Health and Clinical Excellence, 2020) advise the following criteria for diagnosing persistent symptoms of COVID-19:

- **ongoing symptomatic COVID-19** if people present with symptoms 4 to 12 weeks after the start of acute COVID-19 that are not explained by an alternative diagnosis; or
- **post-COVID-19 syndrome** if the person's symptoms have not resolved 12 weeks after the start of acute COVID-19.

Unfortunately, the guidelines do not specify which symptoms should be included in this definition, which could introduce unnecessary variability, but they do recommend that investigation and management should be based in primary care with referral of more complex cases to specialist post-COVID clinics.

In response to the NICE guidance, doctors and patient groups in the **United Kingdom** have called for clearer case definitions and comprehensive descriptions of the variety of known symptoms of Long COVID to ensure health care workers are able to identify cases early (Gorna et al., 2020). They argue that given that the underlying immunological and organ specific effects of SARS-COV-2 are now better understood, this should not be considered a diagnosis of exclusion (Sivan & Taylor, 2020). This would enable prompt assessment and earlier diagnosis, as well as better treatment and rehabilitation.

### *A multidisciplinary approach to assessment and management of Long COVID is essential*

Given the complex nature of the condition, with implications for many aspects of the lives of those affected, NICE guidelines advise that assessment and management should be tailored to the individual's problems, after excluding any coexisting illness that may be giving rise to the symptoms reported. For example, this would include a chest X-ray in those with respiratory symptoms, checking for a postural drop in blood pressure in those with dizziness, and urgent referral to the appropriate specialist for those with, for example, chest pain, palpitations or mental illness. Those who need further care should be referred to multidisciplinary rehabilitation teams (using screening questionnaires such as C19-YRS (Yorkshire Rehabilitation Screen)) (Sivan, Halpin & Gee, 2020) or for specialist input in more complex cases of specific organ dysfunction. The implications for health services of these guidelines are discussed further below (see section 3.2).

## 3. Policy and other responses in Europe

In this section we list a number of responses to Long COVID that have been adopted in different European countries. To that end, we contacted participants in the European Observatory COVID-19 Health Systems Response Monitor and undertook a rapid Internet search. The following examples should not be considered exhaustive, which would be impossible in this rapidly moving field, but do serve to illustrate some of the emerging ideas being considered. It

should also be noted that while the text was checked with national correspondents at the time of publication, it is to be expected that further developments will continue to take place.

### 3.1. Organized national surveillance systems

#### *Surveillance is a critical part of monitoring Long COVID but is not widespread in Europe*

Surveillance of Long COVID is particularly important but is not happening routinely in European countries. A first step in implementing a surveillance system is to define and classify it (Alwan & Johnson, 2020). To support this process, WHO has now introduced post-COVID emergency use ICD codes, which include "Personal history of COVID-19", "Post COVID-19 condition", and "Multisystem inflammatory syndrome associated with COVID-19" (WHO, 2020b) (Box 3).

#### **Box 3: ICD-10 codes for use with Long COVID**

##### **U08.9 Personal history of COVID-19, unspecified**

Note: This optional code is used to record an earlier episode of COVID-19, confirmed or probable that influences the person's health status, and the person no longer suffers of COVID-19.

##### **U09.9 Post COVID-19 condition, unspecified**

Note: This optional code serves to allow the establishment of a link with COVID-19.

This code is not to be used in cases that still are presenting COVID-19.

##### **U10.9 Multisystem inflammatory syndrome associated with COVID-19, unspecified**

Temporally associated with COVID-19:

- Cytokine storm
- Kawasaki-like syndrome
- Paediatric Inflammatory Multisystem Syndrome (PIMS) With COVID-19
- Multisystem Inflammatory Syndrome in Children (MIS-C)
- Excludes: Mucocutaneous lymph node syndrome [Kawasaki] (M30.3)

Although most countries now have COVID-19 data surveillance systems that record the total number of positive diagnoses, deaths, hospital admissions and intensive care unit (ICU) admissions (Alwan, 2020b) we were unable to find any details of specific data streams for Long COVID, although some, such as those in Italy (Istituto Superiore di Sanità, 2020) and Czechia (Ministry of Health of the Czech Republic, 2020), record the proportion of patients who recover, although this usually depends on returning a negative test rather than being free of symptoms (Alwan, 2020a).

### 3.2. Organized health systems responses

#### *Patients with Long COVID often report their difficulties are not taken seriously*

Patients suffering with Long COVID have reported feeling stigmatized and unable to access and navigate services. In particular, they report difficulties in being taken seriously and achieving a diagnosis. The care they received was reported to be disjointed and siloed and specialist care was mostly inaccessible and variable. While some felt supported, many report feeling “fobbed off” (Ladds et al., 2020).

Despite this, health systems in several countries are now developing organized responses.

#### *National health system responses include development of dedicated treatment guidelines and pathways, and creation of post-COVID clinics and online support tools*

As mentioned above, in **England**, NICE, working with patient groups and professional associations, has published a set of guidelines (National Institute for Health and Clinical Excellence, 2020). They propose multidisciplinary assessment services, bringing together physicians with expertise in different body systems, as well as multidisciplinary rehabilitation services, with core teams that could include, but not be limited to, occupational therapy, physiotherapy, clinical psychology and psychiatry, and rehabilitation medicine. These services should be part of a model of care that includes integrated referral patterns between primary, secondary and community care.

Prior to the publication of these guidelines the English National Health Service (NHS) had set out its own care pathway for patients with ongoing symptoms persisting beyond 6 weeks (NHS, 2020a). It stipulated that an initial assessment should be undertaken in primary or secondary care to exclude serious underlying pathology, using a screening tool included in the documentation. Onward referral would then be negotiated by a single point of access to triage and refer on to one or more of three possible pathways for those whose symptoms persist beyond 12 weeks: post-COVID assessment clinics, local rehabilitation clinics or the “Your COVID Recovery” NHS digital programme (<https://www.yourcovidrecovery.nhs.uk>). The NHS announced the launch of 40 such post-COVID assessment clinics in England in Autumn 2020, which adopt standardized functional assessment and screening questionnaires coupled with secondary care specialist referrals for investigation of potential end organ sequelae, where suspected. Physical care is also integrated with mental health care provision, including self-care and self-help groups, community therapy where required and referral to the “Your COVID Recovery” NHS digital programme to support COVID recovery (NHS, 2020b). This digital online platform includes self-management advice on tackling daily activities, returning to work and seeking help. All cases of acute COVID-19 admitted to hospital will also be reviewed remotely and face to face at 6 weeks for a review of symptoms to identify cases for onward referral. It will be important for these clinics to have standard operating procedures for assessment, documentation and long-term

follow-up data of those managed in these clinics. A number of other services have also appeared including online Long COVID support groups (Long COVID Support, 2020), and NHS resources (NHS, 2020a).

In **Germany** some larger university hospitals offer special consultation hours for patients with long-term complaints, including the Jena University Hospital or Hanover Medical School, which opened a post-COVID outpatient clinic in July 2020 where neurologists, cardiologists, pneumologists, psychiatrists, gastroenterologists, occupational physicians, internists and ear, nose and throat doctors provided interdisciplinary care. Unfortunately, access to such clinics was not widespread at the time of writing.

In **Italy**, service delivery for COVID-19 varies regionally but in general is managed in primary and secondary care and facilitated through community care networks, including a combination of reconverted community hospitals, health care hotels, nursing homes and low intensity residential facilities. GPs also coordinate services that include domiciliary care, supported by remote telemonitoring and a new community nurse role. Some hospitals, such as the San Raffaele Hospital in Lombardy, have also created post-COVID wards for rehabilitation of those who experienced prolonged admissions to ICU. Other services include those by AbilityAmo (AbilityAmo, 2020), a non-profit organization, which is dedicated to providing rehabilitative interventions for post-COVID disability and fragility. These services include telemonitoring systems for clinical surveillance, specialist interventions (both in hospitals and at home), psychological support and neurological, respiratory and cognitive post-admission rehabilitation. The organization is also gathering information about patients’ experiences and plans to publish a report on life after COVID-19.

In **Czechia**, the Hradec Králové teaching hospital set up a specialized Post-COVID Care Centre to take care of Long COVID patients with residual symptoms 3 months after their acute infection. The care centre provides a multidisciplinary team of physicians, including pneumologists, cardiologists, neurologists, psychiatrists, nephrologists, dermatologists, gastroenterologists, rheumatologists and rehabilitation physicians. The intention is for patients to be cared for by their GPs, with follow-ups by respiratory doctor until symptoms and any residual organ damage have resolved (Biba, 2021). This particular centre primarily serves the Královehradecký and Pardubický regions but others are also expected to open elsewhere. The Czech Pneumological and Phthiseological Society of the J.E. Purkyně Czech Medical Association (ČLS JEP) also published interim guidance in early January 2021, including a definition, diagnosis and classification of Long COVID and post-COVID syndrome (Czech Pneumological and Phthiseological Society, ČLS JEP, 2021). Patients with ongoing symptoms such as breathlessness have been advised by the Czech Pneumological and Phthiseological Society of the ČLS JEP to seek help from a respiratory doctor, but no specific services seem to have been designed.

Similarly, in **Spain**, hospitals and primary care centres provide COVID-19 patients with guidance on respiratory and physical rehabilitation to face the consequences of COVID-

19 and the Spanish Society of General Practitioners has published guidelines about treating this type of patients in primary care settings (Sociedad Española de Médicos Generales y de Familia, 2020a).

In **Belgium, France and Portugal**, specific services are mainly developed for COVID patients who were hospitalized. In Belgium, services are focused on patients who were admitted to intensive care units, with programmes dedicated to the management of the postintensive care syndrome (PICS). These services can take place at home, in a specialized or a geriatric hospital and include a multi-disciplinary team of doctors, nurses, physiotherapists, occupational therapists, sports therapists, psychologists, speech therapists and social workers. As well as neuromuscular rehabilitation, there are also functional rehabilitation centres for locomotor and neurological disorders, with cognitive rehabilitation interventions provided where necessary. The COVID-19 pandemic has also accelerated the expansion of pre-existing intensive post-care pathways. At the time of writing, at least three Belgian hospitals were developing similar care pathways, while others were considering it. Some hospitals have also dedicated specific care units to rehabilitate these patients, given the limitations of infection control measures for COVID positive patients in hospital.

#### *Responses to Long COVID are also developed by local service providers and professional bodies*

There are also many examples of local initiatives. Thus, the Fondazione Policlinico Agostino Gemelli in **Italy**, a tertiary care centre in Rome, has developed a multidisciplinary health care service called the Post-COVID-19 Day-Hospital, which includes an infectious diseases physician and specialists for pneumological assessments, ophthalmologic assessments, otolaryngologic assessments, neurologic assessments, psychiatric assessments, cardiovascular assessments, nutritional assessments, gut assessment and rheumatologic assessments (Landi et al., 2020). Some hospitals in the **United Kingdom** have also offered information packs with recommendations (Homerton University Hospital, 2020) to improve breathlessness, diet, emotional well-being and conserving energy such as breathing techniques, physical position and relaxation. There are also initiatives by professional bodies. Thus, occupational therapists in the United Kingdom have also released guidance on how to conserve energy (Royal College of Occupational Therapists, 2020), while the Society for Critical Care Medicine has released guidance on PICS and how to manage it.

#### *Services that have been developed in many European countries so far are not universally accessible or multidisciplinary and many do not provide access to disability benefits*

We were unable to find many examples of universally accessible multidisciplinary services for Long COVID that were available to communities in European countries outside the United Kingdom. Similarly, few countries had specific

disability benefits for patients with Long COVID or any mechanisms designed to protect employment in these individuals, although there is some guidance from the Faculty of Occupational Medicine in the United Kingdom to help health care workers support Long COVID patients back to work.

### **3.3. Patient involvement**

#### *Patients have called for recognition, rehabilitation and research*

The patient voice has been critical in shaping awareness about Long COVID (Callard & Perego, 2021), although to a greater extent in some countries than in others. A number of very popular patient advocacy groups have been launched on social media across Europe and in other countries, including the Body Politic group (Body Politic, 2020a), which also conducted some of the first patient-led research to document and raise awareness of the symptoms among sufferers, many of whom describe feeling unheard by doctors (Jensen, 2020).

The United Kingdom arm of Body Politic has set up LongCovidSOS (Body Politic, 2020b), an advocacy group that has appealed to governments to recognize and raise awareness of the needs of Long COVID sufferers among the public, and employers. They called for "Recognition, Research and Rehabilitation"; a call supported by patient associations in Belgium and that has been publicly acknowledged by the Director-General of WHO.

- Recognition involves taking into consideration all aspects of the problem (medical, psychological, social, etc.) and raising the awareness among physicians and other health professionals (physiotherapists, nurses, etc.) about Long COVID.
- Rehabilitation involves the provision of nationally coordinated multidisciplinary programmes for Long COVID patients to assess, test, diagnose and care, including those who were not hospitalized during the acute phase.
- Research calls for coordinated and co-created multidisciplinary studies to understand the clinical sequelae and develop treatment pathways for Long COVID.

Patient groups have also asked authorities to set up working groups to address the needs of Long COVID sufferers; and focus on the economic implications, including the provision of financial and employment support.

In **Spain**, several Long COVID online communities have been formed in collaboration with the Spanish Society of General Practitioners (SEMG) to raise awareness of their condition and improve health care services (Sociedad Española de Médicos Generales y de Familia, 2020b). In France, patients initially organized themselves in social media groups but as of 13 October 2020 they created an association (#AprèsJ20-Association Covid long France) to try to coordinate their advocacy actions (Association COVID Long France, 2020).



Several Facebook groups have been created for doctors suffering from Long COVID, many of whom became infected in the first wave of the pandemic when personal protective equipment (PPE) was in short supply. Some have appealed to the medical profession to recognize their needs, calling for collaboration between politicians, health care services, public health professionals, scientists and society to improve our understanding of the epidemiology, pathophysiology and management of Long COVID, highlighting the need to measure and quantify Long COVID (Alwan et al., 2020). They have also called for timely access to patient-centred services that can investigate and treat pathology and focus on supporting functional recovery, whether or not an individual has been tested for COVID-19.

### 3.4. Self-care and self-help groups

*Self-help groups have been created in many countries and have helped to articulate the patient voice and provide support*

In **Germany**, the earliest Long COVID self-help groups started in March 2020, in hardest-hit areas in North Rhine-Westphalia (e.g. Heinsberg) and Bavaria. Participants use the forums to exchange experiences of the disease, to support each other and to gain new perspectives. Italy has also seen a number of patient initiatives, including a social network group called “We who have beaten COVID” (*Noi che il Covid l’abbiamo sconfitto*) (Noi che il Covid lo abbiamo sconfitto, 2020) with 12 630 subscribers at the beginning of January 2021. **Belgium** has also seen many patients, including health workers, join social media groups in both French and Flemish languages, with some hospitals also setting up their own discussion groups, many of whom are now contributing to research studies into clinical features and management of Long COVID. A group focusing on Long COVID in children (<https://www.longcovidkids.org/>) has been created in the **United Kingdom**.

*Initiatives have also been created in some countries to promote self-care among those with Long COVID, to complement existing services*

In addition to Facebook groups in the **United Kingdom** (some of which have tens of thousands of members), Asthma UK and the British Lung Foundation have come together with the support of others including the British Thoracic Society and the Primary Care Respiratory Society to develop the online Post-COVID HUB (<https://www.post-covid.org.uk>) for people left with breathing difficulties following a COVID-19 infection to access advice and support to manage symptoms (Asthma UK and British Lung Foundation, 2020), while others have united to create self-help pacing groups, supporting each other to monitor and very slowly increase their daily activity within their limits (Hammond et al., 2020). In **Portugal**, the Ministry of Health and the Directorate General of Health have developed a series of online materials targeting mental health of health professionals (Direção Geral da Saúde, 2020a) including a guide for self-care and mental health (Direção Geral da Saúde, 2020b).

### 3.5. Ongoing research

*Studies of Long COVID have been emerging in Europe, offering opportunity to improve our understanding of this new condition*

The COVID-19 Research Project Tracker (UKCDR, 2020) is a live database of funded research projects across the world related to the current COVID-19 pandemic that has been set up by the United Kingdom Collaborative on Development Research (UKCDR) and the Global Research Collaboration For Infectious Disease Preparedness (GLOPID-R) to map research initiatives on to the WHO’s Coordinated Global Research Roadmap for COVID-19.

In the **United Kingdom**, a number of studies are already up and running in relation to Long COVID, and the United Kingdom Research and Innovation (UKRI) and the National Institute for Health Research (NIHR) have also launched research calls for up to £ 20 million to fund several others in 2021 (UKRI, 2020). Existing research is ongoing in the United Kingdom, including the Post-Hospitalisation COVID-19 study (PHOSP-COVID, 2020), which aims to follow-up inpatients with COVID-19 after discharge to document their symptoms, blood markers, imaging and patient reported outcomes. The research team from Leicester have recruited 1 500 people so far and plan to recruit a further 8 500, with an additional aim planned in 2021 to include people with COVID-19 who were not admitted to hospital during the acute phase. A number of subgroups of PHOSP-COVID study have also been set up to conduct research in specific groups including cardiovascular, metabolic, multimorbidity and ethnic subgroups. In addition, working groups from the multidisciplinary Long COVID community clinics will investigate the long-term consequences of COVID-19 and their mechanisms, the impact of acute interventions, and identify future research and intervention needs. These groups will be exploring answers to research questions emerging from the social sciences and the health economic impacts of Long COVID. The PHOSP-COVID study is also linked to other immunology and neuropsychology studies in the United Kingdom and to the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Global COVID-19 Long-Term Follow-Up study (University of Oxford, 2020), which has developed standardized data collection tools to document the clinical sequelae and risk factors for longer term consequences of COVID-19 for up to 3–5 years and to facilitate international comparisons in adults and children. UK\_REACH will be the largest study of prevalence of COVID and Long COVID, complications and wider social impacts on health care workers in the United Kingdom so far. The study will include routinely collected data and will conduct long-term follow-up of 30 000 health care workers (NIHR Leicester Biomedical Research Centre, 2020).

Similar studies are emerging across Europe; for example, in Lombardy, Italy, where researchers are also studying individuals discharged from hospital with COVID-19, while the Spanish Society of General Practitioners has also launched an online anonymous survey to explore ongoing

symptomatology in COVID-19 patients. As part of the Network of University Medicine in Germany, the National Pandemic Cohort Network at University Hospitals (NAPKON) investigates long-term organ damage and subsequent morbidities after infection with SARS-CoV-2 across all disease severities through population-based cohort studies at several sites (ClinicalTrials.gov, 2020a), while others in Munich, Germany, are also examining lung function to help to establish treatment protocols and to target follow-up care.

Another study at the University of Tübingen investigates the long-term consequences of individuals with mild courses of COVID-19 who have never been admitted to hospital due to their illness. The researchers closely collaborate with GPs and public health offices. Finally, the Hradec Králové study on Long COVID from Czechia (described in section 2.4) also plans to repeat all physical examinations twice over the course of the year to establish whether lung function resolves in sufferers of Long COVID and will assess antibody levels and cell-mediated immunity, which is also being examined in the COVIMMUNE study in France (ClinicalTrials.gov, 2020b). There is a hope that the use of standardized methods will facilitate the production of a meta-analysis as findings from these studies start to emerge. Similarly, in Belgium, researchers at the Health Care Knowledge Centre (KCE) are also working to establish the clinical sequelae and risk factors. They are also investigating the experiences and unmet needs of patients.

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#### 4. Implications for policy

##### **Although Long COVID is not yet fully understood, health policy-makers should be preparing to address it**

Although there are still many unanswered questions about the natural history of Long COVID, in particular relating to its likely duration in those affected, it is probable that there will be considerable numbers of people with ongoing symptoms for several years at least. Health policy-makers should be preparing responses to those with this condition.

##### **First step towards dealing with Long COVID should include implementing effective patient registers or other surveillance systems**

A first step will be to ensure that there are effective systems of surveillance in place, ideally creating patient registers which are not entirely dependent on diagnosis by lab

confirmation and including these figures within reported outcome measures for COVID-19. Identification, monitoring and recording of people with Long COVID is imperative to facilitate long-term follow-up and prevent an epidemic of chronic disease with detrimental impacts on health systems and economies and can also act as a critical basis for research. These registries should collect sufficient data to characterize factors that influence the risk of ongoing problems, including initial presentation and sociodemographic data, including ethnicity and occupation. They should also monitor the impact of this condition on the lives of those affected, including conventional measures of quality of life but also the impact on psychological condition, employment and economic situation.

##### **Care guidelines and multidisciplinary services need to be developed to ensure appropriate assessment and management of the condition**

In countries where this has not yet happened, it will be important to develop contextually appropriate guidelines for health professionals caring for those affected, especially in primary care. As described in this policy brief, there is already considerable material that can be drawn upon. Patient groups have emphasized that new nomenclature must not be developed by each individual guideline, but that a proper consultative process occurs by WHO to determine terminology. This will ensure consistency in diagnosis across different regions of the world and therefore better tracking of the impact of COVID on long-term morbidity.

In parallel, it will be necessary to develop multidisciplinary and multispecialty services that can evaluate individuals and ensure that they have access to appropriate management. There is considerable scope for implementation research and, as knowledge accumulates, evaluation of different forms of treatment, ideally in clinical trials. This is an area that will benefit from international cooperation.

##### **Effective response can only be achieved by involving Long COVID patients themselves**

Patient groups have already proven themselves to be instrumental to recognizing, characterizing this condition and advocating for it to be properly and fairly managed. Again, there are many opportunities for cross-country learning and such initiatives should be welcomed, encouraged, and where possible, supported by policy-makers.

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**How do Policy Briefs bring the evidence together?**

There is no one single way of collecting evidence to inform policy-making. Different approaches are appropriate for different policy issues, so the Observatory briefs draw on a mix of methodologies (see Figure A) and explain transparently the different methods used and how these have been combined. This allows users to understand the nature and limits of the evidence.

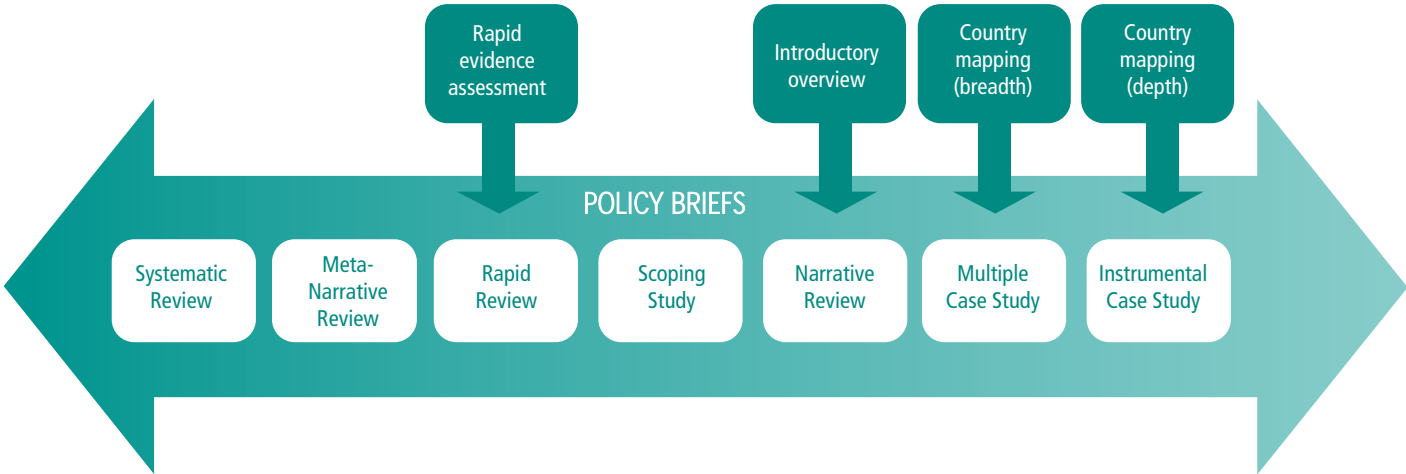
There are two main 'categories' of briefs that can be distinguished by method and further 'sub-sets' of briefs that can be mapped along a spectrum:

- A rapid evidence assessment: This is a targeted review of the available literature and requires authors to define key terms, set out explicit search strategies and be clear about what is excluded.

- Comparative country mapping: These use a case study approach and combine document reviews and consultation with appropriate technical and country experts. These fall into two groups depending on whether they prioritize depth or breadth.
- Introductory overview: These briefs have a different objective to the rapid evidence assessments but use a similar methodological approach. Literature is targeted and reviewed with the aim of explaining a subject to 'beginners'.

Most briefs, however, will draw upon a mix of methods and it is for this reason that a 'methods' box is included in the introduction to each brief, signalling transparently that methods are explicit, robust and replicable and showing how they are appropriate to the policy question.

Figure A: The policy brief spectrum



Source: Erica Richardson

## Joint Policy Briefs

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