EXPERT PANEL ON EFFECTIVE WAYS OF INVESTING IN HEALTH

(EXPH)

Opinion on

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

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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 multidisciplinary 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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100 **ABSTRACT**

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110 Opinion to be cited as:

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127 Expert Panel on effective ways of investing in health (europa.eu)

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175 **MANDATE**

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

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

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

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

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

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

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

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

212 **QUESTIONS FOR THE EXPERT PANEL**

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

215 1. Provide an overview of the current best evidence on what post-COVID-19 condition is,
216   its probable causes and symptoms, using the available literature to date, including
217   the work carried out by the ECDC in this area.
218 2. Provide an analysis of the main knowledge, organisational and resource requirements
219   for healthcare systems to design and develop appropriate health services for post
220   COVID-19 condition.
221 3. Provide guidance on how public health surveillance should be adapted to measure the
222   impact of the post-COVID-19 condition on the population.
223

1. OPINION

1.1. The scope of the opinion

The first step in writing an Opinion on PCC is to decide what should be included and what not. 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 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 of 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.

PCC 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 (PCC), 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 PCC. Case definitions and epidemiological studies should evolve rapidly in order to aid distinction between these conditions and PCC 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

261   can cause severe illness or death. (Jiang et al., 2020) These conditions are beyond the
262   scope of this opinion.

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

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

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

281   **1.2.Best evidence on post-COVID-19 condition, its probable causes and**
282   **symptoms**

283   **1.2.1. Definition of PCC**
284   Having set the scope of the Opinion in the previous section, it is necessary to define what
285   is being discussed. The Mandate given to the Expert Panel refers to post-COVID-19
286   condition (PCC), the term used by the World Health Organization (WHO) and the European
287   Centre for Disease Prevention and Control (ECDC), but notes that it is also referred to as
288   'Long Covid'. This terminology requires some unpacking.

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

295 exclude, minimize, and delegitimize their experience, particularly if the health condition is
296 poorly understood in terms of underlying mechanisms and effective management. An
297 editorial in the journal Nature said that health authorities "must always give proper
298 consideration to the voices of people with COVID-19 and their representatives, who have
299 done so much to put long COVID on the health-research and policy agenda" (Nature,
300 2020).

301 Yet, notwithstanding such concerns, professional bodies have developed their own
302 terminology. In addition to the term post-COVID-19 condition formally used by the WHO
303 (World Health Organization, 2021a), the National Institute for Health and Care Excellence
304 in England proposed the terms "Ongoing symptomatic COVID-19" for those with signs and
305 symptoms lasting 4-12 weeks and "Post-COVID-19 syndrome" where they persisted
306 beyond 12 weeks and are not explained by an alternative diagnosis (National Institute for
307 Health and Care Excellence, 2020). Another term commonly used in the USA is Post acute
308 Sequelae of SARSCoV2 Infection or COVID-19 (PASC) (Groff et al., 2021, Tabak, 2022).
309 All these terms can be found in the literature so, throughout this Opinion, the term used
310 in the item of literature being cited will be used for fidelity to it. Readers should, however,
311 note that the terms are, for all practical purposes, interchangeable.

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

315 *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)*.*
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 impact everyday functioning, may continue or develop after COVID-19 infection, and may fluctuate or relapse over time (Stephenson et al., 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).

316

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

318   For the purposes of this Opinion, it is necessary to select one of these and, given its
319   authority in global health and the participatory process described in reaching this case
320   definition (Soriano et al., 2022), we will use the WHO definition (Box 1); the main challenge
321   in the case definition continues to be how to define "persistence", as thresholds set at 4, 8
322   or 12 weeks massively impact the prevalence and nature of PCC. There are other
323   limitations of the WHO definition that should be kept in mind. The WHO definition is
324   sensitive but involves a considerable trade-off with specificity. High sensitivity allows more
325   people to be recognized as affected and receive care but, on the other hand a stricter
326   definition would be required for research purposes. The WHO definition has a focus on
327   respiratory symptoms and fatigue but does not explicitly mention cardiovascular signs and
328   symptoms, which some current research is also pointing as important.

329

330   *Box 1 WHO clinical case definition of Post COVID-19 condition (PCC)*

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.

331
332   Source: WHO (2021a)

333   **1.2.2. How common is PCC?**

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

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

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

365   The most recent data, as of the time of writing (published August 2022) estimate that as
366   of 2nd July 2022 1.79 million people living in private households in the UK (2.8% of the
367   population) were experiencing self-reported Long COVID (Office for National Statistics,
368   2022b). This figure has been decreasing slightly since it peaked at 1.99 million in April
369   2022. As this decrease was during a wave of Omicron infections, when 586,000 (33% of
370   the total) of those reporting symptoms first experienced them, the number of people
371   recovering seems to be exceeding new cases, even allowing for some deaths, at least in
372   this period. Of people with self-reported Long COVID, 243,000 (14%) first had (or
373   suspected they had) COVID-19 less than 12 weeks previously, 1.4 million people (81%) at
374   least 12 weeks previously, 761,000 (43%) at least one year previously, and 380,000
375   (21%) at least two years previously.

376   The survey questions do not permit an accurate assessment of the need that those
377   reporting symptoms will have on health care. Obviously, those with mild symptoms may
378   need relatively little support beyond advice and symptomatic treatment. However, it can
379   be assumed that those who have more severe symptoms will require more help. The survey
380   estimated, in July 2022, that 1.3 million people (72% of those with self-reported long
381   COVID) had symptoms that adversely affected the day-to-day activities. This equates to
382   about 2% of the population, with 369,000 (21%) whose ability to undertake their day-to-
383   day activities had been "limited a lot". The most common symptom was fatigue (54% of
384   those with self-reported Long COVID), followed by shortness of breath (31%), loss of smell
385   (23%) and muscle ache (22%).

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

390   The ONS supplements these data, used for population-level population estimates, with
391   follow-up of all those with confirmed infection in their survey, asking whether they think
392   they have Long Covid. 11.7% of all those infected (including those asymptomatic) reported
393   Long Covid symptoms at 12 weeks after infection. Out of those initially symptomatic in the
394   acute phase, the prevalence was 17.7% (Office for National Statistics, 2021). In adults

395 who are triple vaccinated, the ONS survey found a prevalence of 4-5% with no evidence
396 of difference by SARSCoV2 variant (Delta, Omicron BA.1 or Omicron BA.2) (Office for
397 National Statistics, 2022c).

398 As with adults, studies of PCC in children suffer from problems of comparability. A
399 systematic review published in December 2021 included 14 studies and estimated a
400 prevalence of Long Covid in children to be between 4% and 66% of those infected
401 (Zimmermann et al., 2021). However, studies were of variable quality and some suffered
402 from testing criteria that relied on symptoms found in adults, poor follow-up, and small
403 sample sizes. The latest ONS data, referenced above, from July 2022 estimate that 98,000
404 children aged 2-16 years in the UK have Long Covid (>4 weeks from onset of illness), with
405 26,000 estimated to have had Long Covid for at least a year from onset of illness. This
406 latter figure equates to 0.6% of children in the 2–11-year-old group and 1.23% in the 12–
407 16-year-old group (Office for National Statistics, 2022b).

408 The most recent systematic review on PCC symptoms available to the Expert Panel is a
409 draft conducted by the ECDC which is still pre peer review. It includes 65 peer-reviewed
410 papers of 61 retrospective or prospective cohort studies that included participants with
411 confirmed SARSCoV2 infection up to February 2021 with follow-up of at least 12 weeks
412 post infection. Twelve studies were conducted in Italy, 8 in Spain, 7 in France, 7 in the US
413 and in Denmark, 3 each in Germany, Norway and the UK each, 2 each in Australia and
414 Canada, and 1 in Turkey. Some preliminary findings are as follows (ECDC Review under
415 peer review).

416 The review stratified cases by initial COVID-19 hospitalization status (hospitalized vs
417 community cases). Looking first at cardiopulmonary manifestations, shortness of breath
418 was reported in 45% of hospitalized cases (22% of community cases), cough in 15% of
419 both hospitalized and community cases, palpitations in 13% (7% of community cases),
420 pain during breathing in 13% of both types of cases, and chest pain in 11% of both types
421 of cases. In hospitalized cases, the prevalence of asthma, COPD, pulmonary embolism,
422 pulmonary hypertension, bronchitis, and emphysema ranged between 0.4 and 1.5% at or
423 after 12 weeks. Myocardial infarction and stroke were also reported at a prevalence of 0.3-
424 0.4%.

425 In terms of neurological and muscular symptoms at or after 12 weeks, limb weakness was
426 reported in 38% of hospitalized and community cases, myalgia or body aches in 24% of
427 hospitalized cases (10% of community cases), joint pain in 20% (6% of community cases),
428 headache in 17% (14% of community cases), concentration problems in 16% of
429 hospitalized and community cases, taste and smell disturbance in 15% (12% of community

430 cases), dizziness in 10% of both types of cases, and "general neurological symptoms" in
431 5% of both types of cases.

432 In terms of gastrointestinal symptoms at or after 12 weeks, constipation was reported in
433 18% of hospitalized cases (8% of community cases), nausea and vomiting in 14% (10%
434 of community cases), stomach upset in 12% of both hospitalized and community cases,
435 diarrhoea in 12% (7% of community cases), reduced appetite in 8% of both types of cases,
436 and weight loss in 8% of both types of cases.

437 In terms of general functioning and mental health symptoms at or after 12 weeks,
438 functional limitations were reported in 51% of both hospitalized and community cases,
439 fatigue in 46% of hospitalized cases (31% of community cases), and reduced quality of life
440 in 37% of both types of cases. Depression was reported in 1.6% of hospitalized cases at
441 or after 12 weeks. There were multiple other symptoms at or after 12 weeks reported in
442 prevalence of less than 5%, including shivering, ringing in ears and feeling cold.

443 The mere listing of symptoms hides the more important issue of characterising multisystem
444 syndromes defined by clusters of symptoms that are jointly present in patients with
445 components that could vary with time and daily life activities and triggers, an aspect
446 deserving further attention (see section 1.2.5).

447 *Box 2 Prevalence estimates of PCC*

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	**20.9%** 95%CI: 12.1-31.3	**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 PCC

While much remains uncertain about the causes and underlying mechanisms of PCC, 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. PCC 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

464 protease 2 (TMPRSS2), a protein found on the surface of many cells (Beyerstedt et al.,
465 2021, Jackson et al., 2022) (although there may be alternative pathways involved in entry
466 to some cells lacking these receptors, such as neurones (Pepe et al., 2022)). These
467 receptors are distributed widely, so that while the virus enters the body through the
468 respiratory tract, it can infect a wide variety of cells, including those in the respiratory,
469 cardiovascular, gastrointestinal and neurological systems. The following section, which
470 draws extensively from reviews by Crook et al. (2021) and by Mehandru and Merad (2022),
471 summarises some of the proposed non-mutually exclusive mechanisms for the more
472 common manifestations. Several main mechanisms, each related to one another, have
473 been proposed (Figure 1).

474 *Figure 1 Potential pathophysiological mechanisms underlying Post-Covid-19*
475 *Condition*

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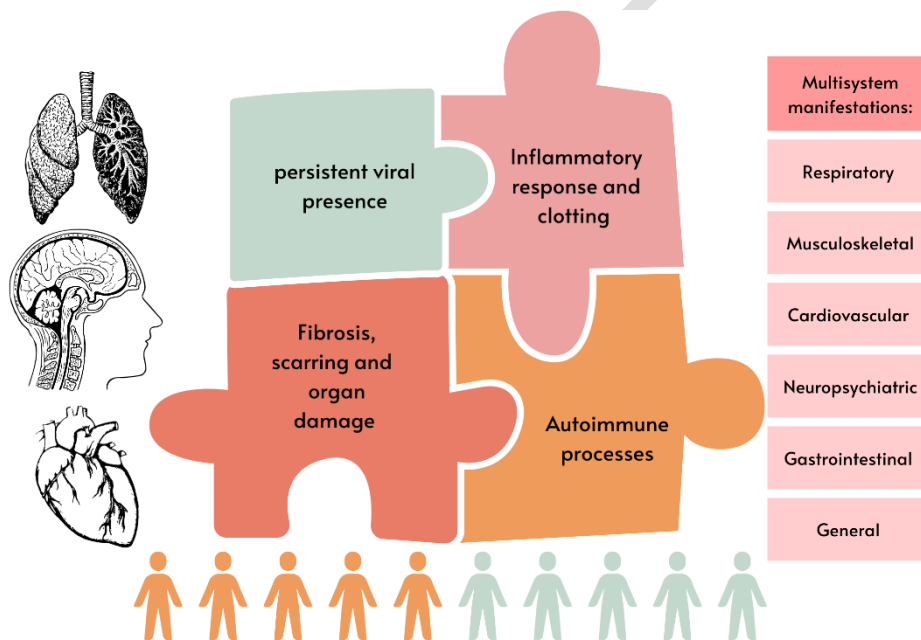
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479 The first is persistence of the virus or parts/remnants of the viral material (Pattle and
480 Farrell, 2006), with evidence that it can be found many months after the acute infection in
481 the gastrointestinal tract, central nervous system, and some other issues, as well as
482 evidence that memory B cells may continue to produce antibodies many months after the
483 acute infection. This is seen with other viruses, such as measles, which can give rise to
484 subacute sclerosing panencephalitis, a condition appearing typically seven to ten years
485 after apparent recovery from an acute infection. There is now some evidence of persistent
486 SARS-CoV-2 antigen, nucleocapsid protein or viral RNA especially in tissues that are
487 partially shielded from the immune system, such as the brain, testes, liver, gallbladder,
488 lymph nodes and gut including colon, appendix, and ileum (Chertow et al., 2021, Brooks
489 and Bhatt, 2021, Cheung et al., 2022). Persistent viral antigen presence may generate

490   pathogen-associated molecular patterns (PAMPs) which can in turn engage in host pattern
491   recognition receptors (PRRs) to trigger immune activation, and/or T and B cells. Chronic
492   stimulation of these lymphocytes can cause chronic inflammation (Choutka et al., 2022).
493   Cryptic SARS-CoV-2 tissue reservoirs have also been linked to persistent microvascular
494   endotheliopathy (Ahamed and Laurence, 2022). However, whether the presence of such
495   viral remnants definitely trigger the type of symptoms collectively known as PCC is still
496   unknown.

497   The second, and potentially triggered by the first, is persistent inflammation, associated
498   with changes in immune homeostasis, including a reduction in tissue-resident
499   macrophages, persistence of pro-inflammatory cells such as monocytes, altered cytokine
500   production, and increased effector T and B cells (Bergamaschi et al., 2021). When this
501   occurs in the vascular endothelium it can have very widespread effects (Ackermann et al.,
502   2020). Crook and colleagues (2021) discuss how these mechanisms affect different tissues.
503   They propose that lung damage occurs as result of chronic inflammation with the sustained
504   production of pro-inflammatory cytokines and reactive oxygen species. Endothelial damage
505   triggers activation of fibroblasts, leading to pulmonary fibrosis. Endothelial damage,
506   coupled with complement activation, platelet activation, release of pro-inflammatory
507   cytokines, and disruption of normal coagulation pathways may cause a prolonged
508   hyperinflammatory and hypercoagulable state, increasing the risk of thrombosis. The heart
509   can be affected by chronic inflammation of cardiomyocytes (Puntmann et al., 2022), which
510   may lead to myositis and death of affected cells.

511   The third and potentially linked to the first two is autoimmunity, with proposed
512   mechanisms, including viral mimicry, breakdown of tolerance against self-antigens, and
513   exposure of cryptic antigens during tissue damage. There is strong evidence of acute
514   COVID-19 triggering autoantibodies (Wang et al., 2021, Chang et al., 2021). Autoimmune
515   activation can also result from the immune system trying to target the pathogen from
516   bystander autoimmune activation unrelated to pathogen structure. B or T cells may
517   become activated if the viral antigens mimic self-antigens (molecular mimicry) (Choutka
518   et al., 2022). Such mechanism has been implicated in the link between EBV and multiple
519   sclerosis (Bjornevik et al., 2022). Dysregulation of the immune system may be in a manner
520   that allows previously harboured pathogens to reactivate and infect new body sites, such
521   as herpes viruses. Cervia et al. (2022) followed up patients who had a COVID-19 infection
522   for a year and identified a distinct SARSCoV2 immunoglobulin signature, with reduced IgM
523   and IgG3 titres during the acute infection, possibly related to reduced type I interferons.
524   It is worth noting that autoimmune diseases are generally more common in women than
525   in men, and we find a similar gender pattern in the prevalence of PCC.

526 A recent preprint of a study that conducted detailed immunological profiling of 215 PCC
527 patients found distinct immunological differences to matched controls including in specific
528 circulating myeloid and lymphocyte populations as well as elevated humeral responses.
529 There was also an observation of raised antibody responses against non-SARSCoV2 viral
530 pathogens, specifically Epstein-Barr virus. Another striking predictor in PCC patients was
531 low serum cortisol levels compared to controls (Klein et al., 2022).

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

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

547 COVID-19 infection has been linked to microbiome changes (Yeoh et al., 2021), which may
548 in turn be linked to immune function (Manfredo Vieira et al., 2018). A systematic review
549 concluded that changes in faecal and respiratory microbiome were common in patients
550 with COVID-19, with opportunistic pathogen abundance (Yamamoto et al., 2021). One
551 follow-up of those with post-acute COVID-19 syndrome (PACS) defined as persistent
552 symptoms three weeks after clearance of SARS-CoV-2 found higher levels of *Ruminococcus*
553 *gnavus*, *Bacteroides vulgatus* and lower levels of *Faecalibacterium prausnitzii* in the gut
554 and various inverse correlations between gut microbiota and symptoms (Liu et al., 2022).
555 It has been suggested that this could allow movement of inflammatory molecules from the
556 gut into the bloodstream.

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

562

563 *Figure 2 Predictors and proposed pathophysiologic mechanisms of Post-Covid-*
564 *19 Condition*

565

566 **Proposed contributing mechanisms**
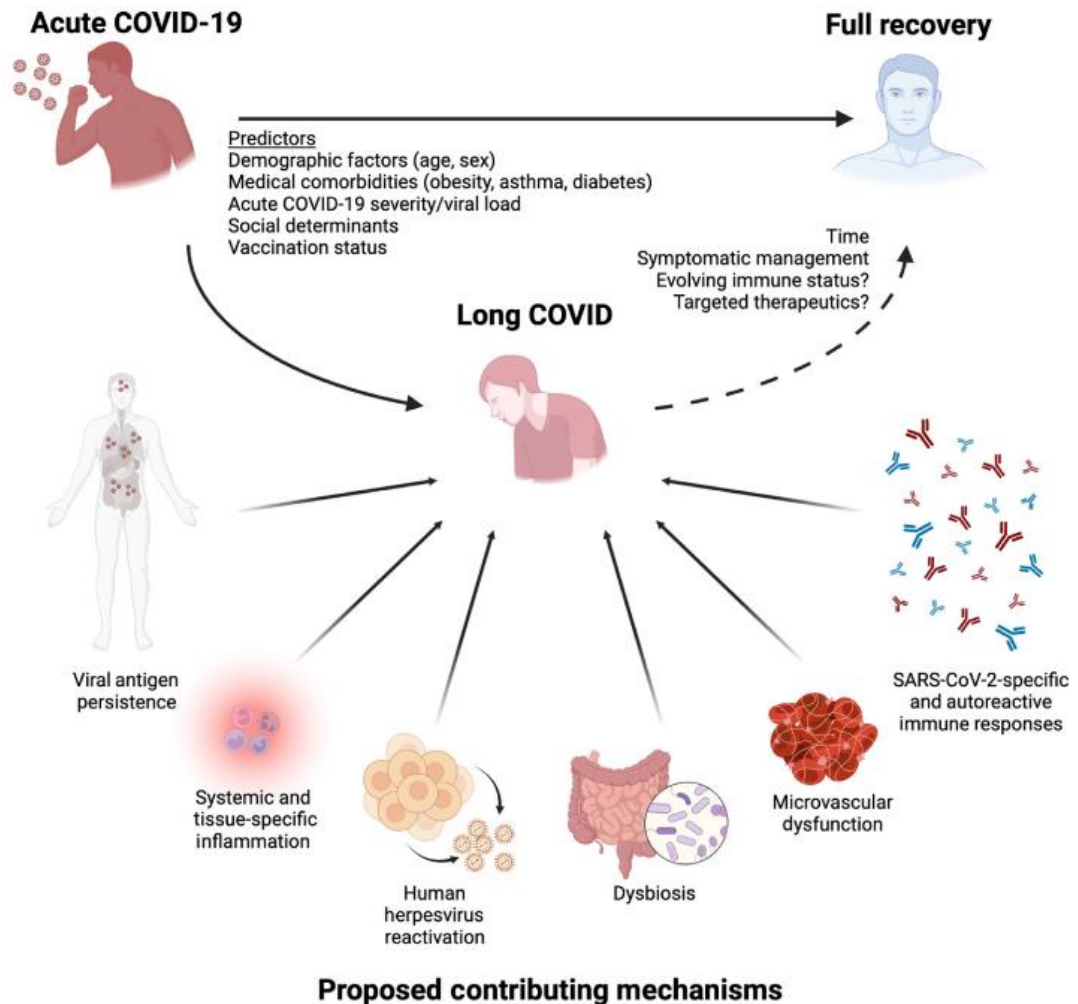
567
568 Source: Peluso and Deeks (2022)
569

570 **1.2.4. Possible risk factors**

571 As with the data on prevalence, clear identification of risk factors is complicated by the

572 plethora of small studies, with different definitions, in different settings, and with different

573 comparators. Some predictors of PCC reported in the literature include:

574 • Older age (Westerlind et al., 2021, Jones et al., 2021);
575 • Female sex (Jones et al., 2021, Huang et al., 2021, Bai et al., 2022)
576 • Hospitalization during the acute phase (Westerlind et al., 2021)

577   •   Immunoglobulin signature (Cervia et al., 2022)

578   •   Number of symptoms in the acute phase (Sudre et al., 2021, Arjun et al., 2022)

579   •   Smoking (Bai et al., 2022)

580   •   Vaccination status (Arjun et al., 2022, Office for National Statistics, 2022d,
581   Ayoubkhani et al., 2022a)

582   •   SARS-CoV-2 variant (Office for National Statistics, 2022d)

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

589 A crucial question is whether vaccination reduces the risk of PCC beyond that achieved by
590 reducing COVID-19 infections. The available evidence suggests that it does. An Italian
591 study with 2560 participants, of whom 739 had COVID-19, found that the number of
592 vaccine doses was associated with lower long COVID prevalence, from 41.8% in
593 unvaccinated patients to 30.0% in those with 1 dose, 17.4% in those with 2 doses, and
594 16.0% in those with 3 doses (Azzolini et al., 2022). Another study, from the United
595 Kingdom, compared just over 3,000 subjects who had COVID-19 after being double
596 vaccinated with those who did so while unvaccinated (Ayoubkhani et al., 2022b).
597 Vaccination was associated with a markedly reduced odds ratio for PCC, at 0.59 (95%
598 confidence intervals 0.50-0.69).

599 ### 1.2.5. The experience of PCC in adults

600 The most commonly reported symptoms of PCC are fatigue, headache, cognitive
601 dysfunction, shortness of breath, muscle aches, palpitations, chest pain/tightness,
602 dizziness, sleep disturbance and joint pain (Ziauddeen et al., 2022, Lopez-Leon et al.,
603 2021). However, a UK analysis of almost half a million patients with a positive test,
604 matched with almost two million others, found 62 symptoms that were significantly more
605 common by 12 weeks post infection (Subramanian et al., 2022). The largest adjusted
606 hazard ratios occur for anosmia (6.49, 95% CI 5.02–8.39), hair loss (3.99, 3.63–4.39),
607 sneezing (2.77, 1.40–5.50), ejaculation difficulty (2.63, 1.61–4.28) and reduced libido
608 (2.36, 1.61–3.47). Importantly, symptoms can fluctuate in severity, can relapse, and can
609 reappear (Brown and O'Brien, 2021). This complicates any attempt to develop
610 characteristic phenotypes.

611 There is evidence that symptoms cluster into systems. One study identified cardiovascular,
612 pulmonary, and neurocognitive clusters (Nalbandian et al., 2021), with another identifying

613 respiratory, cognitive and fatigue clusters. In those who were initially hospitalized with
614 severe COVID-19, a UK-based study identified four clusters of symptom severity at average
615 follow up of 6 months from hospital discharge. These included very severe (17%), severe
616 (21%), moderate along with cognitive impairment (17%) and mild (35%) (Evans et al.,
617 2021). One study concluded that having more severe and multisystem symptom clusters
618 is associated with being female, worse baseline health, lower income, and inadequate rest
619 in the first two weeks of the illness (Ziauddeen et al., 2022).

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

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

641 **PCC in Children and Adolescents**

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

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

PCC Stigma

652 People living with poorly understood health conditions experience health-related stigma,
653 which can get compounded by socio-demographic disadvantage and in turn potentially
654 result in poorer health outcomes (McManimen et al., 2018, Froehlich et al., 2022).
655 Testimonies from people living with PCC describe experiencing scepticism among
656 professionals when they describe their symptoms, giving rise to difficulty accessing support
657 (Ladds et al., 2020, Kingstone et al., 2020). In a study assessing the extent of perceived
658 stigma in people who report having Long Covid with a sample size of 966 UK participants,
659 95% experienced stigma at least 'sometimes' and 76% experienced stigma 'often or
660 always' (Pantelic et al., 2022). Those with a formal clinical diagnosis of Long Covid were
661 most likely to experience stigma. It should also be noted that those with PCC may
662 experience 'double stigma' if they belong to disadvantaged groups such as ethnic
663 minorities, immigrants or economically disadvantaged groups. Their symptoms, especially
664 if they lead to departure from the workforce, may increase the risk of isolation which may
665 compound the experience of stigma, particularly internalized stigma (the expectation of
666 bias or poor treatment by others) (Van de Vyver et al., 2021, Earnshaw et al., 2013).

1.2.6. Future research

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

Box 3 Some unanswered research questions on PCC

1. How does the epidemiology of PCC vary by gender, age group, ethnicity, or socioeconomic status (incidence, recovery)?) also in an inter-sectional perspective?
2. How does clinical severity of acute COVID-19 disease (from asymptomatic infections to severe disease) and pre-existing health condition (especially preexisting comorbidities, medications use, smoking status, obesity) as predict PCC?
3. What are the predictors of recovery from PCC?

4. What are the pathophysiological mechanisms of PCC and what are the implications for developing and using biomarkers?
5. Is there a genetic predisposition to PCC?
6. What are the effective treatments for PCC in adults and children (pharmacological and non-pharmacological)?), with particular attention to gender differences?
7. How to define treatment effectiveness and which measurement tools can be used for the different components of the PCC syndrome?
8. What are the most effective rehabilitation methods and timing for PCC?
9. How to best organise care pathways for individuals with PCC?
10. What is the interaction of different SARS-CoV-2 variants with the occurrence of PCC?
11. What is the interaction of the timing and number of COVID-19 vaccine doses with the occurrence of PCC?
12. What is the relationship of COVID-19 vaccination to the risk of new PCC and modifying the disease course of existing PCC and what is the implication of direct active antiviral for SARS-CoV-2 use during acute illness on the risk of developing PCC?
13. What is the effect of reinfection with the same or different variant of SARSCoV2 to the risk of new onset of PCC and modifying the disease course of existing PCC?
14. What is the role of stigma, social identity change and stereotyping in patients with PCC and how to address such negative effects and maximise positive social mechanisms?
15. What are the wider healthcare, social costs and economic impacts of PCC?

There are, however, many challenges in conducting research on this topic. For example, case definitions of PCC 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 PCC. 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.

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

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

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

750 A related issue, beyond the ability to convene large research teams, is the importance of
751 conducting large-scale studies. This has been recognised in the Horizon 2020-funded
752 ORCHESTRA project, which aims to establish an international large-scale cohort for
753 retrospective and prospective studies, and will be a useful mechanism to study PCC
754 (ORCHESTRA., 2022). Separately, a number of cohorts of patients with PCC have already

755 been established (PHOSP-COVID Collaborative Group, 2022), the largest of which has been
756 assembled International Severe Acute Respiratory and Emerging Infection Consortium
757 (ISARIC) (Garcia-Gallo et al., 2022). It had enrolled over 700,000 patients in 1,500 centres
758 in 60 countries by September 2021. It will be important that other studies, even if not
759 formally part of this consortium, share methodologies and definitions. For example, there
760 is now a proposed core set of outcomes for use in research on PCC (and in clinical practice)
761 established by an international Delphi exercise (Munblit et al., 2022).

762 Similarly, it is important to learn lessons from the issues that plagued therapeutic trials of
763 COVID-19 candidate medicines during the pandemic. A lack of coordination led to large
764 numbers of underpowered trials being conducted. The exception, from the UK, was the
765 RECOVERY trial (Wise and Coombes, 2020). This is an adaptive mononational platform trial
766 that, despite some methodological limitations such as the open-label design, permits
767 evaluation of different target treatments for the same disease on an ongoing basis, with
768 therapies being allowed to enter or leave the platform based on a decision algorithm
769 (Woodcock and LaVange, 2017). Undertaken in partnership with the NHS, this ensured
770 that virtually every patient with COVID-19 was given the opportunity to enter a clinical
771 trial. While it will be possible to conduct very large trials in some member states, there is
772 a danger that patients in some of the smaller ones may be excluded from this process.
773 Coordination between clinical trials to ensure that larger studies are conducted must be a
774 priority, given the emerging evidence, from some member states, of the growing use of
775 unevaluated treatments (Davies, 2022). Yet there are major barriers to undertaking such
776 trials at a European level, as described in a paper that collates the experiences of those
777 involved in one such trial (Diallo et al., 2022). This is EU-RESPONSE, funded by Horizon
778 2020 to enable expansion of the French DisCoVeRy trial to other European and associated
779 countries (Ader, 2020). They also draw on experiences with the EU-SolidAct second-
780 generation pan-European platform trial for COVID-19 treatments, again linked to
781 DisCoVeRy. EU-SolidAct was able to use the Voluntary Harmonization Procedure (VHP)
782 created in 2009 by the Heads of Medicines Agencies, whereby a single application is sent
783 to one reference national competent authority (NCA), coordinating responses of all NCAs,
784 prior to a national phase in each country. This was not possible with EU-RESPONSE because
785 DisCoVeRy had first been authorised in France using a national procedure. While
786 RECOVERY was able to recruit the first patients within 9 days of the first protocol being
787 written, the VHP for EU-SolidAct took 56 days and the subsequent national phases took
788 variable periods from days to months. The expected time frame for any amendments was
789 50 days. In contrast, the UK system enabled amendments to be made within a few days.
790 There were also many trivial but time-consuming problems such as different requirements
791 for information leaflets. The authors note that the new Clinical Trials Regulation 536/2014
792 will address some of the problems experienced but make a series of valuable

793 recommendations about how the Regulation might be interpreted. While the issues raised
794 go beyond those of treatments for PCC, if they are not adequately resolved the conduct of
795 the large-scale European trials that are needed will be compromised. Based on the lesson
796 learned, some initiatives are already ongoing to optimise the EU environment of clinical
797 research; in particular the ACT-EU and the CT-CURE joint action initiatives, which aim to
798 facilitate the conduction of large multinational clinical trials and to provide a harmonized
799 and accelerated assessment for study approval using the Clinical Trial Information System
800 (CTIS).

801 A second consideration is the ability to take advantage of the natural laboratory that the
802 EU offers. While therapeutic interventions, such as new medicines, can be expected to
803 work in the same way everywhere, this is not true for more complex ones, such as the
804 implementation of multidisciplinary teams. Their operations will depend on context, such
805 as historical hierarchies within health organisations. As will be discussed in the next
806 section, the evidence that we already have on the management of complex chronic
807 conditions points to a need for much better team working. However, we know that this is
808 difficult in some countries because of professional boundary disputes. When evaluating and
809 implementing these types of interventions, it will be necessary to find solutions that are
810 consistent with national legislative, regulatory, and cultural contexts.

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

816 The first is a package of research in basic science, building on what is already a large
817 portfolio of studies. It is likely to include further studies on the persistence of the virus in
818 some people, for example, in brain or gastrointestinal tissue. It is also likely to include any
819 impact of the virus on the immune system, and in particular, autoimmunity. This work
820 should also address the need for biomarkers of the various manifestations of PCC. Here
821 there is some promising news from researchers using machine learning who have identified
822 what appear to be specific patterns of immune markers (Klein et al., 2022). As noted
823 above, further research would usefully involve scientists who have been studying the long-
824 term consequences of infection with other viruses. Already, research on SARS-CoV-2 and
825 the host response, have increased our knowledge of the mechanisms involved in the role
826 of viruses in disease causation.

827 The second builds on what is already underway in several countries and involves
828 establishing cohorts of patients who can provide information on the natural history of this

829 condition. As noted above, it will be crucial to coordinate these studies and ensure funding
830 support for them. It is neither necessary nor helpful that they all answer exactly the same
831 question, but it would avoid future problems if they could, at a minimum, use shared
832 definitions and methodologies for capturing key variables.

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

844 It will also be important to clarify what role, if any, the new health emergency organisation
845 HERA might play (Anderson et al., 2021). In addition to that, it is also important to mention
846 the new reinforced role of the European Medicines Agency (EMA) in providing support to
847 the timely development of medicines during public health emergency, as established by
848 the Regulation (EU) 2022/123. In particular an Emergency Task Force (ETF) has been set
849 up to provide guidance to industry and academia and facilitate the conduct and approval
850 of clinical trials in close cooperation with HERA, the EC and the Clinical Trial Coordination
851 Group (CTCG). Among other tasks, the ETF can provide clinical trial protocol assistance
852 and accelerated and free of charge scientific advice to ensure the timely development of
853 high-quality, effective and safe medicines. [Scientific advice and protocol assistance |
854 European Medicines Agency (europa.eu)]

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

860 The fourth is research on the impact of PCC on those affected and on their families, as well
861 as wider population-level health, social and economic inequalities generated by this
862 condition. As with any impairment, that impact will depend on the extent to which it is
863 possible to make reasonable adjustments within their living and working environments.
864 This research will likely include the development of improved tools to monitor quality of

865 life, both physical and mental, and identify interventions that can support affected people,
866 including in their participation in the labour market and in workplace conditions.

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

873 **Box 4.** Early mobilisation of EU funding in COVID 19 pandemia

In summary, EU funding has been mobilised early on, in line with 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 patients enrolment as early as in March 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.

874

875 **1.3.Organisational and resource requirements for healthcare systems to**
876 **design and develop appropriate health services for PCC**

877 **1.3.1. Implications for the health workforce**

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

885 Health workers have been at particular risk of contracting COVID-19 (Gómez-Ochoa et al.,
886 2021) and, consequently, of developing PCC. Even though most have now been vaccinated,

887 and many will also have had infections during the series of waves of new variants, they
888 remain at risk and each new infection brings with it an additional risk of PCC. In some
889 cases, and especially when experiencing a flare-up, their symptoms will be of sufficient
890 severity to prevent them from working. This is occurring at a time when many health
891 systems are struggling to recruit and retain staff as a result of demographic change.

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

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

906 Reducing the risk of new COVID-19 infections in the health workforce means continuation
907 of infection control measures in health facilities as long as the virus is circulating. Measures
908 that are effective have the additional benefit of reducing the risk of other airborne
909 infections, such as seasonal influenza. Thus, organisations with responsibility for health
910 facilities should ensure that they have up to date guidance on infection control. Given the
911 airborne nature of transmission, guidance would be expected to prioritise air quality, with
912 high quality ventilation and filtration as appropriate (Conway Morris et al., 2021), mask
913 wearing (with high quality masks of at least FFP2 standard), and monitoring of air quality
914 with CO_2 monitors. In the longer term it will be important to ensure that building standards
915 for health facilities are updated to take account of the growing body of evidence from
916 aerosol engineers and others about how to ensure clean indoor air (Morawska et al., 2021).
917 The UK's Royal Academy of Engineering has produced two detailed reports on what is
918 required to create infection resilient buildings (Royal Academy of Engineering, 2022).

1.3.3. Supporting health workers with PCC

920 The second imperative is to ensure that there are systems in place to support staff with
921 PCC. In May 2022 the EU Advisory Committee on Safety and Health at Work (ACSH),

922 representing workers and employers, reached agreement on recognising COVID-19 as an
923 occupational disease in health and social care and in domiciliary assistance and, in a
924 pandemic context, in sectors where there is an outbreak in activities with proven risk of
925 infection (European Commission, 2022). They also supported an update of the EU list of
926 occupational diseases to include it. This is only a recommendation as designating diseases
927 as occupational is a national competence. The Expert Panel considers that this is an
928 important step in recognising the risks that health workers face and acts as an incentive
929 for employers to take action to reduce risks. This also links with our previous Opinion on
930 supporting mental health in the health workforce, and specifically emphasizing the need
931 for organisational and managerial support (Expert Panel on Effective Ways of Investing in
932 Health, 2021b). The fluctuating nature of the symptoms may require leave of absences,
933 sometimes at short notice and for initially undetermined periods of time, as well flexible
934 phased return to work schemes. This will require adapted human resources structures and
935 processes.

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

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

954 ### 1.3.4. Preventing patients from getting PCC

955 We previously highlighted the need for those responsible for health facilities to ensure that
956 they are designed and operated in ways that minimise the risk to the health workforce.
957 Many of the measures that were mentioned apply equally to safeguarding patients. While

958 figures will vary over time and place, reflecting different stages in the epidemic curves of
959 successive waves of COVID-19, characteristics of the hospitals involved, and levels of
960 community transmission, it is clear that an appreciable share of COVID-19 infections are
961 acquired in hospitals (Carter et al., 2020, Bhattacharya et al., 2021), with some evidence
962 that official figures substantially underestimate the risk (Lumley et al., 2021).

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

1.3.5. Models of care for patients with PCC

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

989 The latest WHO guidelines on managing COVID-19 set out 3 core components of
990 rehabilitation services - multidisciplinary rehabilitation teams, continuity and coordination
991 of care and people-centred care and shared decision-making. The basic principles involved
992 in implementing these are simple in theory but difficult in practice (Nolte and McKee, 2008).
993 The model of care should be centred on the patient, who will often be on a long and complex

994 journey, sharing their story with a diverse array of health workers each with specialised
995 knowledge or skills. Their journey will often be eased if they have the support of someone,
996 typically a contact point in a primary care team, who can offer them at least a tentative
997 map and who can help co-ordinate their many excursions to seek specialist help. Their
998 overall care package will be better if they play a full role in its design. All of this can be
999 assisted by advances in information technology, and especially the sharing and accessibility
1000 of electronic health records across levels of care. Allowing patients to access their own
1001 electronic health records and share them with health professionals may also help,
1002 depending on the level of maturity of information technology within a given health system,
1003 although care must be taken to not increase the digital divide.

1004 Beyond these broad principles, there are certain challenges that must be considered. First,
1005 recalling that severe COVID-19, including the presence of complications of the acute
1006 infection, such as increased clotting, are more common in patients with pre-existing
1007 conditions, it will be important to recognize that many (but not all) people with PCC have
1008 several other conditions (Office for National Statistics, 2022a). The burden of
1009 multimorbidity increases with age, with the added complication that many older people
1010 also suffer from some degree of frailty or diminished cognitive function and impairment of
1011 other body systems, such as the musculoskeletal, renal, or cardiovascular. In some cases,
1012 the mechanisms giving rise to PCC will have caused particular problems but in others they
1013 exacerbated existing ones. Hence, a holistic person-centred approach to managing such
1014 patients must encompass all of their problems.

1015 Another challenge of PCC in providing a holistic model of care is that it must take account
1016 of the patient's circumstances. Such person-centred and goal-oriented care is an inherent
1017 value in rehabilitation medicine. For example, locomotor problems will impact differently
1018 on someone who lives on the ground floor near to shops than someone living up several
1019 flights of stairs in an isolated area. Similarly, different jobs require different skills and the
1020 extent to which a particular impairment becomes a handicap will vary. The impact of PCC
1021 on the person's ability to function and achieve their set goals should be the focus of
1022 management, with use of shared decision making to determine appropriate treatments.

1023 A third challenge, which is especially relevant to PCC, is the high degree of uncertainty
1024 about the nature, progression, and management of the condition. Unlike, for example,
1025 diabetes, where measuring HbA1c is an established way of monitoring treatment
1026 effectiveness, there are no good biomarkers for PCC at the moment. This uncertainty also
1027 means that health workers will struggle to offer advice on prognosis, information that
1028 patients need to plan their future. A good approach is to provide simple summaries of the
1029 available evidence to clinicians to help answer common questions about the condition and
1030 prognosis (Greenhalgh et al., 2022).

1031 For these reasons, while it is possible to set out certain common pathways to assessment
1032 and management of some of the more common manifestations, a health system response
1033 must incorporate a high level of flexibility, both within the health system and across
1034 sectors.

1035 These challenges were apparent in an exercise that followed best practice by engaging in
1036 co-design of a model of care with patients and health workers who engaged in focus
1037 groups, narrative interviews, and diaries of symptoms (Ladds et al., 2021). This exercise
1038 yielded many important lessons for those developing models of care. Health workers
1039 struggled with signs and symptoms that did not fit their pre-existing medical knowledge.
1040 They reported doing various tests, some of which generated abnormal results, but did not
1041 help them decide what to do next. They made much use of mindlines, internalised and
1042 collectively reinforced tacit guidelines that are widely used in clinical practice, to make
1043 sense of this uncertainty. This involved informal discussions with patients (many of whom
1044 were also professional colleagues) and others to identify what worked or did not in
1045 particular circumstances. In some cases this conflicted with official guidance which was,
1046 sometimes, seen as detached from the reality that the health workers were experiencing.
1047 Support groups of people with PCC were especially useful, generating tacit knowledge on
1048 how to handle PCC. The exercise generated several suggestions for service development,
1049 all of which are intuitive but, as the participants noted, had not, in their experience, been
1050 addressed. The most important was a "one stop shop" situated in primary care, but with a
1051 multidisciplinary team that can offer a wide range of skills and expertise. Their role would
1052 be to enable rapid identification of "red flag" conditions requiring rapid treatment, to detect
1053 and treat comorbidities and complications, and to provide support for symptomatic
1054 management. They should have rapid access to appropriate investigations, both an initial
1055 package to evaluate the patient and more specialized ones where necessary.

1056 Unfortunately, even when much is known about the conditions that the patient is suffering
1057 from, there are many obstacles to developing, implementing, and sustaining such a model.
1058 There are structural barriers, with fragmentation created by administrative borders. There
1059 are procedural barriers, caused by differences in operating methods in different
1060 organisations. Financial barriers exist where budgets cannot follow the patient or do not
1061 rise to meet the new care needs. Professional barriers are common and reflect self-interest,
1062 restrictive practices, and inflexibility. These can be overcome, but only with determined
1063 leadership. Therefore while we can broadly describe what health systems must do to
1064 respond to the challenge of caring with patients who have PCC, we are under no illusion
1065 that it will be easy. When designing models of care for patients with PCC it will be important
1066 to draw on the lessons from successes and failures that have been learned when developing
1067 and implementing these models in each country (Nolte et al., 2008). Systematically

1068   identifying what works and why, for instance drawing on process evaluation methods and
1069   frameworks from the field of implementation science, can help provide valuable insights
1070   into the scale and nature of the obstacles listed above and ways in which they might be
1071   overcome. We now set out some general principles of how health systems should evolve
1072   and adapt to meet the burden of PCC.

1073   ### 1.3.6. A health systems approach to PCC

1074   To consider the second question posed in the mandate, "Provide an analysis of the main
1075   knowledge, organisational and resource requirements for healthcare systems to design and
1076   develop appropriate health services for post COVID-19 condition", we have structured our
1077   opinion around the WHO health systems framework and, in particular, the system building
1078   blocks on the left in Figure 3.

1079   *Figure 3   The WHO Health Systems Framework*

1080
1081   Source: World Health Organization (2010)

1082   ### 1.3.7. Service delivery

1083   At least in the short-term, given the high level of uncertainty about this condition and the
1084   complexity of managing it, there is a strong argument for creating dedicated services for
1085   patients with PCC that bring together a range of specialties and expertise (World Health
1086   Organization, 2022) with a strong role for coordination in primary care. This has several
1087   advantages. First, it offers a means to bring together a range of health professional with
1088   appropriate skills (detailed in the next section) in an integrated team, supported by
1089   continually revised clinical guidelines and with access to well-functioning referral
1090   mechanisms. However, as with all specialised services such as post-myocardial or stroke
1091   rehabilitation, there is a risk that those with one or more other conditions, some of which
1092   may have predisposed them to COVID-19 and may have manifestations that interact with
1093   those of PCC, may find that their overall care is fragmented. Consequently, it will be
1094   necessary to ensure that there are mechanisms to prevent this happening, as well as

1095 supporting both primary and secondary care physicians in managing patients with PCC
1096 (Greenhalgh et al., 2022). The WHO guidelines on rehabilitation services for PCC highlight
1097 core functions that these services should implement including standardised symptom and
1098 outcome measurement, and robust referral and follow up systems (World Health
1099 Organization, 2022). They recommend using a hybrid approach of in-person and remote
1100 models that is integrated across all levels of health care. Specific training and organisation
1101 should be provided to primary care professionals to ensure comprehensive overall care.
1102 This will require extra support, financial and organisation transformation, to be effective.

1103 As already noted, this Opinion draws extensively on existing experience with the
1104 management of complex chronic diseases. One aspect of this that is often overlooked is
1105 the risk that innovative services can widen existing inequalities (Wagenaar and Prainsack,
1106 2021). Consequently, health authorities should undertake exercises during the planning
1107 phase that explicitly look for the potential for this to happen. Ideally, they will involve
1108 vulnerable groups, such as those from ethnic minorities, migrants, remote areas, and
1109 otherwise disadvantaged communities in planning the services. This should include
1110 engagement with communities to build trust and understand barriers to accessing
1111 healthcare, addressing issues such as interpretation, culturally appropriate messaging, and
1112 accessibility, especially for those with disabilities, such as learning disorders (a group that
1113 has suffered disproportionately in the pandemic) or visual or hearing impairment. A related
1114 issue, sometimes overlooked, is the risk of digital exclusion when innovative services take
1115 advantage of the many opportunities provided by, for example, apps on smartphones. This
1116 will also include ensuring that health information systems (see later section) are designed
1117 in ways that will support monitoring of any potential inequalities. There is an extensive
1118 literature on all of these topics that can be drawn upon.

1119 There are existing guidelines on the management of PCC that can be drawn upon in many
1120 countries. Examples include those developed by the UK's National Institute for Health and
1121 Care Excellence (NICE), published in December 2020 and updated in November 2021
1122 (National Institute for Health and Care Excellence, 2020) or by the UK's Royal College of
1123 General Practitioners (Nurek et al., 2021). The WHO's latest guidelines on COVID-19
1124 include up-to-date guidance on the best ways to manage the different symptoms
1125 associated with PCC (World Health Organization, 2022). It is, however, important to
1126 recognize that the evidence base underpinning guidance may change as additional
1127 knowledge becomes available. It is particularly important to ensure that guidance is based
1128 on representative groups of patients, covering the full spectrum of PCC severity and
1129 symptom clusters.

1130 As per the guidance prepared by the English NHS and other sources, there are three main
1131 routes by which individuals with PCC may present to the health system. The first comprises

1132 those whose acute illness was mild but subsequently develop symptoms suggestive of PCC.
1133 They should be assessed by a trained health professional within primary care, or in a
1134 separate designated service to assess physical, cognitive and functional abilities.

1135 Investigations should be based on their signs and symptoms and are directed to identify
1136 serious conditions that may be related to PCC, as well as those that can be linked to other
1137 conditions that may be present. Inevitably, given the lack of any specific biomarkers for
1138 PCC so far, as well as its myriad manifestations, attribution of any signs or symptoms to
1139 PCC will be complicated, although we can expect that there will be scientific advances that
1140 will help in this respect in the future.

1141 The second group comprise those who were hospitalised with COVID-19. As with all
1142 patients in hospital, they should receive a personalised care package upon discharge,
1143 shared with their referring provider (if any), who will often be a member of a primary care
1144 team. Many existing clinical guidelines recommend reviews at four and twelve weeks, with
1145 investigations as appropriate for the patient's signs and symptoms. At the twelve week
1146 point patients should be advised to seek care from their health care provider if new
1147 symptoms arise.

1148 A third group comprises whose who required treatment in intensive care units. Although
1149 formally outside the definition of PCC used in this opinion, these patients are at risk of
1150 post-ICU syndrome but also PCC. Consequently, hospitals should ensure that each patient
1151 is assessed by a multidisciplinary team with expertise in both conditions, and which has
1152 easy access to appropriate referral pathways, especially to rehabilitation services.

1153 In all of these cases it is important to recognise that symptoms typically fluctuate. Some
1154 may resolve and others may appear for the first time. As noted previously, people who
1155 have had COVID-19 are at increased risk of certain complications, such as thrombosis, for
1156 over a year after the initial illness. Patients should be advised of this and that they should
1157 seek further care if needed, using Patient Initiated Follow Up if this is available within the
1158 health system in question. As with all chronic conditions, self-management is an important
1159 part of the overall care package. Patients should be provided with information on
1160 appropriate patient organisations, which can provide support and advice on adjusting in
1161 daily life, accessing the full range of services they may need, including social and
1162 employment support, and generally offering a forum for exchanging information. Some
1163 countries have social prescribing link workers (or similar roles) and can direct patients to
1164 other forms of support.

1165 Finally, a major research effort, incorporating co-production with patients and families, is
1166 required to understand the impact of PCC in children and to develop effective services and

1167 therapies. it will also be important to create processes to care for children and young people
1168 with PCC. These processes must work closely with education providers and social services.
1169 Those providing services must have specialist expertise in paediatric PCC.

1170 These systems and processes will only come about if healthcare systems commit to
1171 addressing PCC. This is discussed below, under the health workforce (co-ordinating care
1172 for individual patients) and leadership and governance (designing systems that reduce
1173 fragmentation).

1.3.8. The health workforce

1175 The burden of PCC in many countries may initiate debates on the need, or is already giving
1176 rise to, a new medical specialty. This is not the first time that this has happened, bearing
1177 in mind the evolution of health workforce in diabetes care or for AIDS.

1178 While services continue, in general, to be led by physicians, clinical management is
1179 increasingly a shared process, with the patient taking on an increasing role in their own
1180 management, and supported by a team of different health professionals.

1181 PCC is, as already noted, a condition with a known cause (COVID-19 infection) that affects
1182 many different body systems. The burden of disease is high. As noted previously, in the
1183 United Kingdom, one of the few countries with high-quality data on prevalence, it affects
1184 about 3% of the population (Office for National Statistics, 2022b). This is lower than
1185 diabetes, which affects about 6% of the adult population in Europe, but much higher than
1186 HIV infection, which has a prevalence of <0.3% in most European countries and a highest
1187 prevalence of just under 1% in Estonia.

1188 There are, however, important differences. While future trends in diabetes and HIV can
1189 broadly be estimated, the future of PCC is very uncertain. It is a function of a complex mix
1190 of characteristics of the virus, including variants causing unpredictable waves, and to some
1191 extent individual-level characteristics, including levels of immunity and underlying health
1192 conditions. Hence, it cannot be known with certainty whether the current need for services
1193 will persist, increase or decrease. Given the time it takes to train a new specialist physician,
1194 and the uncertainty about whether there will be a need for that individual's services in the
1195 medium and long term, there is a strong case, at least in the immediate future, for creating
1196 new teams from existing health professionals with relevant skills. These include history
1197 taking, clinical examination and carrying out relevant bedside tests (which are likely to
1198 include measurement of oxygen saturations on exertion and cognitive assessment). They
1199 should be supported by access to rapid diagnostic tests, likely to include appropriate blood
1200 tests (including any biomarkers that may be identified in the future), chest x-rays, 24-hr

1201   ECGs, and lung function tests, as well as access to specialist multidisciplinary teams for
1202   organ-specific advice. For example, the commonly described symptom of 'brain fog' may
1203   be due to a variety of mechanisms so neurological assessment is likely to be important.

1204   These teams would, ideally, include those with experience in management of disabling
1205   chronic conditions, in particular those that present with fatigue or respiratory problems,
1206   although other experience may also be relevant, such as physical and neurological
1207   rehabilitation. Health authorities must ensure that they have access to the training they
1208   need to take up their new roles and to continuing access to information on what can be
1209   expected to be a rapidly evolving field.

1210   Drawing on the analogies with other complex conditions, we can identify some broad
1211   principles. The first is that health workers caring for patients with PCC must be organised
1212   in multidisciplinary teams. Given the complexity of this condition, coupled with the rapidly
1213   evolving knowledge on its aetiology, there would seem to be a strong argument, at least
1214   at present, that these teams should include a health professional with up-to-date
1215   understanding of PCC.

1216   These teams should include, or at least have rapid access to, a wide-ranging of specialist
1217   expertise. There is growing evidence of the value of care coordinators or patient navigators,
1218   staff who understand complexity of the journey on which the patient is travelling and who
1219   can support their movement along it. This concept draws on the case worker model used
1220   in social work, with individuals who can help patients get the care they need from what is
1221   often a fragmented system. This should include providing advice to patients about what
1222   they can expect in different clinical encounters, recognising these will often be stressful.
1223   They can also help to explain things that the patient finds unclear and can liaise with other
1224   health professionals as necessary. In some countries, this role may be taken on by
1225   specialist nurses who have the additional skills and expertise to arrange and undertake
1226   appropriate investigations, and, in some cases, to prescribe medicines for symptomatic
1227   management of common complications. Given the impact of PCC on issues such as
1228   employment, it is also useful to have a social worker as part of a trans-disciplinary team
1229   (World Health Organization, 2022).

1230   The diversity of professional expertise is illustrated by the following examples (which are
1231   non-exhaustive).

1232   Speech and language therapists can play an important role, supporting rehabilitation of
1233   patients with some of the common PCC symptoms, such as swallowing difficulties, and
1234   respiratory and neurological problems.

1235 Occupational therapists can play a crucial role in supporting patients to regain and maintain
1236 independence in their daily activities, and in particular supporting vocational rehabilitation
1237 and will enable them to re-enter the workforce. The importance of this role is clear from
1238 the growing evidence in some countries of how PCC is depleting the labour force (Lawton
1239 and Alwan).

1240 Psychologists can support patients experiencing cognitive dysfunction and common mental
1241 disorders, while supporting them as they adjust to constraints on their functional capacity.
1242 Dieticians are also important, assisting patients with loss of appetite or swallowing
1243 difficulties. Pharmacists can play a role in medicines reviews and provision of advice on the
1244 use of over-the-counter preparations.

1245 The rules that each of these groups play, in practice, will vary among health systems. One
1246 crucial factor will be the extent to which each health system has embraced modern
1247 approaches to task shifting. Unfortunately, as we have noted in a previous Opinion on this
1248 topic, this is highly variable and, in many countries, there are significant structural and
1249 financial barriers to implementing change (Expert Panel on Effective Ways of Investing in
1250 Health, 2019). Arguably, PCC offers an opportunity to bring about the necessary changes,
1251 which would bring benefits not only for this condition but for many other chronic ones.

1252 ### 1.3.9. Health information systems

1253 Access to high-quality data that capture appropriate information on all patients is a
1254 prerequisite for the effective and efficient functioning of a health system. PCC needs to be
1255 systematically and consistently coded, but it can present several challenges (Mayor et al.,
1256 2021, Meza-Torres et al., 2022). As noted previously, PCC can manifest in many different
1257 ways, presenting to different specialities, and coexisting with other clinical conditions.
1258 Thus, operationalising any of the definitions that have been proposed in routine clinical
1259 practice will be difficult. How this is done in any particular country will vary according to
1260 the organisation of healthcare and the information systems already in place. In this section
1261 we have applied well-established principles in developing and implementing health
1262 information systems to the challenges created by the advent of PCC. However, we stress
1263 that these are principles apply more generally, even if PCC, with its attendant complexities,
1264 makes them more important than previously.

1265 We first examine information governance. It seems self-evident that there should be well
1266 functioning systems to ensure that appropriate data are collected, collated, synthesised,
1267 and transmitted to those who need them at all levels of the health system. This calls for
1268 individuals at all levels with designated responsibility for the timeliness and quality of data.

1269 The next paragraphs set out, in broad terms, what such a system might look like, again
1270 recognising the need to take account of the specificities of the health system concerned.

1271 At a national, regional, or organisational level (depending on the characteristics of the
1272 health system), there should be mechanisms in place for establishing, monitoring, and
1273 revising as appropriate the data systems that are in place to ensure that they are fit for
1274 the purpose of responding to PCC. This is likely to draw on individuals with a range of
1275 expertise, including informatics, clinicians managing PCC, and public health specialists who
1276 can ensure the inclusion of a population perspective. This structure must have a system to
1277 monitor emerging evidence from research and ensuring that it is acted on where
1278 appropriate. Such a structure is desirable for management of all common chronic
1279 conditions and, where one does not already exist, the advent of PCC may be seen as an
1280 opportunity to create one that can have sub-groups with specialist expertise in a range of
1281 these conditions.

1282 Within each major health facility, there is a strong case for having a named clinical lead
1283 who can work with informatics experts to ensure that data systems reflect the goals of the
1284 service (i.e. 'what are the problems and what are we trying to achieve?'), that appropriate
1285 patient-centred outcome measures are being collected (i.e. 'how will we know that our
1286 services have been successful?'), and a minimum demographic dataset to inform service
1287 development and address health inequalities (i.e. 'how will we know where the gaps are in
1288 our services?').

1289 All except the smallest facilities should also have someone responsible for ensuring that
1290 data collection systems are in place, rules for coding have been disseminated, and staff
1291 have received training in their use, guided by the national principles and rules of sensitive
1292 data protection, including valid consent of the patient if applicable. Ideally, the information
1293 collected will permit monitoring of the extent to which the facility meets the needs of all
1294 groups, necessitating the collection of data on characteristics known to be associated with
1295 inequalities in access. Where this is not prohibited by national legislation, this should
1296 include data on ethnicity, as well as on contextually appropriate measures of deprivation,
1297 which may be based on the characteristics of the area in which the patient resides. There
1298 should be mechanisms in place to enable these data to be shared with appropriate higher-
1299 level organisations, which may be organised on a geographical basis, for example, where
1300 county councils are responsible for healthcare, or affiliation, as with sickness funds.

1301 Within each higher-level organisation, there should be a designated team who are
1302 monitoring the quality and completeness of the data reported by providers and who are
1303 tracking, to the extent possible, the quality of the care provided, with a particular focus on
1304 equitable access to appropriate care. Thus, for example, an unusually high or low level of

1305 referral to certain types of specialists might justify further investigation. This team will also
1306 have expertise in information systems and can support smaller health facilities.

1307 The pandemic revealed major shortcomings in the timely access to appropriate health data
1308 within the EU. For example, even though excess mortality was soon identified as a critical
1309 indicator of the impact of COVID-19 on populations, about one third of member states did
1310 not provide data to the EuroMoMo facility (EUROMOMO, 2022). Going forward, and
1311 especially given the imperative to monitor the changing burden of PCC and to learn from
1312 the different experiences of member states, it will be essential to have timely and
1313 comparable data that are easily available. Governments already report health data to
1314 international bodies, including WHO, EUROSTAT, and the OECD. It would be wasteful to
1315 duplicate the systems already in place for collating and transmitting health data. It will be
1316 important to agree on the content of core datasets for international comparisons. The
1317 process to develop them would logically lie with WHO, given the value of comparability
1318 beyond the EU.

1319 The second issue to be considered is the type of data that should be collected. Obviously,
1320 what is possible will vary depending on the information systems that already exist.
1321 Following convention, we divide our comments into those relating to primary, secondary,
1322 and community care.

1323 In primary care, health authorities should define a minimum dataset for anyone with a
1324 diagnosis of PCC. This should include the results of any tests for COVID-19, including both
1325 antigens and antibodies. It should also include information on when PCC was diagnosed
1326 and the evolution of symptoms over time, with particular attention paid to what are termed
1327 "red flag" symptoms, which have been identified as requiring rapid referral or investigation
1328 (World Health Organization, 2022). Ideally, primary care data should also include regular
1329 monitoring of quality-of-life using one of the standard instruments (see later, under
1330 surveillance), such as C19-YRS (Sivan et al., 2020, Sivan et al., 2021, Sivan et al., 2022).

1331 In many countries, information systems development differs in secondary care and in
1332 primary care. Full use should be made of the relevant newly introduced ICD-10 codes,
1333 U08.9 (Personal history of COVID-19, unspecified), U09.9 (Post COVID-19 condition,
1334 unspecified), and U10.9 (Multisystem inflammatory syndrome associated with COVID-19,
1335 unspecified). National authorities should develop and disseminate guidance on the use of
1336 these codes and on other data items relevant to the monitoring of the care of patients with
1337 PCC. This should provide information that can be used to monitor patient trajectories on
1338 what will be, for many of them, complex journeys that take in multiple specialties and
1339 providers.

1340 Data collection in community care is inevitably more complex, due for example to the
1341 multiplicity of providers, some within and some outside formal systems. Again, the precise
1342 arrangements will vary from country to country, but where possible health authorities
1343 should develop guidance on minimum datasets. This should include details of the services
1344 provided.

1345 A final consideration is that health information systems should support research. Given the
1346 considerable uncertainty about the progress of PCC and about its optimal management,
1347 health authorities should ensure that their information systems support research.
1348 Important elements include the ability to identify patients who can be invited to participate
1349 in clinical trials, to be able to follow up cohorts of patients to track the natural history of
1350 this condition, and to link data on patient characteristics, treatments and symptoms to
1351 undertake nonexperimental studies that might shed further light on the nature and
1352 management of this condition. In this respect, the United Kingdom's OPENSafely
1353 programme is one that could usefully be emulated (though depending on the accuracy and
1354 completeness of clinical coding) (EUROMOMO, 2022).

1.3.10.   Access to essential medicines

1356 Although one of the WHO building blocks, the Expert Panel has not identified any specific
1357 issues for PCC here, given the current level of evidence regarding effective treatments for
1358 PCC. Current institutions and mechanisms worked as intended. In case of an essential
1359 medicine appears in the future, the use of joint procurement by EU countries may avoid
1360 tensions inside the EU in differential time access to it, and benefitting from size effects
1361 ensuring access of EU patients to essential medicines.

1362 Within the EU, approval of innovative medicines is the responsibility of the European
1363 Medicines Agency, which has a dedicated webpage bringing together its work on vaccines
1364 and treatments for COVID-19 (European Medicines Agency, 2022). Moreover, the
1365 European Medicines Agency has also a role in monitoring and preventing medicines supply
1366 disruptions and actively coordinating the activities at EU level on potential shortages of
1367 critical medicinal products during public health crisis (Availability of medicines during
1368 COVID-19 pandemic | European Medicines Agency (europa.eu). However, it will be
1369 important to ensure that national authorities that have the capacity to define the list of
1370 essential medicines have access to expert advice, at national or at international level.

1.3.11.   Financing

1372 PCC will inevitably place additional financial strain on health systems, although with current
1373 knowledge, and especially given the uncertainty about the future trajectory of disease

1374   burden, it is only possible to speculate on the scale of the challenge ahead. In a
1375   commentary on the financial implications in the United States, Cutler emphasises that the
1376   medical costs will only be part of the financial consequences for society, with lost
1377   productivity and payments for disability and social support likely much greater (Cutler,
1378   2022). He also cites a study that estimates the annual cost of managing a patient with
1379   chronic fatigue syndrome, which may be similar to PCC in terms of the consequences of
1380   flare-ups, at US$9,000 per year (Jason and Mirin, 2021). However, the given the different
1381   nature of the two conditions and the very different price structures in the United States
1382   and Europe, this figure should be considered as purely illustrative. In general, as yet
1383   another complex chronic disease, PCC is not likely to require major changes to health care
1384   financing structures. The one caveat is that in some systems, typically funded by social
1385   insurance with payments on a fee-for-service basis, it may be difficult to construct
1386   mechanisms that encourage and sustain the multi-professional teams that will be needed.
1387   Another caveat for some health systems is the under-funding of primary care, which may
1388   require more funding in order to address the increased responsibilities associated with PCC
1389   diagnosis and management. The experience of implementing initiatives such as the
1390   German Disease Management Programmes will be important in this respect (Fuchs et al.,
1391   2014, Busse, 2004). Additional funding may become necessary, and should be defined
1392   under the current financing arrangements of each national health system.

1.3.12.   Leadership and governance

1394   As the previous sections have set out, despite gaps in evidence, there is sufficient
1395   knowledge on PCC and on other conditions that have similar characteristics to determine
1396   what is needed, at least in the short term. The challenge is how to implement it. Thus,
1397   those with responsibility for the operation of health systems must ensure that there are
1398   appropriate governance systems in place to ensure that guidance is adhered to. The precise
1399   mechanisms that will be appropriate will depend on the organizational structure of the
1400   health system, taking account of issues of ownership and lines of accountability. As far as
1401   possible they should be informed by knowledge, ideally from locally undertaken research
1402   aligned with larger international studies. This should seek to understand topics such as
1403   adherence to such guidance, including facilitators and barriers to uptake and include
1404   structural and behavioural interventions and accountability mechanisms that can bring
1405   about any necessary changes.

1.3.13.   Moving forward

1407   The mandate asked the Expert Panel to advise on the design of health services in the light
1408   of PCC. Our review has highlighted the great uncertainty about the future, scale and nature
1409   of the burden that will be imposed by PCC. While we do have reasonably accurate

1410   information on the current prevalence, we cannot know with any certainty what will be the

1411   impact of future waves of infection with new variants, some of which may be more or less

1412   likely to cause PCC. Nor can we say with any degree of certainty the impact of recovery

1413   from this condition. In these circumstances, health authorities will be taking a risk by

1414   investing large sums in stand-alone services for a condition that may not be needed in the

1415   future. However, regardless of the future course of the pandemic, the general principles

1416   that apply to the management of PCC are equally applicable to many other conditions,

1417   especially in the growing number of patients who have multi-morbidity. Consequently, we

1418   believe that the most appropriate response to PCC is to see it as an opportunity to bring

1419   about some of the changes that are needed in those health systems that have yet to

1420   respond adequately to the increasing volume of complex chronic diseases. In particular,

1421   these involve a shift to a person-centred integrated model of care and the introduction of

1422   genuine team working, based on collaboration between professionals who have different

1423   skill sets but coming together with the patient to co-produce solutions in non-hierarchical

1424   groups. This will, however, require a new approach to governance of health system is in

1425   some countries, with an explicit commitment to achieving the core goals of a health

1426   system, improved and equitable health outcomes, responsiveness to legitimate public

1427   expectations, and fair financing (adequate funds to achieve the objectives of the health

1428   system, raised in a fair way).

1429   **1.4. How public health surveillance should be adapted to measure the impact**
1430   **of the post-COVID-19 condition**

1431   **1.4.1. General principles**

1432   The principles of disease surveillance are well-established. Surveillance entails the

1433   continuous and systematic collection and analysis of data, and the subsequent reporting

1434   of any significant findings to effect change (Bennett et al., 2020). Surveillance can be

1435   passive or active. Passive surveillance system involves the regular monitoring of reports of

1436   disease appearing in existing health information systems, which include laboratory data,

1437   administrative systems in health facilities and, increasingly, data from digital technology,

1438   including apps and wearables, such as those that monitor heart rhythm. Active surveillance

1439   goes beyond this to include proactive case finding by health professionals, for example, in

1440   household surveys. The former is obviously much less resource intensive than the latter.

1441   Effective surveillance has three main elements:

1442   •   Capture and collation of data

1443   •   Analysis and interpretation of data (to generate information)

1444   •   Dissemination of information

1445 A comprehensive surveillance system will include a fourth element, an action taken when
1446 indicated by the data. Often this is represented as a circle, with lessons from the
1447 surveillance process feeding back into possible changes in how data are collected and
1448 interpreted. This may seem obvious, but it is important to restate it as, too often,
1449 information systems that could contribute to surveillance are created without adequate
1450 attention to how the information will be analysed and used. This situation can arise when,
1451 for example, software vendors convince health authorities to purchase information systems
1452 that collect data, but not necessarily in the form that is needed or are designed in ways
1453 that prevent them from being changed when this becomes necessary. This will be especially
1454 important with PCC, given the contingent nature of temporary knowledge about this
1455 condition. The challenges inherent in procuring complex information technology systems
1456 have been discussed in a previous Opinion by the Expert Panel (Expert Panel on Effective
1457 Ways of Investing in Health, 2021a).

1458 In making recommendations for surveillance in the light of PCC, we have adhered to some
1459 basic principles. First, given the multifaceted presentation of this complex condition,
1460 including many symptoms and signs that are found with other disorders, as far as possible,
1461 surveillance systems should build on what already exists for monitoring disease, potentially
1462 by extending the currently existing mandates. As will be argued, there are situations in
1463 which bespoke solutions are required but, in general, these should be the exception.
1464 Second, surveillance should encompass a range of measures that go beyond the presence
1465 or absence of the condition. It needs to be able to capture its impact on the life of the
1466 affected individual. Third, given the chronic nature of this condition, surveillance should,
1467 as far as possible, include a longitudinal component (following people over time) to allow
1468 its trajectory to be ascertained.

1469

1.4.2. The epidemiology of PCC

1471 Any surveillance system must start by identifying those with the condition in question. The
1472 WHO used a Delphi exercise to develop a clinical case definition of post-COVID-19 condition
1473 (World Health Organization, 2021a) (see Box 1 above).

1474 This poses some obvious challenges. The first is the capture of acute infection with SARS-
1475 CoV-2. Initially, testing data, which then involved PCRs, was limited by laboratory capacity.
1476 Once lateral flow tests became available for home use, there was variable reporting of
1477 results. A second is that the main symptoms associated with PCC (fatigue, shortness of
1478 breath and cognitive dysfunction) are very common in the general population and may be
1479 manifestations of other diseases, some of which will be difficult to exclude in routine

1480   surveillance. A third is that symptoms often fluctuate or relapse over time and people, so
1481   a definition that is applied at one point in time may miss cases.

1482   The limitations of the WHO case definition for surveillance purposes are, perhaps,
1483   inevitable, given the nature of the condition and, crucially, the absence of any biomarkers
1484   that can be used at present. Researchers have invested considerable effort in identifying
1485   putative biomarkers, ranging from certain findings on imaging of different organs, such as
1486   the heart and lungs, persistent viral reservoirs, especially in the intestines, and
1487   abnormalities in the blood, in particular micro-clots. It is likely that each of these plays
1488   some role in of the manifestations of this condition, but current knowledge is still far from
1489   finding anything that can be used in routine practice.

1490   At this point, it is relevant to note that, given the diverse therapeutic journeys along which
1491   people with PCC travel, it will not be possible to gain a comprehensive picture of the
1492   epidemiology of this condition from passive surveillance. Rather, active surveillance with
1493   outreach to the population will be required. One pragmatic solution to this problem, albeit
1494   with obvious limitations, is to use a case definition based on self-report. This is the
1495   approach taken by the UK Office for National Statistics (ONS), whose regular surveys are
1496   one of the only high-quality sources of information on prevalence of PPC at a population
1497   level. Participants in the survey are asked: "Would you describe yourself as having 'long
1498   COVID', that is, you are still experiencing symptoms more than 4 weeks after you first had
1499   COVID-19, that are not explained by something else?" followed by a question on whether
1500   it limits their activities. Limitations of this survey are described before.

1501   The responses to this survey have proven invaluable in tracking the prevalence of PCC, as
1502   well as in providing information on the risks associated with different variants of the virus
1503   or following repeated infections. When linked with other sociodemographic data, they have
1504   been used to assess the economic and labour force impact of the condition. Thus, given
1505   the present state of knowledge, there is a very strong argument that every country should
1506   be conducting regular surveys of this type, potentially harmonised at EU level.

1507   If we assume that cases can be tracked in surveys, such as that undertaken by the ONS,
1508   the next question is what additional information is required. Logically, this would be
1509   standardised across the EU and, ideally, the EEA and in neighbouring countries (Centers
1510   for Disease Control, 2022). This can be facilitated by recent changes in the mandate of
1511   ECDC that provide for the establishment of an EU Health Task Force to assist local
1512   responses to the outbreak of disease, the provision of expertise to EU countries and the
1513   European Commission, for instance in the development, examination and updating of
1514   preparedness plans. The standardised EEA survey would be run by national statistics offices
1515   and EUROSTAT, using advice from ECDC.

1.4.3. Use of health services by patients with PCC

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 come into contact with 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 PCC (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 are 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 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 PCC 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 from other sectors.

At this specific point in time (August 2022), when results from rationally framed RCTs on treatments for PCC are not in place yet, patients with PCC 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 PCC on functioning and quality of life

Most work to date has used well-known and widely used scales, such as the EQ-5D (either with 3 levels or with 5 levels) (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 PCC. Other instruments that have been used include the SF-36, Quality of Life Index and the 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 (PHQ-9, GAD-7, Warwick-Edinburgh mental wellbeing scales) (Arnold et al., 2021, Poyraz et al., 2021, Ma et al., 2020).

1552 The mental health impact of PCC may be an indirect consequence of an individual's ability
1553 to coping with their chronic condition. However, it should not be ruled out that this impact
1554 may be a direct consequence of pathophysiological mechanisms. Disentangling these
1555 impacts in inherently challenging, yet necessary to appropriately treat all the clinical
1556 manifestations of PCC. Comprehensive longitudinal surveillance within the health system
1557 can help in this regard as well. In a one year follow up, patients who were hospitalised with
1558 COVID-19 in the UK experienced a substantial deterioration in median EQ-5D-5L utility
1559 index with at most minimal improvements in outcome measures (Evans et al., 2022). A 2
1560 year follow-up of patients hospitalised with COVID-19 in China found that patients who
1561 reported symptoms consistent with PCC at 2 years had lower HRQoL, worse exercise
1562 capacity, more mental health problems, and increased use of healthcare than those who
1563 did not report symptoms (Huang et al.).

1564 Older people (60 years old and above) seem especially likely to experience problems with
1565 mobility, pain/discomfort and ability to perform daily life activities (Walle-Hansen et al.,
1566 2021). Patients with pre-existing chronic conditions also seem to experience a greater
1567 adverse impact on physical health that those without these conditions (there was no
1568 difference in mental health), although the authors noted that it was not possible to assess
1569 causality (Shah et al., 2021).

1570 Tabacof has proposed using an instrument comprising questions on demographics, past
1571 medical history, acute COVID-19 illness, a symptom checklist, and a battery of patient-
1572 reported outcome measures (National Academies of Sciences Engineering Medicine, 2022):
1573 Fatigue Severity Scale (Hernandez-Ronquillo et al., 2011), MRC Breathlessness Scale
1574 (Stenton, 2008), EuroQol EQ-5D-5L (Herdman et al., 2011), Patient Health Questionnaire
1575 (PHQ-2) (Arroll et al., 2010), General Anxiety Disorder-7 (Spitzer et al., 2006), Neuro-QOL
1576 Cognitive Function 8-item Short Form (Neuro-QOL) (Iverson et al., 2021), and WHO
1577 Disability Assessment Schedule (WHO-DAS) (Üstün et al., 2010)

1578 Others have proposed a new scale, PAC-19QoL – Post-Acute COVID-19 Quality of Life
1579 (Jandhyala, 2021). This measure considers 4 domains, with several elements of interest in
1580 each. The domains are psychological, physical, social and work. The details are: (a)
1581 psychological domain: Mood, Isolation, Motivation, Anxiety; Cognition, Expression, Mental
1582 Exertion; (b) Physical: Exertion, Pain, Travel, Somnolence, Smell/taste, Breathlessness,
1583 Fine motor, Libido; (c) Social: Isolation, Relationships, Hobbies; and (d) Work: Ability to
1584 work.

1585 This proposal has the merit of including quality-of-life measurement dimensions that are
1586 absent from the EQ-5D and SF-36, including more detailed coverage of mental health and
1587 the impact on the ability to work (which may affect the ability to earn income, and as such

51

1588 have an indirect effect on mental and physical health). Another proposal of a specific scale
1589 is the Post-COVID19 Functional Status scale, which overlaps considerably with the EQ-5D
1590 instrument (Klok et al., 2020).

1591 Loss in quality of life can be discussed in terms of depth (how much loss there is) and
1592 breadth (which dimensions are most affected). On the breadth of impact, and with
1593 reference to the most common measure of quality of life used to assess PCC, the EQ-5D
1594 (either the three-levels version, EQ-5D-3L or the five-levels version, EQ-5D-5L), the
1595 common finding is that all dimensions of the EQ-5D instrument are affected, with mobility,
1596 pain/discomfort and anxiety/depression being impacted strongly, while self-care being the
1597 less impacted dimension (the remaining dimension, usual activity, lies in between).

1598 Another measurement instrument for PCC, the COVID-19 Yorkshire Rehabilitation Scale
1599 (C19-YRS) was proposed by Sivan et al. (2021). The C19-YRS sets four domains (symptom
1600 severity, functional disability, additional symptoms and overall health). The domains and
1601 indicators (questions asked to respondents) result from the joint effort of a
1602 multidisciplinary team of rehabilitation professionals, together with patients. The set of
1603 questions asked include most of the domains and dimensions of other scales.[1] This measure
1604 was updated by Sivan et al. (2022), with a redefinition of scales of the domains used in
1605 the initial measure, leading to the C19-YRSm version.

1606 The new indices that have been proposed in the literature go into further details in several
1607 dimensions relevant to patients and to health professionals, compared to pre-COVID-19
1608 QoL widely used measures. The specificities associated with PCC suggest the importance
1609 of using of made-to-purpose measures that are valid across contexts for wide-scale, cross-
1610 country survellience as well. It is likely that further proposals will emerge, although the
1611 C19-YRS did collect support for its regular use in the UK.

1.4.5. Moving forward

1613 There is, at present, remarkably little information on the scale and nature of the burden of
1614 PCC in the EU. Given evidence from the UK, where such evidence is collected, that up to
1615 2% of the population are affected, an appreciable number severely, this situation is
1616 untenable. However, it is unsurprising. While there are nationally representative population
1617 health surveys in many European countries, there are also many gaps. The European
1618 Health Examination Survey, which should have provided the information needed, has been
1619 disappointing (European Health Examination Survey, 2022). The programme has struggled

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

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 PCC 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 PCC 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 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 PCC 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, many of which, it is increasingly clear, are exacerbated by infection with SARS-CoV-2. PCC 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 growing burden of multimorbidity (Barnett et al., 2012). While each has distinctive features, they also have similarities, in particular in 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 PCC, but also for many other conditions.

The second 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

1656 siloes. In other cases they reflect professional boundaries, often a function of long-
1657 established hierarchies that resist change because of the distribution of power within the
1658 system. In an earlier Opinion the Expert Panel has drawn attention to the scope for greater
1659 task shifting (Expert Panel on Effective Ways of Investing in Health, 2019). PCC provides
1660 an impetus for renewed action to implement its recommendations.

1661 In formulating our recommendations, we follow the questions posed in the mandate,
1662 starting with the latest evidence on PCC, followed by the implications for health systems,
1663 and concluding with the challenges involved in surveillance. This challenge is not limited to
1664 the delivery of services to patients. As noted in the discussion on research, we have known
1665 for some time that, with appropriate investment, it is possible to mount large scale clinical
1666 trials rapidly. During the pandemic the United Kingdom's RECOVERY trial confirmed this.
1667 However, this requires an acceptance that research should be embedded in the delivery of
1668 health care, so that every patient can be confident that they will be offered the opportunity
1669 to participate in a clinical trial. We are still a long way from this in many countries.

1670 **Knowledge**

1671 A great deal is already being done to extend our knowledge of PCC, both within members
1672 states and at a European level, for example, the ORCHESTRA programme (ORCHESTRA.,
1673 2022), as well as other cohort studies being done under Horizon Europe funding from the
1674 EC (projects VERDI, EU-CARE and END-VOC, for example), and coordinated by a "cohort
1675 coordination board". Given the rapidly evolving state of knowledge, it would be
1676 inappropriate for the Expert Panel to make specific recommendations, although we have
1677 provided a list of currently unanswered or incompletely answered questions in Box 3. We
1678 do, however, make one exception, reflecting a concern that it may otherwise be relatively
1679 neglected. This is that research on the wider impact of PCC, including on the labour force
1680 and on the economic and social circumstances of those affected and the wide range of
1681 health, social and other services necessary to support them should be prioritised. The
1682 reason we are concerned about possible neglect is that it will require studies that transcend
1683 sectors and disciplines, a type of research that has often struggled to attract funding.
1684 Beyond this, our recommendations address principles that we believe should underpin
1685 research on PCC but, echoing our argument above that the advent of PCC should be seen
1686 as an opportunity to fix weaknesses that have persisted for too long across health research.
1687 Several EC funded HORIZON projects starting in 2022 might, by design, tackle some of
1688 the issues outlined in the recommendations.

1689 **Recommendation 1: Research on PCC should, as far as possible, be explicitly co-**
1690 **produced with people living with the condition, with co-creation of potential**

1691 **therapeutic interventions, as well as a targeted consideration of the pathway**
1692 **along which the findings of the research can achieve impact.**
1693 As noted previously, PCC (or more precisely in this context, Long COVID) was the first
1694 medical condition to be named and delineated by those affected by it using social media.
1695 Those who have been affected by it were the first to characterise the condition through
1696 patient-led research and have described the struggle they have often experienced in having
1697 their problem recognised and in obtaining care. This has sometimes left a legacy of distrust.
1698 We believe that a dialogue based on mutual respect that involves those with PCC, the
1699 health professionals from whom they seek care, the health system directors and managers
1700 who are tasked with organising and financing such care, and the research community will
1701 benefit all parties.

1702 **Recommendation 2: Research on PCC, and especially on potential treatments,**
1703 **needs to be done at sufficient scale to provide definitive answers that take**
1704 **account of any heterogeneity within the population and the contexts in which**
1705 **they are situated.**

1706 Much of the research on therapy for COVID-19 undertaken during the pandemic is
1707 comprised of underpowered studies on often unrepresentative samples of the population.
1708 This is wasteful and, although small studies can be combined in meta-analyses, these often
1709 struggle with differences in case definitions, specifics of treatment, and duration of follow-
1710 up, among other problems. As with almost all health research, certain groups tend to be
1711 systematically excluded, such as children, older people, and those from ethnic minorities,
1712 and gender differences might not be addresses appropriately. These problems are
1713 especially acute where the treatment packages involve behavioural components or are
1714 dependent on characteristics of the health system, such as the extent of multidisciplinary
1715 working. Thus, research on interventions should answer not just the question of what
1716 works, but what works in what circumstances? Aiming to a harmonization of definitions,
1717 establishing valid measurement tools and definition of outcomes, ensuring coordination
1718 within different research projects are also essential points to be considered. The field of
1719 implementation science may provide frameworks, study designs, and other guidance to
1720 assist in this regard.

1721

1722 **Recommendation 3: Health systems need to embed research on PCC at all levels**
1723 **of care including rehabilitation, identifying incentives that can be applied and**
1724 **barriers that can be removed to facilitate the development of health facilities as**
1725 **settings for research and health workers as users of it.**

1726 While there is still considerable uncertainty about the long-term burden of PCC, at least in
1727 the short and medium term it will be substantial. There is an urgent need to understand it
1728 better. This will only happen if those responsible for health systems prioritize the
1729 generation and uptake of knowledge. As long as there is uncertainty about the most
1730 appropriate way to manage PCC and treatment options exist, all patients should be given
1731 the opportunity to participate in clinical trials, both of specific therapeutic agents and
1732 packages of care, such as different forms of rehabilitation. Obviously, it is also important
1733 to ensure that new findings are used. The mechanisms for disseminating new knowledge
1734 from research vary greatly, often reflecting different roles of universities, research bodies,
1735 and professional associations. Thus, it is not appropriate to make specific recommendations
1736 here beyond arguing that the relevant stakeholders in each member state should ensure
1737 that contextually appropriate systems are in place.

1738 **Health systems**

1739 The first consideration in developing recommendations for health systems is the old adage
1740 that "prevention is better than cure". The second consideration is that PCC, in its various
1741 manifestations, is a complex chronic condition.

1742 **Recommendation 4: As COVID-19 infection is the cause of PCC, measures to**
1743 **combat it, including vaccination and reducing transmission, must remain a**
1744 **priority.**

1745 While there may be continuing uncertainty about the precise mechanisms involved, one
1746 thing can be said with certainty. PCC can only arise in people who have been infected by
1747 SARS-CoV-2. While this now includes the majority of the population in many countries, it
1748 does not include everyone. Also, there is growing evidence that avoiding PCC after an initial
1749 infection does not exclude you from developing it after subsequent infections. Despite
1750 evidence that initial and booster vaccination reduces the risk of PCC there remains
1751 substantial numbers of people who have not yet been vaccinated, especially children. While
1752 COVID-19 continues to be transmitted and to cause appreciable numbers of deaths, it is
1753 important to continue measures known to reduce transmission, while recognizing that the
1754 intensity of restrictions at the height of the pandemic will be difficult given changing public
1755 perceptions. However, some of those measures, such as improved ventilation and
1756 installation of air filtration, are effective in reducing other airborne respiratory viruses. This
1757 could be a positive legacy of the pandemic. Similarly, it will be important to maintain
1758 momentum in vaccination campaigns, extending coverage to those who remain
1759 unvaccinated and emphasizing the importance of boosters.

1760 **Recommendation 5: PCC is to be recognized as one of many complex chronic**
1761 **conditions that, in many patients, will co-exist with others, calling for models of**
1762 **care that are co-ordinated in primary care, with mechanisms to ensure rapid**
1763 **referral to specialist teams while avoiding placing patients in "PCC siloes".**

1764 Health systems have been struggling to develop responses to complex chronic conditions
1765 for several decades, with limited success. While some progress has been made in
1766 developing care pathways for patients with a single condition, such as diabetes, the lived
1767 reality for many patients is that they have multiple conditions. This creates major
1768 challenges. First, it can be difficult to determine which of their symptoms is attributable to
1769 which condition, something that may have implications for treatment. This problem is
1770 exacerbated by the difficulty in distinguishing a pathological process from the physiological
1771 process of ageing. Second, the treatments required may interact in unexpected ways with
1772 each other or be influenced by factors such as impaired renal disease or frailty. Third, those
1773 affected need support to manage a complex pathway that can involve interaction with
1774 multiple specialists and health professionals. Fourth, being a woman brings one of the
1775 highest risks for PCC, so gender differences need to be appropriately addressed.

1776 We already know that PCC is also more common in people who are older and have co-
1777 morbidities, so the starting point to develop a health systems response must be to situate
1778 it in the context of probable multimorbidity (including conditions such as new onset
1779 diabetes that may be a direct consequence of infection with SARS-CoV-2) and to centre it
1780 around the needs of the patient. This has two implications. First, it emphasizes the
1781 importance of adopting the principle of person-centred care. Second, it argues against the
1782 creation of a specific vertical system for the management of PCC. Given that many patients
1783 with PCC will have other health disorders, an effective response should be coordinated by
1784 a team with oversight of the patient's care. This will logically be situated in primary care.
1785 However, that team will require specialist support from time to time. This is already the
1786 case in the best functioning models of care for other multi-system conditions such as
1787 diabetes or auto-immune disorders, although it is by no means universal. Thus, it will be
1788 important to develop centres of expertise in PCC, the pathological processes involved, and
1789 the therapeutic options. These will inevitably require multidisciplinary teams including
1790 physiotherapists, occupational therapists, nurses, psychologists, speech and language
1791 therapists, physicians and social workers (World Health Organization, 2022). However, it
1792 is equally important to have robust assessment criteria to ensure that patients that have
1793 problems better managed elsewhere, for example by primary care or medical specialists,
1794 are appropriately referred.

1795 **Surveillance**

1796 In writing this Opinion we have been limited by the lack of high-quality data on the
1797 prevalence and natural history of PCC. We have relied disproportionately on evidence from
1798 a few countries, in particular, the United Kingdom, that has established an ongoing
1799 surveillance study. Consequently, while we would have liked to have produced estimates
1800 for the future burden, in health and economic terms, attributable to PCC for each member
1801 state, it has not been possible.

1802 **Recommendation 6: A coordinated programme of surveillance systems should be**
1803 **established, including data from each member state, using consistent case**
1804 **definitions and methodologies, and encompassing the impact of this condition on**
1805 **health, employment, and the economy.**

1806 The record of the European Union in health surveillance has been mixed. The responsibility
1807 lies, primarily, with member states, although with some coordination by EUROSTAT. This
1808 means that, while there are some commonalities, there may be differences in survey
1809 methods and questions. There may also be problems with comparability of responses to
1810 some questions in different languages. There are a number of different survey projects,
1811 including the European Health Examination Survey (EHES), which is a collaboration
1812 between organizers of national health examination surveys in Europe, and the European
1813 Health Interview Survey (EHIS) which collects data on health status, health care use,
1814 health determinants and socio-economic background variables across all member states.
1815 However each has inherent limitations – EHES only includes 14 member states and the UK,
1816 whereas EHIS is only undertaken every 5 years (European Health Examination Survey,
1817 2022, EUROSTAT, 2022), and the European Social Survey, that includes 32 countries and
1818 addresses self-reported health and general well-being and includes specific modules that
1819 are developed in response to important issues, such as COVID-19 (European Social Survey,
1820 2022).. Given the challenges that have been faced in establishing these surveys, it will be
1821 difficult to achieve a stand-alone survey that can monitor continuously the prevalence and
1822 impact of PCC in all member states. Nonetheless, we call for, at least, a series of surveys
1823 with waves repeated at relatively short intervals for at least the next three years. These
1824 should be of adequate size in each member state to be powered to identify inequalities
1825 within the population, something that may require sample boosts to increase the numbers
1826 from certain groups, such as ethnic minorities. While, if this was to be an ongoing survey,
1827 it would logically reside with EUROSTAT, due to the short-term nature of it might logically
1828 reside initially with another part of the commission, such as DG SANTE. An important
1829 prerequisite will be to ensure that those involved in undertaking the survey use a set of
1830 diagnostic criteria consistent with those being used more widely. This would logically follow
1831 the WHO's lead.

1832   In a broader sense, publishing PCC statistics more regularly alongside the infection and

1833   recovery statistics, ideally on non-scientific web sites that are accessible to a non-specialist

1834   is desirable. Such information easily available to citizens and journalists, will keep

1835   awareness that PCC exists and requires attention from everyone.

1836

1837   **LIST OF ABBREVIATIONS**

1838

1839   >>>

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