

## Literature screening report

# Post COVID-19 Condition: Definition, prevalence, therapy, pathogenesis, socio-economic implications, and relation to post-acute sequelae of other viral infections

Report submission date: 29.05.2023  
Responsible author(s): Vasileios Nittas, Milo A. Puhan  
Affiliation: Epidemiology, Biostatistics and Prevention Institute, University of Zurich  
Co-authors: Julia Kopp  
Coordination contact: Jorgen Bauwens (SSPH+) – [jbauwens@ssphplus.ch](mailto:jbauwens@ssphplus.ch)

## *Preamble*

*A large number of scientific publications become available daily, reflecting the rapid development of knowledge and progress of science on COVID-19 related issues. Leading authorities should base decisions or policies on this knowledge; hence they need to master the actual state of this knowledge. Due to the large number of publications shared daily, decision-makers heavily depend on accurate summaries of these publications, in the different public health domains. Therefore, the authors of this report were mandated by the Swiss School of Public Health Plus (SSPH+), on request of the Federal Office of Public Health (FOPH), to inform the FOPH on recent findings from the literature.*

---

## Table of Contents

---

Background and aims	3
Methods & structure	4
Part 1: Executive summary	5
1.1 Definitions	5
1.2 Prevalence	5-6
1.3 Symptoms, risk factors, and pathogenesis	6-7
1.4 Therapy and rehabilitation	7-8
1.5 Socio-economic implications	8
1.6 Relation to post-acute sequelae of other viral infections	8-9
1.7 Healthcare responses	9-10
Part 2: Research and therapy update	11
2.1 Are there any new and relevant definitions?	11
2.2 What are the reported prevalence estimates?	11
2.2.1 Reported by recent primary studies and reviews	11-12
2.2.2 Reported by national and international organizations	13
2.3 What are the clinical manifestations, symptom clusters, influencing factors, and potential causes?	13
2.3.1 Clinical manifestations	13-14
2.3.2 PCC clusters/subtypes	14
2.3.3 Influencing factors	15
2.3.4 Impact of emerging variants, vaccination, and reinfections	15-16
2.3.5 Pathogenesis	16
2.4 What are the available and potential measures for therapy and rehabilitation?	17
2.4.1 Treatment and rehabilitation research (Switzerland)	17
2.4.2 Treatment and rehabilitation research (globally)	17-19
2.4.3 Preventive treatment research (globally)	20
2.5 What are the socio-economic implications?	20
2.5.1 Impact on employment	20-21
2.5.6 Economic impact on healthcare systems	21
2.6 How does PCC relate to post-acute sequelae of other viral infections?	22-23
2.6.1 Prevalence estimates of post-viral syndromes	23
2.6.2 Myalgic encephalomyelitis/chronic fatigue syndrome	23-24
2.6.3 Treatments of post-viral syndromes	24
Part 3: Response update	25-26

---

## Background and aims

Our knowledge of the long-term health consequences of SARS-CoV-2 is continuously evolving. Post COVID-19, or otherwise widely known as Long COVID, is a multifaceted condition with primary healthcare and broader public health implications.<sup>1</sup> Fully understanding why and how post COVID-19 condition (PCC) develops, how it can be prevented, and how it is best treated is therefore an essential step towards mitigating its burden. Generated knowledge should be holistic, including the broader public health and socio-economic dimensions of PCC. While many European countries have launched initiatives to establish care and support pathways for PCC patients, the need for stronger and more targeted action remains.<sup>1</sup> The Swiss Federal Office of Public Health (FOPH) has commissioned a report that will analyze the current healthcare situation and PCC patient needs.<sup>2</sup>

This living literature screening report aims to provide a concise and regularly updated state of the knowledge, focusing on the following five areas: (1) definitions, (2) prevalence, (3) symptoms, risk factors, and potential causes, (4) therapy and rehabilitation, (5) socio-economic implications, (6) relation to post-acute sequelae of other viral infections, and (7) healthcare and policy responses. The formulated questions are provided in textbox 1. These have been co-defined with the FOPH to provide findings that best serve their policy needs.

### Textbox 1: Focus areas and corresponding questions

#### Definitions

Q1: Are there any new and relevant definitions?

#### Prevalence

Q2: What are the reported prevalence estimates?

#### Symptoms, risk factors, and pathogenesis

Q3: What are the clinical manifestations, symptom clusters, influencing factors, and potential causes?

#### Therapy and rehabilitation

Q4: What are the available and potential measures for therapy and rehabilitation?

#### Socio-economic implications

Q5: What are the socio-economic implications?

#### Relation to post-acute sequelae of other viral infections

Q6: How does PCC relate to post-acute sequelae of other viral infections?

#### Healthcare and policy responses

Q7: What are the healthcare and policy responses in other European nations and North America?

## Methods

We conducted (a) weekly automatic PubMed searches and (b) regular manual searches in Google Scholar and relevant websites (e.g., governmental). Findings are published by the FOPH every three to four months. This first version covers the period from December 2022 to April 2023 and additionally draws from our literature screening report “Long COVID: Evolving Definitions, Burden of Disease and Socio-Economic Consequences” published by the FOPH in December 2022.<sup>3</sup> We included all types of research studies, including systematic reviews and meta-analyses. For Q2 (prevalence), we only reported studies with population-based samples and/or control groups and a mean follow-up of 12 weeks. Studies were classified as population-based if they used sampling procedures that are generally accepted to yield representative samples (e.g., probability sampling or census data). For Q2, we also reported estimates provided by health organizations, such as the United States (US) Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). We triangulated all that evidence to provide prevalence estimates for children and adults. For Q4 (therapy and rehabilitation) we also reported upcoming studies, registered in [clinicaltrials.gov](https://clinicaltrials.gov). For Q7 (healthcare and policy responses), we primarily considered policy and news reports. For all remaining questions, we prioritized studies that we considered to be the most reliable, with representative samples and well-designed methodologies. We did not conduct a formal quality assessment of included studies, however, reported new findings in relation to study limitations and overall data reliability. Narrative reviews, editorials, opinion papers, and case reports were excluded.

## Structure

The findings are presented in three parts. First, a constantly updated, cumulative state of the knowledge summary, covering Q1 to Q7. Second, a research update, covering Q1 to Q6 and presenting the latest evidence. Third, a response update (Q7) that provides an overview of public health responses in Europe, the US, and Canada.

## Part 1: Executive summary

In total, 46 new studies were identified, of which 26 were included. Of these 26 studies, 16 were primary studies and 10 were literature reviews. The next paragraphs (1.1 to 1.7) provide a cumulative state of the knowledge summary, drawing from recent studies (as reported in part 2), as well as from our previously published literature screening report “Long COVID: Evolving Definitions, Burden of Disease and Socio-Economic Consequences”.<sup>3</sup> All 26 studies are listed in appendix 1.

### 1.1: Definitions

Long COVID and post COVID-19 condition are the currently most used terms in the literature. The WHO defines PCC as “(...) a condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis”.<sup>4</sup> Recently, it added a definition of PCC in children and adolescents. The definition strongly overlaps with that for adults, primarily differing in the highlighted symptoms. It states that PCC can be assumed in “individuals with a history of confirmed or probable SARS-CoV-2 infection, when experiencing symptoms lasting at least 2 months which initially occurred within 3 months of acute COVID-19”.<sup>5</sup> The definition highlights fatigue, anosmia, and anxiety as the most common symptoms in children and adolescents.<sup>5</sup>

### 1.2: Prevalence

Among adults, three studies conducted in Switzerland report prevalence estimates between 16% and 26%.<sup>6-8</sup> A recent population-based cohort study in Sweden reported that 1% of non-hospitalized, 6% of hospitalized, and 32% of ICU-treated participants received a PCC diagnosis during follow-up of (90 days minimum).<sup>9</sup> Another recent study in the Netherlands reported a PCC prevalence of 13% (follow-up of 90 to 150 days). Germany’s Robert Koch Institute emphasized that current health insurance data indicate a PCC prevalence (ICD-10 code U09.9) of about 6%.<sup>10</sup> Austria’s Corona Panel Project reported a prevalence of about 18%, similar to the US Household Pulse Survey, which reported a prevalence between 11% and 17%.<sup>11,12</sup> The WHO reported that “studies show that around 10–20% of people infected by SARS-CoV-2 may go on to develop symptoms that can be diagnosed as long COVID”.<sup>13</sup> Not all PCC patients experience severe symptoms. A Swiss study reported that at 6 months, about 70%, 20%, and 10% of PCC patients reported

mild, moderate, and severe impairment, respectively.<sup>8</sup> All reported prevalence estimates are applicable to the definition provided by the WHO.<sup>4</sup>

Among all infected children and adolescents, we estimate the overall PCC prevalence to be about 3%. This estimate is based on two population-based studies.<sup>14,15</sup> The first, the Swiss Ciao Corona study was based on a random sample and encompassed both tested and untested children.<sup>14</sup> The second, a household cohort study conducted in England and Wales also included tested and untested children.<sup>15</sup> In both studies, selection bias (based on actively seeking care and testing) was considered to be low.<sup>3</sup> Both studies were included in our previously published literature screening report.<sup>3</sup> This version of the literature screening report did not find any similar new studies on PCC prevalence in children or adolescents.

### 1.3: Symptoms, risk factors, and pathogenesis

The literature reports over 50 different PCC symptoms. In adults, the most frequently reported symptom is fatigue, followed by headaches, chest pain, breathing difficulties, smell and taste disturbances, muscle and joint pain, cognitive impairments, sleep, and anxiety disorders.<sup>3,16</sup> In children and adolescents, a new meta-analysis reported that altered or lost smell, anxiety, fatigue, headache, loss of appetite, earache/ringing in ears, and sore eyes are the most commonly experienced symptoms (in addition to 21 less common symptoms, outlined in table 1).<sup>5</sup> In most cases, symptoms tend to improve over time. Mean duration is estimated at about nine months among hospitalized and four months among non-hospitalized individuals, with about 15% of PCC patients still experiencing symptoms 12 months post-infection.<sup>16</sup> A recent study has identified the following six PCC subtypes: (1) multisystem and lab, (2) pulmonary, (3) neuropsychiatric, (4) cardiovascular, (5) pain and fatigue, and (6) multisystem and pain (see table 2).<sup>17</sup>

The literature on risk factors is emerging and provides new evidence on the role of vaccines and reinfections.<sup>18-21</sup> In adults, female sex, age (40+ years), comorbidities, the severity of acute disease (hospitalization or intensive care unit (ICU) treatment), obesity, non-vaccination, the presence of IgM and IgG antibodies, and active smoking may be increasing the risk for PCC.<sup>3,18,22</sup> Many of these factors, such as the number of symptoms during acute disease, the severity of acute disease, missing vaccination, increasing age, and comorbidities, have been previously linked to the severity of PCC (e.g., cardiovascular involvement, increased disability, prolonged fatigue).<sup>8,23-25</sup>

In children and adolescents, female sex, age (>10 years), history of allergic conditions, other pre-existing chronic conditions, overall poorer physical and mental health, and severity of acute disease (hospitalization, number of symptoms) may be increasing the risk for PCC.<sup>3,26</sup> Whether and how these factors impact PCC severity for children and adolescents remains an evidence gap.

Early reports highlighted good physical fitness levels, being treated with interferon  $\beta$ -1b based triple antiviral therapy during hospital stay, and a nutrition rich in vitamins B, C, D, E, magnesium, selenium, zinc, flavonoids and polyphenols, curcumin, and sulforaphane during acute disease as potentially protective.<sup>3,27</sup> Recent evidence, including two Swiss studies, suggests that (1) an Omicron infection (as compared to Delta), (2) previous vaccination (2 doses), and (3) reinfection may all be associated with lower chances of new-onset PCC in adults.<sup>18-21,28</sup> Previous evidence suggests that for some, post-infection vaccination may be associated with reduced PCC severity (therapeutic effects).<sup>29-32</sup> Whether and how the remaining protective factors are associated with PCC severity remains an evidence gap.

The evidence on PCC protective factors for children and adolescents is not established yet. Previous evidence suggested that vaccination decreases the chances of severe acute disease in children.<sup>33</sup> Considering that severity of acute disease is a PCC risk factor, it could be assumed that vaccination may act as a protective factor for children and adolescents. Whether and how protective factors impact PCC severity remains an evidence gap.

PCC pathogenesis remains unclear. However, plausible theories are emerging. A recent article summarizes the five most prominent theories, being (1) immune dysregulation, (2) microbiota dysbiosis, (3) autoimmunity and immune priming, (4) blood clotting and endothelial abnormalities, and (5) dysfunctional neurological signaling.<sup>27</sup>

## 1.4: Therapy and rehabilitation

There is currently no established PCC cure. Most treatments aim to reduce symptoms. Currently, there are four ongoing Swiss studies registered in clinicaltrials.gov (see table 3). The first is a phase two randomized controlled trial (RCT) aiming to evaluate the efficacy and safety of temelimab for treating PCC-related neuropsychiatric symptoms.<sup>34</sup> The second RCT aims to evaluate the effects of 10 mg fampridine (4-Aminopyridine) on working memory performance in individuals with PCC and subjective cognitive impairment.<sup>35</sup> A third trial, evaluating the efficacy of BC 007 is expected to start in summer 2023.<sup>36</sup> Beyond

Switzerland, a search in [clinicaltrials.gov](https://clinicaltrials.gov) revealed 13 completed trials on PCC treatment and rehabilitation (see appendix 2). None of the trials had published results yet. A recently published review provided an overview of potential treatment approaches (see table 4).<sup>27</sup> Two trials on preventive treatments reported that early administration of metformin or nirmatrelvir (during acute SARS-CoV-2 infection) may reduce the risk for PCC.<sup>37,38</sup>

The WHO's living guidance for COVID-19 management was recently complemented with a new section on the rehabilitation of adults with PCC.<sup>13</sup> It outlines the importance of (1) standardized symptoms assessment and outcome measurements, (2) adequate follow-up systems, and (3) appropriate referral systems. The guidance also provides rehabilitation recommendations for specific PCC symptoms (see table 5).<sup>13</sup>

## 1.5: Socio-economic implications

In a subset of patients, PCC has a negative impact on quality of life and can lead to functional restrictions, as well as impaired family and social life.<sup>39-42</sup> PCC also negatively impacts work life, primarily in those with moderate to severe symptoms. A recent study from Switzerland reported reduced work ability among individuals with PCC compared to those without, with 5.8% of those with PCC reporting direct work-life disruptions or even complete inability to work (1.6%).<sup>43</sup> A study from Germany reported that 6% of all participants with a previous SARS-CoV-2 infection were unable to work.<sup>22</sup>

Recent reports from the United Kingdom (UK) and the US highlight that about 16-25% of PCC patients had at some point adjusted their working hours or remained out of work.<sup>44,45</sup> First reports on the economic impact of PCC on healthcare systems have recently started to emerge. A UK-based retrospective matched cohort study reported that the incremental costs per patient were significantly higher for those diagnosed with PCC, primarily linked to telephone consultations, and adding up to about £23 million in national costs.<sup>46</sup> The US-based COVID-19 Longhailer Advocacy Project estimates the average medical cost per PCC patient at about \$36,000.<sup>47</sup>

## 1.6: Relation to post-acute sequelae of other viral infections

The long-term symptoms of SARS-Cov-2 are not a surprising or unexpected phenomenon.<sup>48</sup> At least since the Russian and Spanish flu (1898 and 1918) post-viral syndromes have been described with symptoms very similar to those reported for PCC.<sup>49,50</sup> Other well-known viral pathogens, such as polio, Ebola, dengue,



SARS-CoV-1, chikungunya, West Nile virus, and MERS-CoV are linked to the development of largely unexplained post-viral syndromes (see table 6).<sup>51,52</sup> The clinical presentation of post-viral syndromes, including PCC, is heterogeneous but exhibits a set of common systemic symptoms, such as exertion intolerance, fatigue, unrefreshing sleep, flu-like symptoms, neurocognitive and sensory symptoms, as well as muscle and joint pain.<sup>51</sup> Dyspnea, fatigue, reduced exercise capacity, and psychological impairment are common long-term symptoms shared between SARS-CoV-1, SARS-CoV-2, and MERS-CoV.<sup>52</sup>

A key similarity between many post-viral syndromes, including PCC, is the diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).<sup>48,51</sup> A considerable subset of PCC patients meet the criteria for ME/CFS.<sup>27,48</sup> Common symptoms for both PCC and ME/CFS patients are post-exertional malaise, dysautonomia, postural tachycardia syndrome (PoTS), and exercise intolerance. The underlying mechanisms of post-viral ME/CFS are multiple, complex, and remain poorly understood. Viral pathogens (including SARS-CoV-2) likely lead to biological abnormalities, such as the dysregulation of host gene expression, immunity, metabolism, and the brainstem, which in turn cause ME/CFS symptoms.<sup>48</sup> Currently there are no recognized pharmacological or non-pharmacological treatments of post-viral syndromes.<sup>53-56</sup>

At this point, it is difficult to compare the prevalence of post-viral syndromes across pathogens. The main reason is that such population-wide testing for a virus was done for the first time during the COVID-19 pandemic. Thus, population-based studies have a stronger basis for valid estimates of the prevalence of PCC since testing ranged from asymptomatic individuals to patients with severe COVID-19. Such studies could not be conducted before the COVID-19 pandemic. Yet, that has sparked new research that aims to assess long-term symptoms following different pathogens. For example, an ongoing study from Australia (currently only available as a research poster) aims to compare post-viral syndromes following SARS-CoV-2 and influenza infections. Preliminary results are available for the first three months after infections.<sup>57</sup> The study found similar prevalence estimates of long-term symptoms (up to 12 weeks) after SARS-CoV-2 and influenza infections and concluded that there was no evidence of a difference in the risk to develop moderate to severe long-term symptoms.<sup>57</sup>

## 1.7: Healthcare responses

News reports from Switzerland, as well as neighboring countries (e.g., Germany), highlight some PCC patients feel that their medical needs are not adequately addressed.<sup>58,59</sup> That indicates that many European

healthcare systems are not fully prepared to address the entire spectrum of PCC-related care needs. As underlined by experts, the burden of PCC on healthcare systems is likely underestimated.

Some noteworthy new healthcare and policy responses are the UK's "Your COVID Recovery" digital program, the WHO's living guidance on PCC rehabilitation, and Canada's Task Force on PCC.<sup>13,60,61</sup> In Switzerland, two online platforms, Altea and Rafael, offer information, self-management support, links to health care providers and opportunities for exchange for both persons affected by PCC and health care providers.<sup>62,63</sup> Many countries, including the UK, Germany, and France have renewed their commitment to addressing PCC with more funding for research. Table 7 provides some recent healthcare responses and policies in Europe, the US, and Canada.

## Part 2: Research and therapy update

### 2.1: Are there any new and relevant definitions?

No new terms or definitions were identified for PCC in adults. For children and adolescents, the WHO has recently issued a new clinical case definition, generated by a Delphi consensus, and informed by a systematic review and meta-analysis.<sup>5,64</sup> The definition strongly overlaps with that for adults, primarily differing in the highlighted symptoms. It states that PCC can be assumed in *“individuals with a history of confirmed or probable SARS-CoV-2 infection, when experiencing symptoms lasting at least 2 months which initially occurred within 3 months of acute COVID-19”*.<sup>5</sup> Fatigue, anosmia, and anxiety were described as the most common symptoms in children and adolescents. Due to the lack of evidence and the non-specific nature of symptoms, the definition highlights further 21 symptoms that should be considered (see section 2.3.1, table 1).<sup>5</sup>

The definition also states that symptoms *“generally have an impact on everyday functioning, such as changes in eating habits, physical activity, behavior, academic performance, social functions (interactions with friends, peers, family), and developmental milestones”*.<sup>5</sup> Furthermore, it states that *“symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness, and they may also fluctuate or relapse over time”*.<sup>5</sup> A manuscript published in the Lancet Respiratory Medicine described this definition as a good start but emphasized its shortcomings.<sup>64</sup> First, providing a definition that only highlights three symptoms (although children seem to have a constellation of symptoms) might dominate the narrative. Second, the current definition does not include post-exertional symptom exacerbation, which may lead to some children being *“pushed too hard too soon”*. Third, the definition does not distinguish between those children with manageable symptoms and those with severe impairments.<sup>64</sup>

### 2.2: What are the reported prevalence estimates?

#### 2.2.1 Reported by recent primary studies and reviews

A population-based cohort study in Sweden reported the number of PCC diagnoses among adult Stockholm County residents with a previously verified SARS-CoV-2 infection (from May 2020 to July 2021).<sup>9</sup> The study's outcome was PCC diagnosis (ICD-10 code U09.9), recorded 90 days (minimum) after a positive test. Follow-

up was between three and 12 months. The final cohort sample included 204,805 SARS-CoV-2-positive individuals. Of those, 93% were non-hospitalized, 6% were hospitalized, and 1% received ICU treatment. During follow-up, 1.5% received a PCC diagnosis. Further broken down according to disease severity, 1% of non-hospitalized, 6% of hospitalized, and 32% of ICU-treated participants received a PCC diagnosis during follow-up. Limitations: The study most likely underestimated the occurrence of PCC as for a large part of the study, there was no standard clinical definition, likely leading to misclassification and underreporting. The impact of vaccination was not assessed.<sup>9</sup>

A recent population-based cohort study in the Netherlands reported the prevalence of PCC in adults living in the northern parts of the country.<sup>65</sup> The study was conducted between March and August 2021 and included participants with a previous SARS-CoV-2 diagnosis (n=4,231), as well as matched SARS-CoV-2-negative controls (n=8462). Follow-up was between 90 and 150 days. About 21.4% of previously infected participants and 8.7% of negative controls had at least one new or substantially increased symptom. Thus, 12.7% of patients had long-term symptoms that could be attributed to SARS-CoV-2. Limitations: The study assessed only 23 somatic symptoms that were considered key at the beginning of the pandemic, excluding cognitive symptoms (e.g., brain fog). The exact date of SARS-CoV-2 diagnosis was unknown. The study likely underestimates PCC prevalence.<sup>65</sup>

Studies that provide population-based prevalence estimates for children and adolescents are less common. A prospective international cohort study recruited children and adolescents across 36 emergency departments in eight countries (between March 2020 and January 2021). Comparing 1,884 children with a previous SARS-CoV-2 infection and 1,701 SARS-CoV-2-negative frequency matched controls, the study aimed to estimate the prevalence of PCC at 90 days post-infection.<sup>66</sup> Children with a previous SARS-CoV-2 infection were more likely to report long-term symptoms. 4.2% of non-hospitalized SARS-CoV-2-positive children and 2.7% of negative controls reported symptoms at 90 days. 10.2% of previously hospitalized SARS-CoV-2-positive children and 5% of negative controls reported symptoms at 90 days. Limitations: The study assessed PCC through an open-ended caregiver questionnaire which may have underestimated actual prevalence. Matching was conducted on country and not on emergency department level.<sup>66</sup>

## 2.2.2 Reported by national and international organizations

Germany's Robert Koch Institute underlined that current prevalence estimates vary and are not robust enough (e.g., due to a lack of studies with representative sample sizes and control groups). The institute emphasized that current health insurance data indicate a PCC prevalence (ICD-10 code U09.9) of about 6%.<sup>10</sup> France's "Sante Publique" referred to a nationwide survey and estimated current PCC prevalence in persons with confirmed SARS-CoV-2 infection at about 30%. The survey relied on volunteers, recruited from a panel, which likely led to an overestimation.<sup>67</sup> For Austria, the University of Vienna emphasized that there are no official data yet. Based on the findings of the Austrian Corona Panel Project, which surveyed a representative sample of 1,500 randomly selected individuals, the prevalence was estimated at about 18%.<sup>11</sup> The experimental US Household Pulse Survey (n=67,279) reported that as of January 2023, 11% of respondents reported active PCC symptoms, while 17% reported experiencing PCC in the past.<sup>12</sup> Finally, the WHO reported that "*studies show that around 10–20% of people infected by SARS-CoV-2 may go on to develop symptoms that can be diagnosed as long COVID*".<sup>13</sup>

## 2.3: What are the clinical manifestations, symptom clusters, influencing factors, and potential causes?

### 2.3.1 Clinical manifestations

For adults, all symptoms have been described extensively in our previous literature screening report.<sup>27</sup> Recent studies did not add any new symptoms but confirmed that the most common symptoms include fatigue, dyspnea, muscle pain, concentration problems, chest tightness, loss of smell and taste, and memory impairments.<sup>68</sup>

For children and adolescents, the evidence is emerging. A recent systematic review undertaken for WHO's clinical case definition reported the findings of 60 studies (n=328,875) and described a range of PCC symptoms.<sup>5</sup> Meta-analyses suggested that children with a previous SARS-CoV-2 infection had significantly higher proportions of the following symptoms: altered or lost smell, anxiety, fatigue, headache, loss of appetite, earache/ringing in ears, and sore eyes. The study highlighted a total of 24 symptoms, all listed in table 1. Limitations: Only 37% of those studies assessed outcomes at three months and beyond.<sup>5</sup>

Table 1. PCC symptoms in children and adolescents<sup>5</sup>

Fatigue	Altered smell or anosmia	Anxiety
Chest pain	Cognitive difficulties	Cough
Diarrhoea	Dizziness	Dyspnoea
Earache	Fever	Headache
Insomnia	Joint pain or swelling	Light sensitivity
Loss of appetite	Mood swings	Myalgia
Nausea	Palpitations	Postural symptoms
Rash	Stomach pain	Sore eyes or throat

\*this table was extracted from the original publication without any major language adjustments<sup>5</sup>

### 2.3.2 PCC clusters/subtypes

Reese and colleagues used machine learning to stratify PCC patients into clusters and define PCC subtypes.<sup>17</sup> Data were retrieved from the US National COVID Cohort Collaborative, which integrates multiple electronic health record data across multiple organizations. The cohort included 6,469 individuals with PCC and identified six clusters, summarized in table 2. Limitations: Study inclusion required a U09.9 code, which was introduced recently and therefore excludes PCC patients from earlier phases of the pandemic.<sup>17</sup>

Table 2. Machine-learning identified PCC clusters/subtypes<sup>17</sup>

Cluster	Description
Cluster 1: multisystem and lab	Symptoms across multiple system categories and abnormal laboratory findings. Cluster with large proportions of older patients, highest clinical severity, and highest mortality.
Cluster 2: pulmonary	Symptoms such as hypoxia and cough. Cluster with large proportions of older patients.
Cluster 3: neuropsychiatric	Symptoms such as headache, insomnia, depression, sleep apnoea, mobility, and sensory issues.
Cluster 4: cardiovascular	Symptoms such as tachycardia, palpitations, and hypoxemia.
Cluster 5: pain and fatigue	Symptoms such as pain, chest pain, and fatigue.
Cluster 6: multisystem and pain	Highest frequency of pain. Similarities with cluster 1, yet much lower laboratory abnormalities. Cluster with large proportions of female patients.

\*this table was extracted from the original publication with minor language adjustments<sup>17</sup>

### 2.3.3 Influencing factors

The evidence on risk and protective factors is evolving but mostly confirmed previous findings.<sup>27</sup> A study from Germany conducted an online survey among 199,377 registered potential stem cell donors (18-61 years).<sup>22</sup> Of these, 12,609 reported previous SARS-CoV-2 infection, with the remaining 186,768 acting as controls. Participation was completed in September 2021. The severity of acute infection and age were reported as risk factors. The 40-61 age group had a higher risk than all other age groups for 18 out of 20 symptoms (except loss of taste and smell, and diarrhea). Limitations: The findings are only generalizable to Germany's working-age population.<sup>22</sup>

A systematic review and meta-analysis assessed PCC risk factors (in adults) based on 41 primary studies (n=860,783).<sup>18</sup> Pooled odds ratios (ORs) suggested that female sex (OR, 1.56; 95% CI, 1.41-1.73), age (OR, 1.21; 95% CI, 1.11-1.33), high body mass index (BMI) (OR 1.15; 95% CI 1.08-1.23), smoking (OR 1.10; 95% CI 1.07-1.13), comorbidities (OR 2.48; 95% CI 1.97-3.13 ), and previous hospitalization or ICU treatment (OR 2.37; 95% CI 2.18-2.56) may all be PCC risk factors. The only reported protective factor was vaccination (two doses) (OR 0.57; 95% CI 0.43-0.76). Limitations: Some meta-analyses had strong statistical heterogeneity.<sup>18</sup>

For children, a systematic review described in more detail under 2.2.1 reported the following risk factors: older age (>10), female sex, poor physical and mental health, and severe acute disease (higher number symptoms, hospitalization).<sup>26</sup>

### 2.3.4 Impact of emerging variants, vaccination, and reinfections

A recent cohort study in Norway (n=1,323,145) found that up to 90 days post-infection, those with a previous Omicron infection had a similar risk of certain PCC symptoms (e.g., fatigue, cough, heart palpitations, shortness of breath, and mental health disturbances) as individuals with a previous Delta infection.<sup>69</sup> Beyond 90 days post-infection, those with an Omicron infection had a lower risk of having any PCC symptom than those with a previous Delta infection. Limitations: The included sample was probably more health conscious than the general population, and to test and receive care. Some of the study's outcomes may have been misclassified, underreported, and underpowered.<sup>69</sup>

A recent study in Switzerland assessed PCC at 12 weeks after an Omicron infection (BA.1 and BA.2) compared with negative controls.<sup>19</sup> The study also assessed associations between PCC prevalence and

vaccination status. Participants (1,807 cases and 882 controls) were recruited through the CoviCare program of the Geneva University Hospitals. About 11.7% of cases reported PCC symptoms at 12 weeks post-infection compared with 10.4% of negative controls. Vaccinated cases reported fewer symptoms (9.7%) than non-vaccination cases (18.1%). Limitations: The study's response rate was low (30%), increasing the risk of participation bias and limiting generalizability.<sup>19</sup>

The latest systematic review on the role of vaccines in preventing or treating PCC was recently published in the BMJ Medicine.<sup>20</sup> The review included 16 studies. Twelve studies assessed the role of vaccination before infection (preventive). Of these, 10 reported significantly lower PCC risk. Overall, odds ratios for developing PCC ranged between 0.22 and 1.03 after one dose; 0.25 and 1 after two doses; and 0.48 and 1.01 after any dose. Five studies assessed the role of vaccination after SARS-CoV-2 infection (therapeutic). Odds ratios ranged between 0.38 and 0.91, suggesting potential therapeutic effects. Limitations: The risk of bias in primary studies was assessed to be high, with often missing adjustments for confounders. The overall evidence remains low.<sup>20</sup>

A community-based cohort study (n=140,647) used data from the UK COVID-19 Infection Survey (a random sample of the population) to assess the risk of PCC after SARS-CoV-2 reinfection.<sup>21</sup> Of the total sample, 126,108 were first infections and 14,539 were reinfections (between November 2021 and October 2022). The follow-up time was 14 weeks (median). Compared to participants with initial infections, reinfected participants (16 years or older) had 28% lower odds of new-onset PCC (any severity) and 34% lower odds of severe new-onset PCC (after adjusting for vaccination status). Limitations: Participants with short reinfection times (<12 weeks) were excluded. The study is still under review (preprint) and should be viewed with caution.<sup>21</sup>

### 2.3.5 Pathogenesis

A review article recently published in Nature Reviews Microbiology, summarized the major findings on PCC theories of pathogenesis.<sup>27</sup> The five most prominent theories of pathogenesis include (1) immune dysregulation (which may reactivate dormant pathogens such as Epstein-Barr virus, (2) microbiota dysbiosis, (3) autoimmunity and immune priming, (4) blood clotting and endothelial abnormalities, and (5) dysfunctional neurological signaling.<sup>27</sup>



## 2.4: What are the available and potential measures for therapy and rehabilitation?

### 2.4.1 Treatment and rehabilitation research (Switzerland)

There is no established PCC cure. Most treatments that are currently explored aim to reduce diverse PCC symptoms. A search in [clinicaltrials.gov](https://clinicaltrials.gov) revealed four ongoing studies in Switzerland (see table 3). Both trials are active and have no published results yet. A third trial, evaluating the efficacy of BC 007 is expected to start in summer 2023.<sup>70</sup> The effects of Pycnogenol (extract from the bark of the French maritime pine) on PCC will be evaluated with a randomized controlled trial conducted by the University of Zurich. The trial is currently in the registration process.

Table 3. Ongoing PCC trials in Switzerland ([clinicaltrials.gov](https://clinicaltrials.gov))

Trial	Description
Temelimab as a Disease Modifying Therapy in Patients with Neuropsychiatric Symptoms in Post-COVID-19 or PASC Syndrome <sup>34</sup>	<ul style="list-style-type: none"> <li>Phase: Phase two RCT (24 weeks), recruiting</li> <li>Aims: To evaluate the efficacy and safety of temelimab (54mg/kg) for treating PCC-related neuropsychiatric symptoms in patients who had SARS-CoV-2 but did not receive ICU treatment</li> </ul>
Influence of Fampridine on Working Memory in Individuals with Post COVID-19 Condition with Subjective Cognitive Impairment <sup>35</sup>	<ul style="list-style-type: none"> <li>Phase: recruiting</li> <li>Aims: To evaluate the effects of 10 mg fampridine (4-Aminopyridine), a potassium channel-blocking agent, on working memory performance in individuals with PCC with subjective cognitive impairment</li> </ul>

### 2.4.2 Treatment and rehabilitation research (globally)

A search in [clinicaltrials.gov](https://clinicaltrials.gov) revealed 13 completed trials on PCC treatment and rehabilitation (see appendix 2). None of the trials had published results yet. The review article by Davis and colleagues, published in Nature Reviews Microbiology provided a table with the most prominent therapy approaches to date. Part of the table was extracted in its original form (see table 4). For more detailed information, please refer to the publication.<sup>27</sup>

Table 4. Potential PCC treatments<sup>27</sup>

Symptoms and/or biological mechanism	Potential treatment(s)
Post-exertional malaise	Pacing
POTS	Pharmacological: $\beta$ -blockers, pyridostigmine, fludrocortisone, midodrine Non-pharmacological: increase salt and fluid intake, intravenously administered salt, compression stockings
Immune dysfunction	Intravenous immunoglobulin
Cognitive dysfunction	Cognitive pacing and post-concussion syndrome protocols
Fatigue	Coenzyme Q10, d-ribose
Pain, fatigue, neurological symptoms	Low-dose naltrexone
Fatigue, unrefreshing sleep, brain fog	Low-dose aripiprazole
Autoimmunity	BC007
Abnormal clotting	Anticoagulants
Abnormal clotting	Apheresis
Viral persistence	Paxlovid
Endothelial dysfunction	Sulodexide
Gastrointestinal symptoms	Probiotics
Dysautonomia	Stellate ganglion block
Endothelial function, microcirculation, inflammatory markers, and oxidative stress	Pycnogenol

\*this table was extracted from the original publication with no major language adjustments<sup>27</sup>

In addition, the WHO's living guidance for COVID-19 management was recently complemented with a section on the rehabilitation of adults with PCC.<sup>13</sup> The document outlines three key elements for successful rehabilitation delivery: (1) interdisciplinary rehabilitation teams, (2) continuity and coordination of care, and (3) people-centered care, and shared decision-making. These elements depend on (1) standardized symptoms assessment and outcome measurements, (2) adequate follow-up systems, and (3) appropriate referral systems. The guidance also provides rehabilitation recommendations for specific PCC symptoms (see table 5). The WHO outlined that the evidence for all recommendations remains weak.<sup>13</sup>

Table 5. WHO living guidance PCC rehabilitation recommendations<sup>13</sup>

Symptom/ Condition	Recommendations
Post-exertional malaise	<ul style="list-style-type: none"> <li>Education and skills training on energy conservation techniques (pacing)</li> </ul>
Arthralgia	<ul style="list-style-type: none"> <li>Pain education, skills training on self-management strategies, prescription of short-term anti-inflammatory drugs, and physical exercise training</li> </ul>
Dyspnoea	<ul style="list-style-type: none"> <li>Education and skills training on self-management strategies such as breathing control techniques, pacing approaches, and physical exercise training</li> </ul>
Cognitive impairments	<ul style="list-style-type: none"> <li>Education, skills training on self-management strategies, and cognitive exercises</li> </ul>
Fatigue	<ul style="list-style-type: none"> <li>Education, skills training on energy conservation techniques (pacing), and a cautious physical exercise training</li> </ul>
Depression	<ul style="list-style-type: none"> <li>Psychological support, mindfulness-based approaches, peer support, and physical exercise training</li> </ul>
Olfactory dysfunction	<ul style="list-style-type: none"> <li>Education and skills training for olfactory training</li> </ul>
Orthostatic intolerance	<ul style="list-style-type: none"> <li>Education and skills training on self-management strategies and physical exercise training</li> </ul>
Dysphagia	<ul style="list-style-type: none"> <li>Education and skills training on positioning, manoeuvres and dietary modifications, and swallowing exercises</li> </ul>

\*this table's content was extracted from the original publication with minor language adjustments<sup>13</sup>

### 2.4.3 Preventive treatment research (globally)

The COVID-OUT trial was a US-based multi-site clinical trial assessing the effects of three drugs (metformin, ivermectin, and fluvoxamine) on PCC development among overweight or obese adults (>30 years of age).<sup>37</sup> The drugs were prescribed during acute SARS-CoV-2 infection in an outpatient setting. The trial included 1,323 participants, 1,125 of which were followed up to nine months (and beyond). Findings suggested a 42% (relative) and 4.3% (absolute) decrease in PCC incidence among participants who started metformin early (within four days after SARS-CoV-2 symptom onset) (HR 0.37; 95% CI 0.15-0.95). No effects were found for ivermectin or fluvoxamine. Limitations: The trial excluded low-risk patients (low BMI and below 30 years of age) and the effects may therefore not be generalizable to all PCC patients. The results are currently under review (preprint).<sup>37</sup>

A recently published cohort study used data from US Department of Veterans Affairs and explored the potential impact of early treatment (<5 days after a positive SARS-CoV-2 test) with the antiviral drug nirmatrelvir on PCC development.<sup>38</sup> The study included 35,717 cases (treated with nirmatrelvir) and 246,076 controls (no antiviral or antibody treatment). Overall, nirmatrelvir was found to be associated with reduced PCC risk (RR 0.74; 95% CI 0.72-0.77), reduced mortality (HR 0.53; 95% CI 0.46-0.61), and reduced post-acute hospitalization (HR 0.76; 95% CI 0.73-0.80), irrespective of vaccination status and number of previous infections. Limitations: The cohort primarily included older, white, male adults, and the results might therefore be not generalizable beyond that group.<sup>38</sup>

## 2.5: What are the socio-economic implications?

### 2.5.1 Impact on employment

A recent study used data from a population-based, prospective cohort (n=672) in the Canton of Zurich and assessed the impact of PCC on work ability and occupational adjustments.<sup>43</sup> All participants were of working age (18-64), infected with wildtype SARS-CoV-2, and not vaccinated at the time of infection. The study reported strong evidence (1) of reduced work ability among individuals with PCC compared to those without, and (2) for lower odds to report higher ability (physical or mental demands) among individuals with PCC compared to those without. Work ability reduction was stronger with increasing age and among those with previous psychiatric illnesses. The study also found that 5.8% of individuals with PCC reported that their symptoms directly impacted their work life, while 1.6% had to completely stop working. Among those who reported occupation disruptions, 43% also faced financial difficulties. Limitations: The study has

a limited generalizability to individuals with more severe acute infection or those that have been vaccinated. The study is currently under review and published as a preprint.<sup>43</sup>

A survey (n= 3,296) by the UK's Trade Union Congress found that about 20% of respondents who reported PCC symptoms were not working at the time of the survey, while about 16% had to adjust their working hours.<sup>44</sup> An updated Brookings Metro report used recent data from the US Household Pulse Survey to estimate the impact of PCC on the US labor market.<sup>45</sup> The report stated that in 2022 around 16 million US citizens (aged 18 to 65) reported living with PCC. About two to four million were at some point out of work due to the condition which might total up to \$170 billion of lost annual wages.<sup>45</sup>

### 2.5.2 Economic impact on healthcare systems

First reports on the overall economic implications of PCC have recently started to emerge. A UK-based retrospective matched cohort study (n=472,174) compared the costs related to primary care among individuals with previous SARS-CoV-2 infection and a propensity score matched negative control group.<sup>46</sup> The study compared costs after 12 weeks of acute infection without hospitalization. Incremental costs per patient were significantly higher for those with a previous SARS-CoV-2 infection (£2.44) and much higher for those diagnosed with PCC (£30.52). The study links most of these additional costs to primary care telephone consultations and estimates about £23 million in national costs related to PCC. Limitations: The used primary care records often lacked a PCC diagnosis. Despite the propensity score matching, some confounding risks remained.<sup>46</sup>

A historical cohort study in Israel analyzed data from 180,759 individuals with a previous SARS-CoV-2 infection and compared medical costs between PCC and non-PCC groups over 12 months.<sup>71</sup> Compared to pre-infection periods, PCC was associated with doubled direct medical costs (across all in- and outpatient medical services). In comparison, the cost increase among individuals without PCC was relatively low (7.5%). Limitations: The used data often lacked physician-diagnosed PCC diagnosis, as well as information on symptom length. The study could therefore not distinguish between ongoing symptomatic COVID-19 (<12 weeks) and PCC (>12 weeks).<sup>71</sup>

## 2.6: How does PCC relate to post-acute sequelae of other viral infections?

The long-term symptoms of SARS-CoV-2 are not a surprising or unexpected phenomenon.<sup>51</sup> Many other well-known viral pathogens are linked to the development of long-term symptoms, and although they cause a significant healthcare burden, they remain largely unexplained.<sup>51</sup> Two reviews published in Nature Medicine and Science Immunology explore the literature and describe other common post-viral syndromes (see table 6), as well overlapping themes and underlying mechanisms.<sup>51,52</sup> The following paragraphs summarize parts of these two reviews.

Table 6. Viral pathogens with known post-viral conditions<sup>51,52</sup>

Viral pathogen	Name(s) of post-viral condition
Ebola	Post-Ebola syndrome, post-Ebola virus disease syndrome
Dengue	Post-dengue fatigue syndrome
Polio	Post-polio syndrome
SARS-CoV-1	Post-SARS-syndrome
Chikungunya	Post- chikungunya chronic inflammatory rheumatism, post-chikungunya disease
Epstein-Barr virus	N/A
West Nile virus	N/A
Ross River virus	N/A
Coxsackie B virus	N/A
H1N1/09 influenza	N/A
Varicella-zoster virus	N/A
MERS-CoV	N/A
Respiratory syncytial virus	N/A
Rhinovirus	N/A

\*this table's content was extracted from the original publications with minor language adjustments<sup>51,52</sup>

The clinical presentation of post-viral conditions, including PCC, is heterogeneous, yet exhibits a set of common systemic symptoms.<sup>51</sup> These are listed in textbox 2.

Textbox 2: Common symptoms of post-viral syndromes<sup>51</sup>

(1) Exertion intolerance, fatigue, unrefreshing sleep
(2) Flu-like symptoms: fever, malaise, sweating, feeling ill
(3) Neurocognitive and sensory symptoms: brain fog, memory, and concentration difficulties, sensory impairments, irritability, and signs of depression
(4) Pain (myalgia, arthralgia)

\*this textbox was extracted from the original publication with minor language adjustments<sup>51</sup>

Dyspnea, fatigue, reduced exercise capacity, and psychological impairment are common long-term symptoms shared between SARS-CoV-1, SARS-CoV-2, and MERS-CoV.<sup>52</sup> Beyond these shared symptoms, post-viral conditions exhibit a range of broad, heterogeneous trigger-specific symptoms.<sup>51</sup> For example, Ebola seems to be linked to chronic eye inflammations, while polio and West Nile virus seem to lead to motor impairments and muscle weakness.<sup>51</sup>

### 2.6.1 Prevalence estimates of post-viral syndromes

The poor understanding of post-viral syndromes leads to lacking clinical recognition, underdiagnosis, and inadequate care.<sup>51</sup> Thus, data on their prevalence are limited.<sup>51</sup> Broadly, available data suggest that for most post-viral syndromes, as with PCC, the prevalence gradually decreases over time, with a subset of patients exhibiting symptoms over multiple years (e.g., Ebola, chikungunya).<sup>51</sup> An ongoing study from Australia (n=19,758, currently only available as a research poster) aims to compare post-viral syndromes following SARS-CoV-2 and influenza infections. Preliminary results are available on only the first three months after infections.<sup>57</sup> The study found that among those with SARS-CoV-2 infections (n=2,195), 21.4% reported symptoms at 12 weeks and 4.1% faced moderate to severe limitations. Similarly, among those with a previous influenza infection (n=951), 23% reported symptoms at 12 weeks and 4.4% experienced moderate to severe limitations. The study concluded that there was no evidence of a difference in the risk to develop long-term symptoms (up to 12 weeks) between SARS-CoV-2 and influenza infections.<sup>57</sup>

### 2.6.2 Myalgic encephalomyelitis/chronic fatigue syndrome

Two further reviews, one published in Nature Reviews Microbiology and the other in Frontiers in Microbiology, discuss the underlying mechanisms of PCC, as well as major theories of pathogenesis.<sup>27,48</sup> Both emphasize the linkages between PCC and the diagnosis of ME/CFS. This is not surprising, as around 75% of ME/CFS cases are triggered by infections.<sup>27,48</sup> Dengue fever is one of the better-known causes of post-viral fatigue, followed by the H1N1/09 influenza virus, as well as the varicella-zoster virus. ME/CFS has been linked to PCC, with a large subset of PCC patients meeting the criteria for ME/CFS.<sup>27</sup> Common symptoms for both PCC and ME/CFS patients are post-exertional malaise, dysautonomia (especially PoTS), and exercise intolerance. Common abnormalities include mitochondrial dysfunction, altered fatty acid metabolism, redox imbalance, impaired oxygen extraction, endothelial dysfunction, micro-clots, and hyperactivated platelets.<sup>27</sup>

The underlying mechanisms of post-viral ME/CFS remain poorly understood. It is likely that viral pathogens lead to certain biological abnormalities, such as the dysregulation of host gene expression, immunity, and metabolism, leading to ME/CFS symptoms.<sup>48</sup> Changes and inflammation of the brainstem have been linked both to SARS-CoV-2 and ME/CFS, presenting one potential link between the two conditions.<sup>48</sup> Another recent study (n=120) links body temperature, peripheral oxygen saturation, increased oxidative toxicity, and lowered antioxidant defenses during acute SARS-CoV-2 infections to the development of ME/CFS symptoms.<sup>72</sup> The overall evidence remains weak.

### 2.6.3 Treatment of post-viral syndromes

Currently, there are no recognized pharmacological or non-pharmacological treatments for post-viral syndromes.<sup>53-55</sup> Most approaches mainly aim to alleviate individual symptoms. For ME/CFS, there are currently no approved drugs or widely accepted treatments.<sup>56</sup> Therapies mainly target symptom management, often focusing on overall well-being and psychological sequelae. Until recently, evidence supported the use of cognitive behavioral therapy and graded exercise therapy. Recent reports highlight that both approaches mostly lead to adaptation and not recovery. The U.K. National Institute for Care and Health Excellence recently stated that graded exercise therapy should not be considered a recommended ME/CFS treatment anymore.<sup>56</sup>



## Part 3: Response update

Below we provide all new/ or recent healthcare and policy responses in Europe, the US and Canada. We would like to highlight the UK’s “Your COVID Recovery” program. This new program offers a digital, interactive, and tailored recovery and rehabilitation program that has been co-developed by experts and patients to help people living with PCC manage their recovery at home. It contains a range of resources, such as mental health support, advice on returning to normal activities, symptom management support, as well as nutritional advice. Patients can set goals and select resources to achieve those goals. Program access is only possible after referral by a healthcare professional.<sup>60</sup>

Table 7: Recent healthcare and policy responses in Europe, the US and Canada

Country/Region	Healthcare and policy responses
Switzerland	<ul style="list-style-type: none"> <li>Long Covid Schweiz, Sulser &amp; Partner, and Altea have published a guide for employers who want to support workers affected by PCC to return to work<sup>73</sup></li> </ul>
United Kingdom	<ul style="list-style-type: none"> <li>NHS England will invest a further £90 million in PCC services in 2022/2023<sup>74</sup></li> <li>Introduction of “Your COVID Recovery” as part of the NHS support for PCC patients<sup>60</sup></li> <li>Expansion of the number of facilities that provide specialized post-covid services<sup>74</sup></li> </ul>
Germany	<ul style="list-style-type: none"> <li>Baden-Wurttemberg supports PCC research with €2 million to four university hospitals (Freiburg, Heidelberg, Tübingen, Ulm). The goal is to have a care concept at the end of the 18-month project<sup>75</sup></li> </ul>
France	<ul style="list-style-type: none"> <li>The government has committed €14 million in funding for PCC research<sup>76</sup></li> </ul>
Belgium	<ul style="list-style-type: none"> <li>Researchers at Ku (Katholieke Universiteit) Leuven have been working to develop evidence-based guidelines to help healthcare professionals provide PCC care. Launched in November 2022 for general practitioners, physiotherapists, occupational therapists, psychologists, and dieticians<sup>77</sup></li> </ul>

- 
- |               |  |
|---------------|--|
| United States | <ul style="list-style-type: none"><li>▪ Expansion of post-COVID care clinics<sup>78</sup></li><li>▪ Department of Health and Human Services published National Research Action Plan on Long COVID as a response to the Presidential Memorandum on addressing the long-term effects of COVID-19<sup>79</sup></li><li>▪ Department of Health and Human Services published the “Services and Supports for Longer-Term Impacts of COVID-19 Report” as a response to the Presidential Memorandum on addressing the long-term effects of COVID-19<sup>80</sup></li></ul>           |
| Canada        | <ul style="list-style-type: none"><li>▪ New investment of 9 million to create and evaluate evidence-based guidelines and tools to support patients, caregivers, and health professionals<sup>81</sup></li><li>▪ Budget 2022 also provides 20 million over 5 years to the Canadian Institutes of Health Research. Supports research related to the long-term effects of COVID-19 infections<sup>81</sup></li><li>▪ Task Force on Post COVID-19 Condition Report published recently<sup>61</sup></li></ul>   |
| WHO           | <ul style="list-style-type: none"><li>▪ Addition of “Rehabilitation of adults with Post COVID-19 condition” in the Living Guidance for Clinical Management of COVID-19<sup>13</sup></li><li>▪ In September 2022, WHO/Europe partnered with Long COVID Europe to develop 3 goals (the 3 Rs), calling upon governments and health authorities to focus attention on PCC and those affected by it through greater: (1) recognition and knowledge sharing, (2) research and reporting, and (3) rehabilitation that is based on evidence and effectiveness<sup>82</sup></li></ul> |
-

## References

1. Chmiel C. *Long COVID MedIX Factsheet*.  
[https://www.medix.ch/media/fs\\_long\\_covid\\_26.4.2023.pdf?16825094502023](https://www.medix.ch/media/fs_long_covid_26.4.2023.pdf?16825094502023).
2. BAG. Coronavirus: Laufende Arbeiten. 2023.
3. Nittas V, Milo AP. *Long COVID: Evolving Definitions, Burden of Disease and Socio-Economic Consequences*. [www.bag.admin.ch2022](http://www.bag.admin.ch2022).
4. WHO. *A clinical case definition of post COVID-19 condition by a Delphi consensus*.  
[https://www.who.int/publications/i/item/WHO-2019-nCoV-Post\\_COVID-19\\_condition-Clinical\\_case\\_definition-2021.1#2021](https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1#2021).
5. WHO. *A Clinical Case Definition for Post-COVID-19 Condition in Children and Adolescents by Expert Consensus 2023*.
6. Desgranges F, Tadini E, Munting A, et al. Post-COVID-19 Syndrome in Outpatients: a Cohort Study. *J Gen Intern Med*. Jun 2022;37(8):1943-1952.
7. Menges D, Ballouz T, Anagnostopoulos A, et al. Burden of post-COVID-19 syndrome and implications for healthcare service planning: A population-based cohort study. *PLoS One*. 2021;16(7):e0254523.
8. Ballouz T, Menges D, Anagnostopoulos A, et al. Natural course of post COVID-19 condition and implications for trial design and outcome selection: A population-based longitudinal cohort study. *MedRxiv*. 2022.
9. Hedberg P, Granath F, Bruchfeld J, et al. Post COVID-19 condition diagnosis: A population-based cohort study of occurrence, associated factors, and healthcare use by severity of acute infection. *J Intern Med*. Feb 2023;293(2):246-258.
10. Institut RK. Coronavirus SARS-CoV-2 - Long COVID (Stand: 28.4.2023). 2023.
11. Wien U. Austrian Corona Panel Project (ACPP). 2023.
12. Burns A. Long COVID: What Do the Latest Data Show? 2023.
13. WHO. *Living Guidance for Clinical Management of COVID-19: Rehabilitation of adults with post COVID-19 condition*. <https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.12023>.
14. Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term Symptoms After SARS-CoV-2 Infection in Children and Adolescents. *JAMA*. Jul 21 2021;326(9):868-869.
15. Miller F, Nguyen DV, Navaratnam AM, et al. Prevalence and Characteristics of Persistent Symptoms in Children During the COVID-19 Pandemic: Evidence From a Household Cohort Study in England and Wales. *Pediatr Infect Dis J*. Dec 1 2022;41(12):979-984.
16. Global Burden of Disease Long CC, Wulf Hanson S, Abbafati C, et al. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. *JAMA*. Oct 25 2022;328(16):1604-1615.
17. Reese JT, Blau H, Casiraghi E, et al. Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programmes. *EBioMedicine*. Jan 2023;87:104413.

18. Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Risk Factors Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis. *JAMA Intern Med.* Mar 23 2023.
19. Nehme M, Vetter P, Chappuis F, Kaiser L, Guessous I, CoviCare Study T. Prevalence of Post-Coronavirus Disease Condition 12 Weeks After Omicron Infection Compared With Negative Controls and Association With Vaccination Status. *Clin Infect Dis.* May 3 2023;76(9):1567-1575.
20. Byambasuren O, Stehlik P, Clark J, Alcorn K, Glasziou P. Effect of covid-19 vaccination on long covid: systematic review. *BMJ Med.* 2023;2(1):e000385.
21. Bosworth ML, Shenhuy B, Walker AS, et al. Risk of new-onset Long Covid following reinfection with SARS-CoV-2: community-based cohort study. *MedRxiv.* 2023.
22. Bernas SN, Baldauf H, Real R, et al. Post-COVID-19 condition in the German working population: A cross-sectional study of 200,000 registered stem cell donors. *J Intern Med.* Mar 2023;293(3):354-370.
23. Iqbal FM, Lam K, Sounderajah V, Clarke JM, Ashrafian H, Darzi A. Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. *EclinicalMedicine.* Jun 2021;36:100899.
24. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med.* Mar 2022;28(3):583-590.
25. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Prevalence and Determinants of Fatigue after COVID-19 in Non-Hospitalized Subjects: A Population-Based Study. *Int J Environ Res Public Health.* Feb 19 2021;18(4).
26. Zheng YB, Zeng N, Yuan K, et al. Prevalence and risk factor for long COVID in children and adolescents: A meta-analysis and systematic review. *J Infect Public Health.* May 2023;16(5):660-672.
27. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol.* Mar 2023;21(3):133-146.
28. Ballouz T, Menges D, Kaufmann M, et al. Post COVID-19 condition after Wildtype, Delta, and Omicron SARS-CoV-2 infection and prior vaccination: Pooled analysis of two population-based cohorts. *PLoS One.* 2023;18(2):e0281429.
29. Arnold DT, Milne A, Samms E, Staddon L, Maskell NA, Hamilton FW. Are vaccines safe in patients with Long COVID? A prospective observational study. *MedRxiv.* 2021.
30. Gaber T, Ashish A, Unsworth A, Martindale J. Are mRNA Covid 19 vaccines safe in Long Covid patients? A Health Care Workers perspective. *BJMP.* 2020;14(1).
31. Strain WD, Sherwood O, Banerjee A, Van der Togt V, Hishmeh L, Rossman J. The Impact of COVID Vaccination on Symptoms of Long COVID: An International Survey of People with Lived Experience of Long COVID. *Vaccines (Basel).* Apr 21 2022;10(5).
32. Nehme M, Braillard O, Salamun J, et al. Symptoms After COVID-19 Vaccination in Patients with Post-Acute Sequelae of SARS-CoV-2. *J Gen Intern Med.* May 2022;37(6):1585-1588.
33. Klein N, et al. Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA Vaccination in Preventing COVID-19-Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Nonimmunocompromised Children and Adolescents Aged 5–

- 17 Years — VISION Network, 10 States, April 2021–January 2022. *Morbidity and Mortality Weekly Report*. 2022;71(9).
34. Keddad K, Berthuy N. Temelimab as a Disease Modifying Therapy in Patients With Neuropsychiatric Symptoms in Post-COVID 19 or PASC Syndrome. 2022.
35. Gerhards C, Faludi T. Influence of Fampridine on Working Memory in Individuals With Post COVID-19 Condition With Subjective Cognitive Impairment (FamC). 2022.
36. Cures B. Strong Pipeline – Multiple applications based on BC 007 platform technology. 2023.
37. Bramante CT, al. e. Outpatient treatment of COVID-19 and the development of Long COVID over 10 months: a multi-center, quadruple-blind, parallel group randomized phase 3 trial. *SSRN preprints* 2023.
38. Xie Y, Choi T, Al-Aly Z. Association of Treatment With Nirmatrelvir and the Risk of Post-COVID-19 Condition. *JAMA Intern Med*. Mar 23 2023.
39. Raman B, Cassar MP, Tunnicliffe EM, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine*. Jan 2021;31:100683.
40. Lerum TV, Aalokken TM, Bronstad E, et al. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. *Eur Respir J*. Apr 2021;57(4).
41. van den Borst B, Peters JB, Brink M, et al. Comprehensive Health Assessment 3 Months After Recovery From Acute Coronavirus Disease 2019 (COVID-19). *Clin Infect Dis*. Sep 7 2021;73(5):e1089-e1098.
42. Willi S, Luthold R, Hunt A, et al. COVID-19 sequelae in adults aged less than 50 years: A systematic review. *Travel Med Infect Dis*. Mar-Apr 2021;40:101995.
43. Kerksieck P, Ballouz T, Haile SR, et al. Post COVID-19 Condition, Work Ability and Occupational Changes: Results from a Population-based Cohort. *MedRxiv*. 2023.
44. Congress TU. *Workers' experiences of long Covid*.  
<https://www.tuc.org.uk/sites/default/files/2021-06/Formatted%20version%20of%20Long%20Covid%20report%20-%20v1.3.pdf>2023.
45. Bach K. New data shows long Covid is keeping as many as 4 million people out of work. 2022.
46. Tufts J, Zemedikun DT, Subramanian A, et al. The cost of primary care consultations associated with long COVID in non-hospitalised adults: a retrospective cohort study using UK primary care data. *MedRxiv*. 2023.
47. C-19LAP. COVID-19 Longhailer Advocacy Project (C19LAP). 2020.
48. Proal AD, VanElzakker MB. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms. *Front Microbiol*. 2021;12:698169.
49. Honigsbaum M. "An inexpressible dread": psychoses of influenza at fin-de-siecle. *Lancet*. Mar 23 2013;381(9871):988-989.
50. Stefano GB. Historical Insight into Infections and Disorders Associated with Neurological and Psychiatric Sequelae Similar to Long COVID. *Med Sci Monit*. Feb 26 2021;27:e931447.
51. Choutka J, Jansari V, Hornig M, Iwasaki A. Unexplained post-acute infection syndromes. *Nat Med*. May 2022;28(5):911-923.

52. Narasimhan H, Wu Y, Goplen NP, Sun J. Immune determinants of chronic sequelae after respiratory viral infection. *Science Immunology*. 2022;7.
53. Chandan JS, Brown KR, Simms-Williams N, et al. Non-Pharmacological Therapies for Post-Viral Syndromes, Including Long COVID: A Systematic Review. *Int J Environ Res Public Health*. Feb 16 2023;20(4).
54. Li Hi Shing S, Chipika RH, Finegan E, Murray D, Hardiman O, Bede P. Post-polio Syndrome: More Than Just a Lower Motor Neuron Disease. *Front Neurol*. 2019;10:773.
55. Bandara S, et al. Management of Dengue and Post Dengue Complication Syndrome: A Review. *Acta Scientific Microbiology*. 2019;2(4).
56. Toogood PL, Clauw DJ, Phadke S, Hoffman D. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): Where will the drugs come from? *Pharmacol Res*. Mar 2021;165:105465.
57. Brown M, al. e. Long COVID: the next public health crisis? A comparison with influenza in Australia. In: Health QDo, ed. *3rd ECCMID, Denmark 2023*.
58. Garn L. Long Covid in Sachsen-Anhalt: Unvorbereitetes Gesundheitssystem - Erkrankte fühlen sich allein gelassen. *Mitteldeutsche Zeitung*2023.
59. Hubacher C. Ist Long Covid ein Fall für die IV? *SRF*2023.
60. NHS. Your COVID Recovery. 2023.
61. Canada Go. *Post-COVID-19 Condition in Canada: What we know, what we don't know, and a framework for action (Pre-Report)*. <https://science.gc.ca/site/science2023>.
62. Network ALC. Long COVID: Altea informs and helps. 2023.
63. Geneve HU. Rafael Post-COVID Platform. 2023.
64. Burki T. Clinical case definition of post-COVID-19 condition in children: a good start, but improvements are needed. *Lancet Respir Med*. Apr 2023;11(4):314.
65. Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM, Lifelines Corona Research I. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet*. Aug 6 2022;400(10350):452-461.
66. Funk AL, Kuppermann N, Florin TA, et al. Post-COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection. *JAMA Netw Open*. Jul 1 2022;5(7):e2223253.
67. France Sp. COVID long. 2023.
68. Bowyer RCE, Huggins C, Toms R, et al. Characterising patterns of COVID-19 and long COVID symptoms: evidence from nine UK longitudinal studies. *Eur J Epidemiol*. Feb 2023;38(2):199-210.
69. Magnusson K, Kristoffersen DT, Dell'Isola A, et al. Post-covid medical complaints following infection with SARS-CoV-2 Omicron vs Delta variants. *Nat Commun*. Nov 30 2022;13(1):7363.
70. watson.ch. Long-Covid-Medikament von Schweizer Firma erhält Genehmigung für Studie2023.
71. Tene L, Bergroth T, Eisenberg A, David SSB, Chodick G. Risk factors, health outcomes, healthcare services utilization, and direct medical costs of patients with long COVID. *Int J Infect Dis*. Mar 2023;128:3-10.
72. Al-Hakeim HK, Al-Rubaye HT, Al-Hadrawi DS, Almulla AF, Maes M. Long-COVID post-viral chronic fatigue and affective symptoms are associated with oxidative damage, lowered

- antioxidant defenses and inflammation: a proof of concept and mechanism study. *Mol Psychiatry*. Feb 2023;28(2):564-578.
73. Bieri M, Rangelov N, Rudolf P, Scherrer F, Simonet A, Utiger A. *Ratgeber Zurück zur Arbeit*2023.
  74. NHS. NHS sets out long COVID action plan for thousands of people with persistent symptom. 2022.
  75. Laend Pot. Land unterstützt Long-COVID-Forschung mit zwei Millionen Euro. 2023.
  76. Senat LG. Réponse du Ministère de la santé et de la prévention publiée le 19/01/2023. 2022.
  77. Leuven K. Nieuwe richtlijn scheidt duidelijkheid over behandeling van aanhoudende COVID-klachten. 2022.
  78. Hospitals NH. COVID-19 Services. 2022.
  79. Department of Health and Human Services U. *National Research Action Plan on Long COVID*. <https://www.covid.gov/assets/files/National-Research-Action-Plan-on-Long-COVID-08012022.pdf>2022.
  80. Department of Health and Human Services U. *Services and Supports for Longer-Term Impacts of COVID-19*. <https://www.covid.gov/assets/files/Services-and-Supports-for-Longer-Term-Impacts-of-COVID-19-08012022.pdf>2022.
  81. Canada Go. Government of Canada invests new funding for post COVID-19 condition, in line with recommendations from the Chief Science Advisor's repor. 2023.
  82. Europe W. Increasing Recognition, Research and Rehabilitation for Post COVID-19 Condition (long COVID). 2023.
  83. Wang F. Machine learning identifies long COVID patterns from electronic health records. *Nat Med*. Jan 2023;29(1):47-48.
  84. Zhang H, Zang C, Xu Z, et al. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes. *Nat Med*. Jan 2023;29(1):226-235.
  85. Brunvoll SH, Nygaard AB, Fagerland MW, et al. Post-acute symptoms 3-15 months after COVID-19 among unvaccinated and vaccinated individuals with a breakthrough infection. *Int J Infect Dis*. Jan 2023;126:10-13.
  86. Fawzy NA, Abou Shaar B, Taha RM, et al. A systematic review of trials currently investigating therapeutic modalities for post-acute COVID-19 syndrome and registered on WHO International Clinical Trials Platform. *Clin Microbiol Infect*. May 2023;29(5):570-577.
  87. O'Mahoney LL, Routen A, Gillies C, et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *EClinicalMedicine*. Jan 2023;55:101762.



## Appendices

### Appendix 1: New included studies

1. Clinical case definition of post-COVID-19 condition in children: a good start, but improvements are needed <sup>64</sup>
2. Long COVID: major findings, mechanisms and recommendations <sup>27</sup>
3. Machine learning identifies long COVID patterns from electronic health records <sup>83</sup>
4. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes <sup>84</sup>
5. Post COVID-19 condition diagnosis: A population-based cohort study of occurrence, associated factors, and healthcare use by severity of acute infection <sup>9</sup>
6. Post-acute symptoms 3-15 months after COVID-19 among unvaccinated and vaccinated individuals with a breakthrough infection <sup>85</sup>
7. Post-COVID-19 condition in the German working population: A cross-sectional study of 200,000 registered stem cell donors <sup>22</sup>
8. Risk Factors Associated With Post-COVID-19 Condition: A systematic Review and Meta-analysis <sup>18</sup>
9. Prevalence and risk factor for long COVID in children and adolescents: A meta-analysis and systematic review <sup>26</sup>
10. Prevalence of Post-COVID Condition 12 Weeks After Omicron Infection Compared With Negative Controls and Association With Vaccination Status <sup>19</sup>
11. Risk factors, health outcomes, healthcare services utilization, and direct medical costs of patients with long COVID <sup>71</sup>
12. A systematic review of trials currently investigating therapeutic modalities for post-acute COVID-19 syndrome and registered on WHO International Clinical Trials Platform <sup>86</sup>
13. Characterising patterns of COVID-19 and long COVID symptoms: evidence from nine UK longitudinal studies <sup>68</sup>
14. Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programmes <sup>17</sup>
15. A systematic review and meta-analysis conducted by UCL Great Ormond Street Institute of Child in collaboration with the World Health Organization <sup>5</sup>
16. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: a systematic review and meta-analysis <sup>87</sup>



17. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study <sup>65</sup>
18. Effect of covid-19 vaccination on long covid: systematic review <sup>20</sup>
19. Risk of new-onset Long Covid following reinfection with SARS-CoV-2: community-based cohort study <sup>21</sup>
20. Outpatient Treatment of COVID-19 and the Development of Long COVID Over 10 Months: A Multi-Center, Quadruple-Blind, Parallel Group Randomized Phase 3 Trial <sup>37</sup>
21. Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition <sup>38</sup>
22. Post-covid medical complaints following infection with SARS-CoV-2 Omicron vs Delta variants <sup>69</sup>
23. Post–COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection <sup>66</sup>
24. Unexplained post-acute infection syndromes <sup>51</sup>
25. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An overview of biological factors that may contribute to persistent symptoms <sup>48</sup>
26. Immune determinants of chronic sequelae after respiratory viral infection <sup>52</sup>

Appendix 2: *Completed* PCC treatment and rehabilitation trials globally (clinicaltrials.gov)

Study title (as indexed in clinicaltrials.gov)	Intervention (type)
Pilot Study into LDN and NAD+ for Treatment of Patients with Post-COVID-19 Syndrome	Naltrexone (drug)
Personalized Computerized Training Program for Cognitive Dysfunction after COVID-19	Personalized computerized cognitive training (device)
Clinical Trial of Efficacy and Safety of Prospekta in the Treatment of Post-COVID-19 Asthenia	Prospekta (drug)
Vagus Nerve Stimulation for Post-COVID-19 Syndrome	Auricular transcutaneous vagus nerve stimulation (device)
Effects of PEA-LUT on Frontal Lobe Functions and GABAergic Transmission in Long COVID Patients	Palmitoylethanolamide co-ultramicronized with antioxidant flavonoid luteolin (dietary supplement)
Feasibility of Cannabidiol for the Treatment of Long COVID	MediCabilis Cannabis sativa 50 (drug)
The Effects of a Multi-factorial Rehabilitation Program for Healthcare Workers Suffering from Post-COVID-19 Fatigue Syndrome	Exercise (procedure)
Stellate Ganglion Block to Treat Long COVID-19 Case Series	Stellate Ganglion Block (procedure)
Transcranial Direct Stimulation for Persistent Fatigue Treatment Post-COVID-19	Active tDCS (device)
Effects of Cranial Electrotherapy Stimulation (CES) on Anxiety of Patients after COVID-19	Application of CES via ear clips (device)

---

Feasibility Pilot Clinical Trial of Omega-3 Supplement vs. Placebo for Post-COVID-19 Recovery Among Health Care Workers	Omega-3 (dietary supplement)
Telerehabilitation Program in Persistent COVID-19	Exercise and tele-coaching (procedure)
Inspiratory Muscle Trainer and SARS-CoV-2 (COVID-19) Persistent Symptoms	Inspiratory muscle trainer (device)

---