

## Literature screening report

# Post COVID-19 Condition: Definition, prevalence, therapy, pathogenesis, socio-economic implications, and relation to post-acute sequelae of other viral infections (update 1)

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## *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.*

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## 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. 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 current covers the period from May to August 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). For Q4 (therapy and rehabilitation) we also reported upcoming studies, registered in 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, 34 new studies were identified and included (a total of 60 studies). The studies included in the report's previous versions are listed in Appendix 1. The new studies are listed in Appendix 2. 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>

### 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> The debate for a clearer distinction between the terms Long COVID and post-COVID has been recently intensifying.<sup>6</sup>

### 1.2: Prevalence

According to recent evidence, the prevalence of PCC among adults with confirmed SARS-CoV-2 infections in Switzerland is estimated at about 23% at six months post-infection and 17% at 12 months post-infection.<sup>7</sup> Germany's Robert Koch Institute reported analyses conducted by Germany's central health insurance institute, indicating a PCC prevalence (ICD-10 code U09.9) between 7% and 13%.<sup>8</sup> Prevalence estimates based on the ICD-10 code tend to be lower, primarily due to the current underutilization of the code. 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>9,10</sup> In early 2022, Santé Publique France conducted a study of the prevalence and impact of PCC, which showed that 30% of respondents infected with SARS-CoV-2 had PCC (according to the WHO definition). This corresponds to a prevalence of 4% in the general population.<sup>11</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>12</sup> When considering that, over the entire duration of the pandemic, around 1 out of 4 infections were diagnosed by a SARS-CoV-2 test,<sup>13</sup> the prevalence of PCC among all infected adults might range between 5-10%. All reported prevalence estimates apply to the definition provided by the WHO unless otherwise stated.<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> Two recent studies, both from the UK, reported higher prevalence estimates. The first, a cross-sectional population-based survey reported a prevalence of 4.4% for children aged 5–11 years and 13.3% for children aged 12-17 years.<sup>16</sup> The second, a national cohort study, included children between the ages of 11 to 17 years and reported a PCC prevalence of 14.2%.<sup>17</sup> Both studies had limitations that might overestimate PCC prevalence. The first did not include a control group and the second had a low response rate.

### 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>3,18</sup> In children, altered or lost smell, anxiety, fatigue, headache, loss of appetite, earache/ringing in ears, sore throat, sore eyes, fever, sleep disturbances, and muscle fatigue are some of the most commonly reported symptoms (in addition to 34 less common symptoms, outlined in table 1).<sup>5,19,20</sup> Children with PCC may also be at higher risk for mental health problems.<sup>21</sup> In most cases (among children and adults), symptoms tend to improve over time.<sup>22</sup> Mean duration is estimated at 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>18</sup> A recent publication identified four PCC phenotypes: (1) minimal symptoms, (2) aches, cough, fatigue, (3) head, eyes, ears, nose, and throat symptoms, (4) multisystem (see table 2).<sup>23</sup> In terms of prognosis, A recent publication of an ongoing population-based cohort study (Zurich SARS-CoV-2 Cohort) reported recovery and symptom trajectories in Switzerland.<sup>7</sup> At 12, 18, and 24 months, 18.5%, 19.2%, and 17.2% of persons

with a previously confirmed SARS-CoV-2 infection reported persistent symptoms respectively. At 24 months, 10.4% reported mild, 3.9% moderate, and 1.9% severe PCC.<sup>7</sup>

For adults, the literature on risk factors is emerging and provides new evidence on the role of vaccines and reinfections.<sup>24-27</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>3,24,28,29</sup> A population-based cohort study from Scotland reported that depression and socioeconomic deprivation were more common in PCC patients with worsening symptoms between six- and 12-months post-infection.<sup>30</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>31-34</sup> In children and adolescents, female sex, age (12-17 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>3,16,35</sup> Whether and how these factors impact PCC severity for children and adolescents remains an evidence gap.

Regarding protective factors, 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 might be associated with lower PCC risk.<sup>3,36</sup> Recent evidence, including one German and two Swiss studies, suggested that (1) an Omicron infection (as compared to Delta and wild-type), (2) previous vaccination (two doses), and (3) reinfection may all be associated with lower chances of new-onset PCC in adults.<sup>24-27,29,37-39</sup> A recent meta-analysis reported that also one vaccine dose was associated with lower PCC odds.<sup>38</sup> Previous evidence suggested that for some, post-infection vaccination may be associated with reduced PCC severity (therapeutic effects), yet, the evidence remains mixed and unclear.<sup>40-43</sup> Whether and how the remaining protective factors are associated with PCC severity remains an evidence gap. In children, the evidence on PCC protective factors is not established yet. Previous evidence suggested that vaccination decreases the chances of severe acute disease in children.<sup>44</sup> Considering that the 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. A recent study reported that for children between 12 and 17 years, (1) male sex, (2) being of Asian ethnic background, and (3) living

in more affluent neighborhoods were associated with lower odds for PCC development.<sup>16</sup> Asymptomatic acute disease and an Omicron infection were also both associated with lower PCC risk in children.<sup>45</sup>

PCC pathogenesis remains unclear. However, plausible theories are emerging. Previous and recent publications highlight the 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, (6) prolonged various persistence and/or reactivation of other viruses, (7) unrepaired tissue damage.<sup>36,46,47</sup> A recently published review proposed the theory that tachykinins, primarily substance P, could be one causal factor for PCC.<sup>48</sup> The identification of PCC-related biomarkers is evolving (see table 3).

#### 1.4: Therapy and rehabilitation

There is currently no established PCC cure. Most treatments aim to reduce symptoms. Currently, there are six ongoing Swiss studies registered in clinicaltrials.gov (see table 4). 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>49</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>50</sup> The third trial aims to evaluate the effects of Pycnogenol®.<sup>51</sup> A fourth trial aims to evaluate the efficacy of BC 007.<sup>52</sup> The fifth aims to assess the effects of respiratory training on dyspnoea and exercise breathing, and the sixth to describe the kinetics of cardio-pulmonary exercise training.<sup>53,54</sup> Beyond Switzerland, a search in clinicaltrials.gov revealed 14 recently completed trials (total of 27) on PCC treatment and rehabilitation (see Appendix 3). Results were identified for five of those (see appendix 3). Three new studies contributed to the list of prominent therapy approaches to date (see table 5).<sup>36</sup> Three trials on preventive treatments reported that early administration of metformin, nirmatrelvir, or molnupiravir (during acute SARS-CoV-2 infection) may reduce the risk for PCC.<sup>55-57</sup>

The WHO's living guidance for COVID-19 management provided recommendations on the rehabilitation of adults with PCC.<sup>12</sup> It outlined 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 Appendix 4).<sup>12</sup> The patient-led association Long COVID Physio recently published a list of principles and recommendations for safe PCC rehabilitation (see table 6).<sup>58</sup> Two recent publications, one systematic review, and one RCT reported first



evidence of the effectiveness of respiratory rehabilitation and exercise training rehabilitation on improving respiratory symptoms and the quality of life of PCC patients.<sup>59,60</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>61-64</sup> PCC also negatively impacts work life, primarily in those with moderate to severe symptoms. A study from Switzerland reported 5.8% of patients with PCC had direct work-life disruptions or even complete inability to work (1.6%).<sup>65</sup> Reports from the United Kingdom (UK) and the US highlighted that about 16-25% of PCC patients had at some point adjusted their working hours or remained out of work.<sup>66,67</sup>

Robust and reliable data on the socio-economic implications of PCC remain scarce, yet first reports have 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>68</sup> The US-based COVID-19 Longhailer Advocacy Project estimated the average medical cost per PCC patient at about \$36,000.<sup>69</sup> A recent study from Germany estimated the PCC-related costs due to production loss between €3.4 and €5.9 billion (in 2021).<sup>70</sup> In the same year, pension costs related to rehabilitation were estimated at around €2.1 billion, and the economic burden on the healthcare system at around €332 million.<sup>70</sup> The US Household Pulse survey found that respondents reporting PCC symptoms were about twice as likely to experience significant housing insecurity.<sup>71</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>72</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>73,74</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 7).<sup>75,76</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>75</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>76</sup>

A key similarity between many post-viral syndromes, including PCC, is the diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).<sup>72,75</sup> A considerable subset of PCC patients meet the criteria for ME/CFS.<sup>36,72</sup> Common symptoms for both PCC and ME/CFS patients are post-exertional malaise, dysautonomia, postural tachycardia syndrome, and exercise intolerance. Current theories suggest that autoimmunity, viral mimicry, Epstein-Barr virus reactivation, and autonomous dysfunction could all lead to PCC with ME/CFS.<sup>77</sup> Furthermore, endothelial dysfunction and autoantibodies to G protein-coupled receptors may also play a role in the development of ME/CFS in PCC patients.<sup>77</sup> A recent German study reported that PCC patients with ME/CFS had more severe symptoms, with stronger fatigue, post-exertional malaise, and slower improvement over time.<sup>77</sup> Currently there are no recognized pharmacological or non-pharmacological treatments of post-viral syndromes.<sup>78-81</sup> For ME/CFS, there are currently two drugs being researched. The first is rintatolimod, a TLR-3 agonist, and the second is N-acetylcysteine.<sup>82</sup> Graded exercise therapy should not be considered a recommended ME/CFS treatment anymore.<sup>81</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, notably before one can establish a diagnosis of PCC according to the WHO definition.<sup>83</sup> The study found similar prevalence estimates of prolonged 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 of developing moderate to severe long-term symptoms.<sup>83</sup>

## 1.7: Healthcare responses

Some noteworthy new healthcare and policy responses are Germany's "BMG-Initiative Long COVID", initiated by the federal ministry with the aim to educate the population about PCC, the US National

Institutes of Health RECOVER initiative, as well as Canada’s Post-COVID-19 Interdisciplinary Clinical Care Network.<sup>84-86</sup> The health ministers of the G7 countries agreed that there is an urgent need for stronger research on PCC and promised a joint research initiative to be initiated in 2024.<sup>87</sup> Table 8 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. As the terms long COVID and post-COVID dominate the literature, there has been a recently intensifying discussion on how these should be defined. Two publications call for a clear distinction between these two terms, as the currently blurred definitions make proper diagnosis and therapy difficult.<sup>6,88</sup> That is rooted in the need to differentiate between prolonged form of acute disease (due to longer presence of allergens or anti-idiotypic antibodies) and long-term post-acute sustained damage.<sup>6</sup> Lippi et al. have therefore suggested a tentative definition that keeps two terms apart. They defined post-COVID as the continuation of symptoms that have started during acute infection, and Long COVID as the continuation of initial or post-acute symptoms three months after acute disease.<sup>88</sup> The WHO definitions for adults and children remain the most widely acknowledged definitions to date.

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

#### 2.2.1 PCC prevalence in adults

A recently published population-based survey from the US reported PCC among individuals infected during the Omicron surge.<sup>89</sup> The survey assessed testing, symptoms, outcomes, and the prevalence of PCC, defined as the persistence of symptoms for >4 weeks. The study's final analysis included 3,042 respondents. PCC was reported in 25.1% of those. In age and sex standardized analyses, the highest prevalence was reported by the age group 35-44 (27.6%) and females (27.4%). Limitations: The study defined PCC as the persistence of symptoms for >4 weeks is not in line with the WHO definition and might have led to an overestimation of prevalence. The study's methodology might have led to some selection and recall bias.<sup>89</sup>

#### 2.2.2 PCC prevalence in children and adolescents

A recently published serial cross-sectional population-based study reported prevalence estimates for children and teenagers aged between five and 17 years in the UK.<sup>16</sup> During each study round (monthly), a random sample was selected from the National Health Service general practitioner's list and invited to participate. Participants were asked to provide a throat and nose swap and complete an online questionnaire. The study's 10<sup>th</sup> round included a questionnaire on long-term symptoms (>3 months) and

included 1,059 children and adolescents. PCC prevalence was estimated at 4.4% for children aged 5–11 years and 13.3% for children aged 12-17 years. Of all participants reporting PCC, 11.2% also reported that their symptoms impacted their daily lives a lot. Limitations: The study did not include a SARS-CoV-2-negative control group. Its design may have introduced some recall bias and PCC prevalence might have been overestimated.<sup>16</sup>

Another recently published national cohort study (CLoCk cohort) from the UK assessed SARS-CoV-2 outcomes in children and teenagers aged between 11 and 17 years, matched to a test-negative control group.<sup>17</sup> Participants were recruited through the UK's national SARS-CoV-2 testing dataset. The final sample consisted of 1,658 non-hospitalized participants and 1,737 negative controls, followed up for six months. Among the children and teenagers with a previous SARS-CoV-2 infection, 14.2% reported at least one PCC-related symptom at month six. Limitations: A low response rate at month six and recall bias at baseline might influence the credibility of the study's findings.<sup>17</sup>

### 2.2.3 Reported by national and international organizations

In early 2022, Santé Publique France conducted a study of the prevalence and impact of PCC, which showed that 30% of respondents infected with SARS-CoV-2 had PCC (according to the WHO definition). This corresponds to a prevalence of 4% in the general population. A new, more robust study was carried out between September and November 2022. The results remain to be officially presented.<sup>11</sup>

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

### 2.3.1 Clinical manifestations & trajectories

For adults, all symptoms have been described extensively in our previous literature screening report.<sup>36</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>90</sup> A recent publication of an ongoing population-based cohort study (Zurich SARS-CoV-2 Cohort) reported recovery and symptom trajectories in Switzerland.<sup>7</sup> The study recruited a random sample of 1,106 adults with a confirmed SARS-CoV-2 infection in 2020 or early 2021 and residing in the canton of Zurich, as well as a control group of 628 uninfected individuals. Of the 1,106 participants, 86%

(n=951) were symptomatic, and 4.3% (n=48) were hospitalized during acute infection. The study reported recovery and symptom trajectories for up to 24 months after acute infection. At month six, 22.9% reported PCC (not yet recovered), while 16.2% reported mild, 3.6% moderate, and 2.7% severe symptoms. The proportion of those reporting PCC decreased over time. At 12, 18, and 24 months, 18.5%, 19.2%, and 17.2% reported persistent symptoms respectively. At 24 months, 10.4% reported mild, 3.9% moderate, and 1.9% severe PCC. Limitations: The study entirely relied on self-reported measures of a predefined symptoms list. Individuals with higher health awareness might have been more motivated to participate, while those experiencing PCC might be more motivated to remain in the study. Therefore, information and selection bias cannot be fully excluded. Overall, the study's population-based approach, high retention, and thorough analyses increase its credibility.<sup>7</sup>

For children and adolescents, the evidence is emerging. Altered or lost smell, anxiety, fatigue, headache, loss of appetite, earache/ringing in ears, sore eyes, sore throat, fever, and sleep disturbances are some of the most commonly reported symptoms.<sup>5,20</sup> A recent multidisciplinary review undertaken by researchers in Italy further explores PCC symptoms in children and teenagers.<sup>19</sup> The review confirmed all previous symptoms (see updated table 1), and added the following: exercise intolerance, variations in heart rate, constipation, dysphagia, nasal congestion, and rhinorrhea. These symptoms have been added to table 1. Limitations: The review does not thoroughly describe its methodological approach.<sup>19</sup> Another recently published systematic review summarized the findings of 31 studies on long-term symptoms in children and adolescents.<sup>20</sup> The review confirmed all previous symptoms and added the following: sleep disturbances, paresthesia, tinnitus, muscle weakness, and tremors (see updated table 1). Limitations: Many primary studies were assessed to be prone to recall and non-response bias. The included studies were quite heterogeneous in the PCC definitions they used, hindering comparability.<sup>20</sup>

A recent systematic review and meta-analysis highlighted the long-term mental health effects of COVID-19 on children and teenagers.<sup>21</sup> The review analysed 13 primary studies and reported that children with a previous SARS-CoV-2 infection had higher odds for various mental health problems, including anxiety, depression, concentration problems, sleep disturbances, mood swings, and appetite loss. Limitations: The included studies were highly heterogeneous.<sup>21</sup> The CLoCk study (described in more detail under 2.2.2) reported that the prevalence of many symptoms declined between baseline, three, and six months in comparison to test-negative participants, it is also likely that some of the symptoms occur unrelated to a SARS-CoV-2 infection.<sup>17</sup>

Table 1. PCC symptoms in children and adolescents<sup>5,19,20</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
Exercise intolerance	Heart rate variations	Dysphagia
Nasal congestion	Constipation	Rhinorrhoea
Sleep disturbances	Paraesthesia	Muscle weakness
Tremors		

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

### 2.3.2 PCC clusters/subtypes

Gottlieb and colleagues used data from INSPIRE, a national US-based study across eight large healthcare systems to identify PCC phenotypes.<sup>23</sup> The study included symptomatic participants with a previous SARS-CoV-2 infection and followed them up for six months, collecting self-reported symptoms at baseline, three, and six months. Using responses of 4,056 participants at month three and 2,856 at month six, the study identified four general symptom-based PCC phenotypes, detailed in table 2. Limitations: Surveys did not assess symptom severity and the study design might have introduced selection and response bias.<sup>23</sup>

Table 2. PCC phenotypes<sup>23</sup>

Phenotype	Description
Phenotype 1: minimal symptoms	Lower probability of all symptoms
Phenotype 2: aches, cough, fatigue	High probability of aches, cough, and tiredness
Phenotype 3: head, eyes, ears, nose, and throat symptoms	High probability of symptoms in the head region
Phenotype 4: multisystem	High probability of symptoms across multiple systems

\*this table was extracted from the original publication with minor language adjustments<sup>23</sup>

### 2.3.3 Influencing factors (incl. variants, vaccination, reinfections)

The evidence on risk and protective factors for adults is evolving but mostly confirmed previous findings.<sup>36</sup> A study using data from a large database of German primary care practices applied machine learning and reported PCC predictors.<sup>29</sup> Study inclusion required a previous SARS-CoV-2 diagnosis (ICD-based), as well as a PCC diagnosis (ICD-based). The final dataset included 5,440 PCC-diagnosed patients. The strongest predictor was the dominating strain at the time of diagnosis. Patients infected during the Omicron surge had a lower likelihood of being diagnosed with PCC. Those infected during the wild-type phase of the pandemic had a higher probability of being diagnosed with PCC. Age was another strong predictor, with the highest probability of being diagnosed with PCC between the ages of 39 and 80, and very low chances before the age of 15. Having multiple other diagnoses and more sick days before COVID-19 were also associated with PCC. Similarly, those with longer-lasting acute infections seemed to be at higher risk. Male sex and having received two vaccine shots were associated with a lower probability of being diagnosed with PCC. Limitations: The study relied on ICD-10 codes which at that time were still underutilized.<sup>29</sup> A large population-based cohort study from Scotland (n=23,973) further reported that depression and socioeconomic deprivation were more common in PCC patients who reported worsening symptoms between six- and 12 months post-infection.<sup>30</sup>

The latest systematic review and meta-analysis on the role of vaccines in preventing or treating PCC was recently published in *Brain Behavior and Immunity*.<sup>38</sup> The review included 23 studies. Results from the meta-analysis suggested that at least one vaccine dose (prior to infection) was associated with lower PCC odds (OR 0.539; 95% CI 0.295-0.987) in comparison to those not vaccinated. Results from the narrative synthesis on the treatment effects of vaccination (after PCC diagnosis) revealed mixed findings, yet most studies reported that most patients did not experience any changes in their PCC symptoms after receiving one or more vaccine doses. The authors continued to explain the protective effects of vaccines, emphasizing that breakthrough infections tend to be milder (reduced immune response, faster viral clearances, lower risk for organ damage and immune dysfunction) and are therefore less likely to lead to PCC. Limitations: Due to large heterogeneity, the review could not conduct a meta-analysis on the potential treatment effects of vaccines.<sup>38</sup>

Brannock and colleagues recently published a study that used electronic health records through the US National COVID Cohort Collaborative, exploring the associations between SARS-CoV-2 vaccination and PCC



diagnosis.<sup>39</sup> The study included a clinic-based cohort (n=47,404), in which patients were diagnosed with PCC by a healthcare provider, and a model-based cohort (n=198,514), in which patients were classified by machine learning. About 55.6% (n=26,354) of the clinic-based cohort were fully vaccinated and 1.5% (n=695) received a PCC diagnosis. About 43.4% (n=86,248) of the model-based cohort were fully vaccinated and 1.7% (3,391) were classified as PCC patients. The minimum follow-up time was about five months. After adjusting for sex, demographics, and medical history, the study found that full vaccination was associated with lower odds of being diagnosed/classified with PCC for both the clinic-based (OR 0.70, 95% CI 0.60-0.81) and model-based (OR 0.70; 95% CI 0.65-0.75) cohorts. Limitations: Reliance on electronic health records missed patients who did not seek healthcare (or were not able to access care).<sup>39</sup>

The evidence on risk and protective factors for children and teenagers is evolving but mostly confirms previous findings.<sup>3,35</sup> A population-based study from the UK (described in more detail under 2.2.2.) reported a list of factors associated with PCC in children between five and 17 years.<sup>16</sup> The study reported that older children (12-17 years) were three times more likely to report PCC compared with younger children (OR 3.4; 95% CI 2.8 to 4.0). Among older children (12-17 years), male sex, being of Asian ethnic background, and living in more affluent neighborhoods were all associated with a lower likelihood to report PCC. A Delta infection was associated with a higher likelihood of reporting symptoms compared with a wild-type strain infection (OR 1.6; 95% CI 1.3–1.8).<sup>16</sup> A prospective cohort study (n=1,243) from Italy followed up children (0-18 years) with a previously confirmed SARS-CoV-2 infection for up to 18 months.<sup>45</sup> The study found that the following factors were associated with higher PCC risk: (1) being older than 10 years (OR 1.23; 95% CI 1.18–1.28), (2) having any comorbidities (OR 1.68; 95% CI 1.14–2.50), and (3) have been hospitalized during acute disease (OR 4.80; 95%CI 1.91–12.1). One dose of vaccine was associated with reduced risk, yet not a significant reduction. Asymptomatic acute disease (OR 0.40; CI 0.22–0.73) and an Omicron infection (OR 0.60, CI 0.45–0.81) were both associated with reduced risk for PCC.<sup>45</sup> Limitations: The first study (UK) lacked a SARS-CoV-2 negative control group and the second study (Italy) was conducted in one specialized pediatric center, which potentially inflated PCC prevalence. Both studies lacked any insights on potential treatments.<sup>16,45</sup>

### 2.3.4 Pathogenesis

A review article recently published in *Molecular Psychiatry* (Nature), summarized four major theories of pathogenesis.<sup>46</sup> These are (1) prolonged virus presence, and/or reactivation of other viruses, (2) autoimmunity, (3) unrepaired tissue damage due to micro-thrombi, and (4) microbiome dysbiosis. The review also outlined a list of potential biomarkers for four major groups of sequelae summarized in table

3. Similar pathways are reported in publications that address PCC in children and teenagers.<sup>46</sup> Another review published in Nature Reviews immunology added to the list of dominant theories the following: (1) vascular endothelium activation or dysfunction, (2) mast cell activation, (3) changes in inflammatory activation systematic immunity, immune subsets, and their transcriptional profiles.<sup>47</sup>

Table 3: Potential PCC biomarkers<sup>46</sup>

Symptom area	Potential biomarkers
Immune	Inflammatory proteins (e.g., d-dimer, CPR, SAA)
	Cytokines (e.g., IFN- $\beta$ , IFN- $\gamma$ )
	Metabolites (e.g., glycyproline, long-chain acylcarnitine, kynurenine)
Cardiovascular	NT-proBNP
	Hs-TnI
	Suppression of tumorigenesis-2
	Diffuse
Gastrointestinal	ACE2
	Transmembrane protease serine 2
	Cytokines (e.g., IFN- $\gamma$ , IL-17 A)
	Zonulin
Neuropsychological	Inflammatory proteins (e.g., CRP, fibrinogen)
	IL6
	Nervous system proteins (e.g., GFAP, NfL, p-tau 81)
	miRNAs (e.g., miR-146a, miR-155)
	SpO2SII

Another recently published review proposed the theory that tachykinins, primarily substance P, could be one causal factor for PCC.<sup>48</sup> Tachykinins are neuropeptides involved in many pathophysiological processes, including inflammation and cell proliferation. P substance is an essential molecule for neuroimmune communication. The authors narratively explored current evidence and identified that certain predictors/biomarkers of PCC, such as obesity, female sex, IL-1 $\beta$ , IL-6, and TNF- $\alpha$  are strongly correlated with substance P. Based on that, they developed the theory that substance P could be one potential PCC cause. This pathogenetic mechanism remains a suggestion and requires further research.<sup>48</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 and Google revealed three new ongoing studies (six in total) in Switzerland (see updated table 4). The first aims to assess the effects of respiratory training on dyspnoea and exercise breathing, and the second the efficacy of BC 007.<sup>52,53</sup> The third study aims to describe the kinetics of cardio-pulmonary exercise training in PCC patients<sup>54</sup>. All studies are active and have no published results yet.

Table 4. Ongoing PCC trials in Switzerland (updated)

Trial	Description
<a href="#">Temelimab</a> as a Disease Modifying Therapy in Patients with Neuropsychiatric Symptoms in Post-COVID-19 or PASC Syndrome <sup>49</sup>	<ul style="list-style-type: none"> <li>▪ <u>Phase:</u> Phase two RCT (24 weeks), recruiting</li> <li>▪ <u>Aims:</u> 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 <a href="#">Fampridine</a> on Working Memory in Individuals with Post COVID-19 Condition with Subjective Cognitive Impairment <sup>50</sup>	<ul style="list-style-type: none"> <li>▪ <u>Phase:</u> recruiting</li> <li>▪ <u>Aims:</u> 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>
<a href="#">PYCNOVID</a> Study <sup>51</sup>	<ul style="list-style-type: none"> <li>▪ <u>Phase:</u> Recruiting</li> <li>▪ <u>Aims:</u> To evaluate whether Pycnogenol® improves overall health in individuals with post-COVID-19 syndrome</li> </ul>

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Disease-related Fatigue Monitoring Based on Body Signals Measured on the Skin ( <a href="#">Fatignals</a> ) <sup>53</sup>	<ul style="list-style-type: none"><li>Phase: Recruiting</li><li>Aims: To assess the use of physiological parameters as predictors of disease-related fatigue. Wearable devices are used to monitor cancer and PCC patients during their stay in a rehabilitation clinic. The study will also assess the effects of respiratory training in reducing dyspnoea and improving exercise breathing patterns in PCC patients</li></ul>
A Prospective, Double-blind, Randomized, Parallel Group, Placebo Controlled, Multicentre, Phase II Study to Investigate the Efficacy, GPCR Autoantibody Neutralizing Effect, Safety, and Tolerability of <a href="#">BC 007</a> in Participants With Long COVID <sup>52</sup>	<ul style="list-style-type: none"><li><u>Phase:</u> Recruiting</li><li><u>Aims:</u> To investigate the efficacy, GPCR autoantibody neutralizing effect, safety, and tolerability of BC 007 in PCC patients</li></ul>
Kinetics of Physiological and Symptomatic Responses to <a href="#">CardioPulmonary</a> Exercise Testing (CPET) in Subjects With Persistent Exercise Intolerance After COVID-19: an Open-Source Exercise Network <sup>54</sup>	<ul style="list-style-type: none"><li><u>Phase:</u> Ongoing</li><li><u>Aims:</u> To describe the kinetics of cardio-pulmonary exercise training conducted by pulmonologists and cardiologists across French-speaking regions of the world (including Canada, France, and Switzerland)</li></ul>

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#### 2.4.2 Treatment and rehabilitation research (globally)

A search on clinicaltrials.gov revealed 14 new completed trials (a total of 27) on PCC treatment and rehabilitation (see Appendix 3). We identified associated publications (results) for only five of those (references to full manuscripts added in Appendix 3). A list of ongoing drug trials is provided in the publication of Sheibenbogen et al.<sup>82</sup> Three new studies contributed to the list of prominent therapy approaches to date (see updated table 5).<sup>82,91,92</sup> Parts of the table were extracted in their original form. For more detailed information, please refer to the publications.<sup>36,82,91,92</sup>

Table 5. Potential PCC treatments (updated)<sup>36,82,91,92</sup>

Symptoms and/or biological mechanism	Potential treatment(s)
Post-exertional malaise	Pacing
	Pharmacological: $\beta$ -blockers, pyridostigmine, fludrocortisone, midodrine
Postural tachycardia syndrome	Non-pharmacological: increase salt and fluid intake, intravenously administered salt, compression stockings
Immune dysfunction	Intravenous immunoglobulin
Cognitive dysfunction, depression, anxiety	Cognitive pacing and post-concussion syndrome protocols, famotidine
Fatigue	Coenzyme Q10, d-ribose
Pain, fatigue, neurological symptoms	Low-dose naltrexone
Fatigue, unrefreshing sleep, brain fog	Low-dose aripiprazole
Autoimmunity / autoantibodies	BC007, CD20 monoclonal antibodies, C19 monoclonal antibodies, BTK inhibitor
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®
Inflammation (overall)	Kinase inhibitors, antihistamines, minocycline, metformin
Vascular damage	Pyridostigmine, $\beta$ 2/3 reception antagonists, PDE5 inhibitor
Neuromodulation	Low dose aripiprazole, methylphenidate, Guanfacine
Myocardial dysfunction	Hyperbaric oxygen therapy

\*this table was extracted from the original publication with no major language adjustments<sup>36</sup>

Beyond the WHO’s living guidance for COVID-19 management and PCC rehabilitation (see appendix 4), Long COVID Physio, a patient-led association met in September 2022 to discuss what constitutes safe PCC rehabilitation.<sup>12,58</sup> Combining lived experience and expertise, the association created a list of principles and recommendations, summarized in table 6. Parts of the table were extracted in their original form. For more detailed information, please refer to the publication.<sup>58</sup>

Table 6. Principles and recommendations for the rehabilitation of people living with PCC<sup>58</sup>

Principles	Recommendations for rehabilitators
Avoiding acute events and symptom flare-ups	Screen carefully and modify programs according based on symptoms
Personalization	Tailor rehabilitation to the needs and preferences of each patient
Facilitating expectations	Manage expectations through clear and transparent communication with all stakeholders (patient, family, friends)
Psychologically supportive	Be non-judgmental and create safe spaces

Two recent publications on the rehabilitation of PCC evaluated the effects of respiratory and exercise training. The first, a systematic review and meta-analysis assessed how respiratory rehabilitation, including (1) respiratory muscle training, (2) breathing training, (3) aerobic exercise, and (4) strengthening exercises impacts pulmonary sequelae and quality of life.<sup>59</sup> Final analysis included 12 primary studies and a total of 596 PCC patients. Findings suggested that respiratory rehabilitation was effective in improving forced expiratory volume in one second, forced vital capacity, total lung capacity, 6-minute walking distance, and quality of life. Effects were stronger for (1) patients without comorbidities, (2) programs with all four rehabilitation types, and (3) a rehabilitation frequency of three or more times a week.<sup>59</sup>

Second, an RCT evaluated the effects of exercise training rehabilitation on dyspnoea and quality of life among PCC patients who previously received intensive care and continued to experience respiratory symptoms three months after discharge.<sup>60</sup> Intervention participants (n=27) received exercise training rehabilitation (two 60-minute sessions weekly) and control participants (n=33) standard physiotherapy (two 30-minute sessions) for 90 days. Those undergoing exercise training had significantly reduced improved dyspnoea scores compared with those who received standard physiotherapy.<sup>60</sup> Limitations: The main limitation of the review was the high heterogeneity of primary studies. The main limitations of the

RCT were the small sample size and the lack of assessment of important clinical endpoints such as the 6-minute walking test and peak oxygen consumption.<sup>59,60</sup> The overall evidence on effective PCC rehabilitation remains weak.

### 2.4.3 Preventive treatment research (globally)

A cohort study recently published in the BMJ examined the effects of early antiviral treatment (first five days of SARS-CoV-2 infection) with molnupiravir on prolonged symptoms.<sup>57</sup> The study enrolled 229,286 test-positive US veterans with at least one PCC risk. The group that received molnupiravir during the first five days of acute disease (n=11,472) was compared to the non-treatment group. Findings suggested that molnupiravir was associated with reduced PCC risk (RR 0.86; 95% CI 0.83-0.89). Reduced risk was also observed in those not vaccinated, as well as those re-infected. Limitations: The study included only veterans and might thus have limited generalizability. Analysis was focused on 13 PCC symptoms and did not include all possible PCC manifestations.<sup>57</sup>

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

Robust and reliable data on the socio-economic implications of PCC remain scarce. A recently published study from Germany used a range of secondary data sources (insurance, sickness funds, government institutions) and estimated the PCC-related costs related to employment loss and healthcare (in 2021).<sup>70</sup> Assuming that every PCC patient is on average absent from work for 12 weeks, the production loss per person was estimated at €10,500. Considering the number of infections among the working-age population this could result in a production loss between €3.4 and €5.9 billion. At the federal level, the estimated loss of gross value due to productivity reductions was estimated at €5.7 billion. Pension costs related to rehabilitation were estimated at around €2.1 billion. The economic burden on the healthcare system was relatively lower. Assuming approximately an average of €3,000 in rehabilitation costs per PCC patient, the total cost would have been around €332 million in 2021. Limitations: Estimates are subject to uncertainty as many of the parameters and data are of limited reliability.<sup>70</sup>

A population-based cohort study from Israel used records of one of the country's largest health funds and estimated the average monthly excess costs per person, likely attributed to PCC.<sup>93</sup> Every case (previously infected) was randomly matched to a test-negative control leading to a study sample of 642,868 pairs, followed up between one and 20 months. PCC-attributable costs were estimated as difference in

difference, accounting for cost differences at baseline (pre-pandemic). The average monthly net excess cost for cases was estimated at \$7.6 per patient. Excess costs were much higher for the subgroup of cases that were hospitalized during acute infection (US\$91.6). Most of these costs were attributed to hospital bills. The lowest costs were incurred by younger patients (20-39 years), while the highest costs were incurred by patients aged 60 and above. Limitations: The study used data from a single health fund, limiting its generalizability to other populations. Analyses did not explore costs in relation to different symptoms, allowing only for a limited clinical interpretation. The effects of Omicron could not be assessed due to earlier recruitment.<sup>93</sup>

A secondary analysis of the US Household Pulse Survey (n=203,807) aimed to assess whether PCC is associated with higher housing insecurity.<sup>71</sup> The study used survey data on functional impairment, PCC symptoms, symptom impact on daily life, and current housing situation. The study found that respondents reporting PCC symptoms were about twice as likely to experience significant housing insecurity. That included not having enough money to meet household needs (PR 1.85; 95% CI 1.74-1.96), paying rent (PR 1.76; 95% CI 1.57-1.99), and facing potential evictions (PR 2.12; 95% CI 1.58-2.86). The association between PCC and housing insecurity was strongest in PCC patients reporting functional limitations and symptoms that impact daily living, thus, more severe PCC cases. Limitations: PCC assessment was only limited to those with a confirmed diagnosis of SARS-CoV-2 infection, excluding those who were not able to access care and testing. The duration of PCC symptoms and their impact on housing insecurity could not be assessed.<sup>71</sup>

A recent first-of-its-kind study estimated the years lived with disability (YLDs) and disability-adjusted life years (DALYs) due to PCC between 2021-2022 in Australia.<sup>94</sup> Calculations were conducted using prevalence estimates and symptom trajectories from previously published studies. The study estimated that PCC was responsible for about 74% of all YLDs from SARS-CoV-2 infections during that time in Australia. Furthermore, it was estimated that PCC was responsible for about 2.4% of all expected DALYs for all diseases during the period. Limitations: Estimates were limited by high uncertainty. PCC prevalence likely overestimated in primary studies that were used for calculations.<sup>94</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>75</sup> Many other well-known viral pathogens are linked to the development of long-term symptoms (see updated table 7).<sup>75</sup> A recently published hypothesis-driven review discusses that muscle fatigue, observed in PCC and other



viral illnesses (e.g., Human Herpes Virus, Powassen, and Epstein-Barr virus), might have a common molecular mechanism. The review emphasised the alteration of adaptive immunity as a plausible molecular mechanism underlying muscle fatigue after a viral infection.<sup>95</sup>

Table 7. Viral pathogens with known post-viral conditions (updated)<sup>75,76,95</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
Human Herpes Virus (HHV6)	N/A
Powassen virus	N/A

\*this table's content was extracted from the original publications with minor language adjustments<sup>75,76</sup>

We did not identify any new studies comparing the symptoms of PCC to other post-viral conditions. All previous findings are summarized in the report's first part (section 1.6)

### 2.6.1 Prevalence estimates of post-viral syndromes

The poor understanding of post-viral syndromes leads to a lack of clinical recognition, underdiagnosis, and inadequate care.<sup>75</sup> Thus, data on their prevalence are limited.<sup>75</sup> Pre-COVID-19, the prevalence of ME/CFS was estimated between 0.2-0.8% .<sup>77</sup> We did not identify any new relevant prevalence estimates for post-viral syndromes. All previous findings are summarized in the report's first part (section 1.6).

### 2.6.2 Myalgic encephalomyelitis/chronic fatigue syndrome

It is by now well established that a subset of PCC patients fulfils all diagnostic criteria of ME/CFS. The underlying mechanisms remain unclear.<sup>77</sup> Current theories suggest that autoimmunity, viral mimicry,

Epstein-Barr virus reactivation, and autonomous dysfunction could all lead to PCC with ME/CFS. Furthermore, endothelial dysfunction and autoantibodies to G protein-coupled receptors may also play a role in the development of ME/CFS in PCC patients.<sup>77</sup> A prospective observational cohort study recently published in *eClinical Medicine* assessed PCC symptom severity and biomarkers (hand grip strength, cardiovascular function, laboratory parameters).<sup>77</sup> The study was conducted in Germany and included PCC patients (n=106) with moderate to severe fatigue and exertion intolerance, followed up for 20 months. The aim was to compare disease trajectories between PCC patients with and without ME/CFS. Those patients with ME/CFS had more severe symptoms throughout the follow-up period. Those patients without ME/CFS showed faster symptom improvement. Fatigue and post-exertional malaise were prevalent in both groups, yet stronger in ME/CFS patients. Low baseline hand grip strength was correlated with longer symptom duration, primarily for ME/CFS patients. Limitations: The study had a high dropout and missing data rate.<sup>77</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>78-80</sup> Most approaches mainly aim to alleviate individual symptoms. For many post-viral syndromes, and especially ME/CFS, there has been little interest in treatment research by the pharmaceutical industry.<sup>82</sup> The complexity and unknown underlying factors of many post-viral syndromes were major barriers.<sup>82</sup> For ME/CFS, there are currently no approved drugs or widely accepted treatments. Currently, two drugs being researched for ME/CFS. The first is rintatolimod, a TLR-3 agonist, and the second is N-acetylcysteine.<sup>82</sup>

## Part 3: Response update

Below (updated table 8), we provide all ongoing and new healthcare and policy responses in Europe, the US and Canada.

Table 8: 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>96</sup></li> <li>▪ Medix recently updated its factsheet and guidelines for PCC for primary care<sup>1</sup></li> <li>▪ Inselspital Bern developed the Long-COVID App “INSELhealth cofit” with the aim to support patients with PCC as well as medical professionals<sup>97</sup></li> <li>▪ FOPH funding for research between 2021 and 2023<sup>2</sup></li> <li>▪ Recommendations on Post-Covid-19 Condition for primary care, organized and paid by the FOPH<sup>98</sup></li> <li>▪ Switzerland offers at least 49 specialized PCC consultations and 47 rehabilitations across the country<sup>99</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>100</sup></li> <li>▪ Introduction of “Your COVID Recovery” as part of the NHS support for PCC patients<sup>101</sup></li> <li>▪ Expansion of the number of facilities that provide specialized post-covid services<sup>100</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>102</sup></li> <li>▪ BMG-Initiative Long COVID: The federal ministry started the initiative to educate the population about PCC<sup>84</sup></li> <li>▪ The Hanover University of Medicine plans to set up a virtual rehabilitation clinic that will bundle scientific findings and practical treatment knowledge on PCC. The aim is to support physicians in treating patients affected by PCC in Lower Saxony<sup>103</sup></li> </ul>

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	<ul style="list-style-type: none"><li>▪ Researcher at UKSH (University Hospital of Schleswig-Holstein) developed a “Post-Covid-Score” to help physicians refer patients to the right specialists<sup>104</sup></li></ul>
France	<ul style="list-style-type: none"><li>▪ The government has committed €14 million in funding for PCC research<sup>105</sup></li><li>▪ PCC support and coordination units that can be contacted by professionals, patients, and carers. The support units provide information, identify medical and social care providers, and help to set up and coordinate them</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>106</sup></li></ul>
Netherlands	<ul style="list-style-type: none"><li>▪ The Ministry of Health, Welfare, and Sport is collaborating with various organizations to better comprehend PCC and offer aid to those affected<sup>107</sup></li></ul>
United States	<ul style="list-style-type: none"><li>▪ Expansion of post-COVID care clinics<sup>108</sup></li><li>▪ Department of Health and Human Services published the National Research Action Plan on Long COVID as a response to the Presidential Memorandum on addressing the long-term effects of COVID-19<sup>109</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>110</sup></li><li>▪ A budget of \$10 million has been allocated to Agency’s for Healthcare Research and Quality Fiscal Year 2023 budget to tackle PCC<sup>111</sup></li><li>▪ The National Institutes of Health created the RECOVER Initiative to generate more knowledge on PCC<sup>85</sup></li><li>▪ A new Office of Long COVID Research and Practice is formed to study the condition and help those who have been diagnosed with it<sup>112</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>113</sup></li></ul>

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- 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>113</sup>
  - Task Force on Post COVID-19 Condition Report published recently<sup>114</sup>
  - Post-COVID-19 Interdisciplinary Clinical Care Network that offers research, education and care<sup>86</sup>
- WHO
- Addition of “Rehabilitation of adults with Post COVID-19 condition” in the Living Guidance for Clinical Management of COVID-19<sup>12</sup>
  - 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>115</sup>
- G7
- Health ministers of the G7 countries agreed that there is a need for stronger research on PCC. A joint research initiative will be created for this purpose, which is to be initiated in the year 2024 under the Italian Presidency<sup>87</sup>
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134. Ibrahim A, et al. A randomized controlled trial examining the impact of low vs. moderate-intensity aerobic training in post-discharge COVID-19 older subjects. *European Review for Medical and Pharmacological Sciences.* 2023.

## Appendices

### Appendix 1: Studies included in previous reports

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1. Clinical case definition of post-COVID-19 condition in children: a good start, but improvements are needed<sup>116</sup>
  2. Long COVID: major findings, mechanisms and recommendations<sup>36</sup>
  3. Machine learning identifies long COVID patterns from electronic health records<sup>117</sup>
  4. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes<sup>118</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>119</sup>
  6. Post-acute symptoms 3-15 months after COVID-19 among unvaccinated and vaccinated individuals with a breakthrough infection<sup>120</sup>
  7. Post-COVID-19 condition in the German working population: A cross-sectional study of 200,000 registered stem cell donors<sup>28</sup>
  8. Risk Factors Associated With Post-COVID-19 Condition: A systematic Review and Meta-analysis<sup>24</sup>
  9. Prevalence and risk factor for long COVID in children and adolescents: A meta-analysis and systematic review<sup>35</sup>
  10. Prevalence of Post-COVID Condition 12 Weeks After Omicron Infection Compared With Negative Controls and Association With Vaccination Status<sup>25</sup>
  11. Risk factors, health outcomes, healthcare services utilization, and direct medical costs of patients with long COVID<sup>121</sup>
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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>122</sup>
  13. Characterising patterns of COVID-19 and long COVID symptoms: evidence from nine UK longitudinal studies<sup>90</sup>
  14. Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programmes<sup>123</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>124</sup>
  17. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study<sup>125</sup>
  18. Effect of covid-19 vaccination on long covid: systematic review<sup>26</sup>
  19. Risk of new-onset Long Covid following reinfection with SARS-CoV-2: community-based cohort study<sup>27</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>55</sup>
  21. Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition<sup>56</sup>
  22. Post-covid medical complaints following infection with SARS-CoV-2 Omicron vs Delta variants<sup>126</sup>
  23. Post–COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection<sup>127</sup>
  24. Unexplained post-acute infection syndromes<sup>75</sup>
  25. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An overview of biological factors that may contribute to persistent symptoms<sup>72</sup>
  26. Immune determinants of chronic sequelae after respiratory viral infection<sup>76</sup>
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## Appendix 2: New included studies

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1. Post-COVID or long-COVID? That is the question<sup>6</sup>
  2. COVID-19 vaccination for the prevention and treatment of long COVID: A systematic review and meta-analysis<sup>38</sup>
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3. Addressing standardized definitions of post- COVID and long-COVID<sup>88</sup>
  4. Recovery and symptom trajectories up to two years after SARS-CoV-2 infection: population based, longitudinal cohort study<sup>7</sup>
  5. Long COVID in Children: A Multidisciplinary Review<sup>19</sup>
  6. Epidemiology, clinical presentation, pathophysiology, and management of long COVID: an update<sup>46</sup>
  7. Tachykinins and the potential causal factors for post- COVID-19 condition<sup>48</sup>
  8. Long COVID risk and pre-COVID vaccination in an EHR-based cohort study from the RECOVER program<sup>39</sup>
  9. Trajectory of Post-COVID Self-Reported Fatigue and Dyspnoea in Individuals Who Had Been Hospitalized by COVID-19: The LONG-COVID-EXP Multicenter Study<sup>22</sup>
  10. Long COVID in children and adolescents: Prevalence, Clinical Manifestations, and Management Strategies<sup>128</sup>
  11. Mechanisms and Severity of Exercise Intolerance Following COVID-19 and Similar Viral Infections: A Comparative Review<sup>95</sup>
  12. Fighting Post-COVID and ME/CFS – development of curative therapies<sup>82</sup>
  13. Effectiveness of respiratory rehabilitation in patients with COVID-19: A meta-analysis<sup>59</sup>
  14. A Systematic Review of Persistent Clinical Features After SARS-CoV-2 in the Pediatric Population<sup>20</sup>
  15. Long COVID: Costs for the German economy and health care and pension system<sup>70</sup>
  16. Estimating the economic burden of long-Covid: the additive cost of healthcare utilisation among COVID-19 recoverees in Israel<sup>93</sup>
  17. Characteristics and predictors of persistent symptoms post-COVID-19 in children and young people: a large community cross-sectional study in England<sup>16</sup>
  18. The effect of hyperbaric oxygen therapy on myocardial function in post-COVID-19 syndrome patients: a randomized controlled trial<sup>91</sup>
  19. Effect of famotidine on cognitive and behavioral dysfunctions induced in post-COVID-19 infection: A randomized, double-blind, and placebo-controlled study<sup>92</sup>
  20. Prevalence of mental health problems among children with long COVID: A systematic review and meta-analysis<sup>21</sup>
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21. Long COVID Clinical Phenotypes up to 6 Months After Infection Identified by Latent Class Analysis of Self-Reported Symptoms<sup>23</sup>
22. Predictive Attributes for Developing Long COVID—A Study Using Machine Learning and Real-World Data from Primary Care Physicians in Germany<sup>29</sup>
23. The health impact of long COVID during the 2021–2022 Omicron wave in Australia: a quantitative burden of disease study<sup>94</sup>
24. The immunology of long COVID<sup>47</sup>
25. What is Safe Long COVID Rehabilitation?<sup>58</sup>
26. Association of Long COVID with housing insecurity in the United States, 2022-2023<sup>71</sup>
27. Natural history of long-COVID in a nationwide, population cohort study<sup>30</sup>
28. Effectiveness of exercise training on the dyspnoea of individuals with long COVID: A randomised controlled multicentre trial<sup>60</sup>
29. COVID-19, post-acute COVID-19 syndrome (PACS, “long COVID”) and post-COVID-19 vaccination syndrome (PCVS, “post-COVIDvac-syndrome”): Similarities and differences<sup>129</sup>
30. The prevalence of SARS-CoV-2 infection and long COVID in U.S. adults during the BA.4/BA.5 surge, June–July 2022<sup>89</sup>
31. Long COVID—six months of prospective follow-up of changes in symptom profiles of non-hospitalised children and young people after SARS-CoV-2 testing: A national matched cohort study (The CLoCk) study<sup>17</sup>
32. Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study<sup>45</sup>
33. Molnupiravir and risk of post-acute sequelae of covid-19: cohort study<sup>57</sup>
34. Long-term symptom severity and clinical biomarkers in post-COVID-19/chronic fatigue syndrome: results from a prospective observational cohort<sup>77</sup>

### Appendix 3: Completed PCC treatment and rehabilitation trials globally (clinicaltrials.gov)

Study title (as indexed in clinicaltrials.gov)	Intervention (type)
*trials with published results (see reference)	
Pilot Study into LDN and NAD+ for Treatment of Patients with Post-COVID-19 Syndrome	Naltrexone (drug)

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*Personalized Computerized Training Program for Cognitive Dysfunction after COVID-19 <sup>130</sup>	Personalized computerized cognitive training (device) Prospekta (drug)
Clinical Trial of Efficacy and Safety of Prospekta in the Treatment of Post-COVID-19 Asthenia	
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-ultramicrosized 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 <sup>131</sup>	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 <sup>132</sup>	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)

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Inspiratory Muscle Trainer and SARS-CoV-2 (COVID-19) Persistent Symptoms	Inspiratory muscle trainer (device)
Biosound Therapy as a Treatment for Long COVID Patients	Biosound Therapy System (procedure)
*Effects of Sodium Pyruvate Nasal Spray in COVID-19 Long Haulers <sup>133</sup>	Sodium pyruvate nasal spray (drug)
COVID-19 Sequelae: Treatment and Monitoring. A Dietary Supplement Based on Sea Urchin Eggs With Echinochroma A	Echinochrome A (dietary supplement)
Homeopathic Treatment of Post-acute COVID-19 Syndrome	Homeopathic Medication (drug)
Vortioxetine for Post-COVID-19 Condition	Vortioxetine (drug)
Effects of Cardiopulmonary Rehabilitation in Participants With Post-COVID 19 Syndrome.	Pulmonary rehabilitation exercises at the Rehabilitation Center or Home Intervention (procedure)
Effectiveness of Supportive Psychotherapy Through Internet-Based Teleconsultation on Psychological and Somatic Symptoms, Neutrophil-Lymphocyte Ratio, and Heart Rate Variability in Post Covid-19 Syndrome Patients	Supportive Psychotherapy (procedure)
Circuit Training Program in Post COVID-19 Patients	Circuit Training Exercise Program or Aerobic Training Exercise Program (procedure)

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Aerobic Exercise in People With Post-COVID-19	Aerobic exercise or Conventional rehabilitation
Effectiveness of Modified Diaphragmatic Training for Gastroesophageal Reflux Disease Post Covid-19	Modified diaphragmatic training (procedure)
Quality of Life and Lung Function on Post Covid-19 Patient (Covid-19)	Breathing exercise, Aerobic exercises (procedure)
Exercise Training Six-Months After Discharge in Post-COVID-19 Syndrome	Aerobic exercise and strength training (procedure)
Community-based Individualized Homeopathic Rehabilitation in Post COVID-19 Patients	Homeopathy (drug)
*Low Versus Moderate-intensity Aerobic Training in Post-discharge COVID-19 Subjects <sup>134</sup>	Aerobic exercise (procedure)

Appendix 4: WHO living guidance PCC rehabilitation recommendations<sup>12</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>

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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>

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\*this table's content was extracted from the original publication with minor language adjustments<sup>12</sup>