EVIDENCE SYNTHESIS BRIEFING NOTE

TOPIC: **UNDERSTANDING LONG COVID**

Information finalized as of October 29, 2021.[a]

This Briefing Note was completed by the Research, Analysis, and Evaluation Branch (Ministry of Health) based on information provided by a member of the COVID-19 Evidence Synthesis Network. Please refer to the Methods section for further information.

Purpose: This note summarizes the research evidence associated with 'long COVID', including definitions, risk factors, symptomatology, prognosis, therapeutics, and other emerging research findings.
Key Findings: Commonly, long COVID is characterized as the persistence of any COVID signs and symptoms that continue or develop between four to 12 weeks after acute COVID-19, including both ongoing symptomatic COVID-19 and post-COVID-19 syndrome.

- **Emerging Research Findings**: Research from systematic reviews, narrative reviews, and living reviews, and individual studies yielded the following details:
  - Diagnosis: Long COVID is primarily diagnosed based on two factors: 1) having been infected with COVID-19 in the past; and 2) presenting with long COVID symptoms.
  - Prevalence: Prevalence estimates vary widely; for example, 5% to 80% of people with confirmed COVID-19 may have symptoms past the acute phase of illness. Recent reports (September 2021) suggest that 150,000 Canadians currently have long COVID, though it is unclear if this is limited to people with confirmed COVID-19.
  - Risk factors: The following factors may increase the risk for long COVID: a higher acuity of COVID-19 infection or presence of many acute COVID-19 symptoms, being female, being of older age, having a higher body mass index (e.g., obesity), pre-existing comorbidities (e.g., asthma, autoimmune disease), psychiatric disorders, and being a health care worker. Ethnicity and socioeconomic factors have been investigated but show mixed findings.
  - Symptomatology: The most common symptoms include: chronic fatigue, dyspnea (e.g., shortness of breath), headache, pain (e.g., chest, joint, muscle), poor sleep quality, and reduced exercise capacity. In addition, persistent symptoms have also been described for the cognitive, musculoskeletal, respiratory, nervous, gastrointestinal, cardiac, and psychological systems (e.g., post-traumatic stress disorder, anxiety, depression).
- **Management of Long COVID Patients**: Research suggests that treating people with long COVID requires a multidisciplinary approach including evaluation, symptomatic treatment, treatment of underlying problems, physiotherapy, occupational therapy, and psychological support.

Limitations: The evidence base currently precludes a precise definition of long COVID-19 symptoms and prevalence. In addition, no identified studies provided evidence regarding prognosis for individuals with long COVID. There is a clear need for robust, controlled, prospective cohort studies, including different at-risk populations and settings, incorporating appropriate investigations, collected, and recorded in a standardised way.
Analysis for Ontario: Since the time frame for assessing the risk factors and symptoms associated with long COVID has just been several months, there has been scant time to understand the longer-term implications of COVID-19 infection. The knowledge regarding long term effects and treatment options is still evolving.

[a] This briefing note includes current available evidence as of the noted date. It is not intended to be an exhaustive analysis, and other relevant findings may have been reported since completion.

Supporting Evidence

Table 1 below summarizes the emerging research evidence associated with 'long COVID', including definitions, risk factors, symptomatology, prognosis, and emerging trends or findings. In the Appendix, additional details on proposed approaches to classifying long COVID are provided in Table 2, reports from 18 systematic and narrative reviews are provided in Table 3, and the results of six single studies are included in Table 4. Finally, Table 5 describes potential models of care for long COVID.

Much of the research summarized in the Scientific Evidence (Table 1) comes from a recent report from the Canadian Agency for Drugs and Technologies in Health:

- Vu, T., & McGill, S. (September 2021). CADTH Horizon Scan: An Overview of Post COVID-19 Condition (Long COVID). *Canadian Journal of Health Technologies, 1* (9), pp. 31.

Table 1: Summary of Emerging Research on Long COVID

Scientific Evidence	• **Long COVID Defined**: A CADTH (September 2021) report on 'post-COVID condition' states that consensus on the terminology has yet to be reached in the research.[1] The World Health Organization (WHO) uses the term post-COVID-19 condition but notes that multiple names are in use, such as: long COVID; chronic COVID syndrome; late sequelae of COVID-19; post-acute sequelae of SARS-CoV-2 infection (PASC); and long haul COVID.[2] Different groups may use slightly different definitions for any of these terms;[3] and formal definitions have also been proposed (see Table 2). For example: ○ CADTH's report (September 2021) uses the term post-COVID-19 condition, which refers to symptoms beyond the acute infection phase (i.e., four weeks after being infected).[4,b] • **Symptomatology**: Emerging evidence about the type of symptoms and long-term health effects of long COVID suggests that many adults can experience a heterogeneous range of symptoms after their initial COVID-19 infection.[5] The most common symptoms reported in the literature were: chronic fatigue, dyspnea (e.g., shortness of breath), headache, pain (e.g., chest, joint, muscle), poor sleep quality, and reduced exercise capacity. In addition, persistent symptoms have also been described for the cognitive, musculoskeletal, respiratory, nervous, gastrointestinal, cardiac, and psychological systems (e.g., post-traumatic stress disorder, anxiety, depression).[6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21] ○ Long COVID and Other Coronaviruses: CADTH (September 2021) summarizes research that suggests there are similar long-term health consequences resulting from COVID-19, SARS, and MERS.[22] For example: ▪ A systematic review (May 2020) on survivors of SARS and MERS reported that six months after hospital discharge patients had symptoms similar to those of long COVID, including lung abnormalities, reduced exercise capacity, and psychological

[b] It has been suggested that some patient advocates may dislike the term 'post-COVID-19', as it may be interpreted as having no active disease process or suggest that they have recovered (CADTH, 2021).

impairment. An estimated 40% of people who had SARS had chronic fatigue 3.5 years after being diagnosed.[23]

- Pediatric Population: Symptoms of long COVID among children range widely with the most frequent including: pain, breathing difficulties, fatigue, cough, and headache. Other symptoms include insomnia, rash, and neuropsychiatric symptoms, such as concentration difficulties.[24] The CADTH report (September 2021) highlighted a study (preprint) of children with symptoms lasting for more than four weeks; the study reported that symptoms lasted, on average, for months and that 94% of study participants reported experiencing at least four symptoms.[25,26]
- Subtypes in Children: Long COVID in children may include multiple subtypes or syndromes. Based on an analysis of 570 pediatric patients, the US Centers for Disease Control and Prevention (CDC) suggest that there may be three subtypes: multisystem inflammatory syndrome in children (MIS-C), atypical Kawasaki disease, and pediatric long COVID.[27]

- **Diagnosis**: Currently, long COVID is primarily diagnosed based on two factors: 1) having been infected with COVID-19 in the past; and 2) presenting with above-noted long COVID symptoms.[28]
- **Prevalence**: Estimates on prevalence vary widely across studies.[29] For example:
  - A systematic review (2021) reported estimates ranging from 5% to 80%.[30,c]
  - Two systematic reviews (March 2021; one preprint) estimated 63% to 84% of people with confirmed COVID-19 had symptoms four weeks after either diagnosis or hospitalization; and 46% to 56% experienced symptoms after 12 weeks.[31,32]
  - Three cohort studies (February 2021; July 2021; September 2021) reported that 33% to 39% of people may experience symptoms after six to nine months. Two cohort studies reported that 28% to 49% of people who had been hospitalized for COVID-19 experienced symptoms after 12 months.[33]
  - Studies of people who had been hospitalized during the acute phase tend to show a higher prevalence of long COVID compared to people who had milder acute illness and who did not require hospitalization.[34]
- **Prevalence When Including Suspected COVID-19**: Emerging evidence indicates that people who were initially asymptomatic or had mild acute illness can develop long COVID. Studies that include suspected cases, together with confirmed COVID-19 cases, estimate that 21% to 23% of people who had COVID-19 develop ongoing or new symptoms after four weeks or 30 days, and approximately 14% experience symptoms after 12 weeks. Limited studies about long-term (beyond 12 weeks) prevalence rates among this subset of people was identified.[35]
- **Prevalence in Canada**: A rapid systematic review (2021) estimated that 150,000 Canadians have long COVID, although the CADTH report (September 2021) states it is unclear if this is limited to confirmed COVID-19.[36] A survey of 1,048 people in Canada with suspected or confirmed long COVID conducted by the COVID Long-Haulers Support Group Canada found that 80% of respondents had symptoms for more than three months and almost 50% had symptoms for more than 11 months.[37]

[c] Results may be due to various factors, including: 1) study methodology; 2) inconsistent definitions for long COVID; and, 3) local factors (e.g., COVID-19 testing availability for different areas at different times) (CADTH, 2021).

- **Risk Factors**: The following factors may increase the risk for long COVID: a higher acuity of COVID-19 infection or presence of many acute COVID-19 symptoms, having a higher body mass index (e.g., obesity), pre-existing comorbidities, psychiatric disorders, and being a health care worker.[38,39,40,41,42,43,44,45,46,47,48,49,50,51] In addition:
  - Severity of Acute Illness: The CADTH report (September 2021) states that multiple studies suggest that people who were hospitalized may have a higher risk of developing or having a more severe long COVID compared to those with milder symptoms. Acute illness severity may be associated with specific long COVID symptoms or with post-intensive care syndrome (PICS).[52]
  - Gender: Specific symptoms may vary by sex, and may change over time.[53] Being female may be associated with higher risk of developing long COVID, although some research identified no correlation.[54,55] For example, one review (January, 2021) suggested that women are twice as likely to develop symptoms of long COVID.[56]
  - Older Age*:* Research suggests older people (defined variably) are more likely to develop long COVID.[57,58,59,60] One review (2021) suggests that patients with the condition are around four years older than those without.[61] Symptoms may peak for people between ages 40 and 60 years.[62]
  - Comorbidities: CADTH (September 2021) reported that asthma, autoimmune disease, and obesity have been associated with greater risk of long COVID. A survey cohort study (July 2021) and a preprint cohort study (2021) reported that anxiety, depression, and neurologic disabilities may also be risk factors. However, another cohort study (November 2020) reported no association between comorbidities and the presence of COVID-19 condition.[63]
  - Symptoms in Acute Phase: People who experience specific symptoms in the acute phase, and a higher number of these, may be more likely to develop long COVID (e.g., fatigue, shortness of breath, headache, voice hoarseness, muscle aches and pains).[64,65,66]
  - Ethnicity and Socioeconomic Factors: These factors have been investigated but show mixed findings.[67]
- **Prevention**: Two studies (April 2021; June 2021) of early rehabilitation clinics that treated people after the acute COVID-19 phase reported improvements in pulmonary symptoms and physical performance (e.g., six-minute walking distance) when comparing participants before and after completing rehabilitation. These studies were short, eight-week interventions for people who had been hospitalized. It is unclear how rehabilitation may affect people who had not been hospitalized, particularly people who present with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)-like symptoms such as post-exertional malaise.[68,d]
- **Rehabilitation Care Models**: A rapid systematic review that focused on care models for long COVID identified several studies from the United States, United Kingdom, Spain, and Italy, with multiple common focuses across different models including: 1) principles (e.g., multidisciplinary teams, integrated care); 2) medical specialists (e.g.,

[d] Post-exertional malaise is the worsening of symptoms after even minor physical, mental, or emotional exertion, also known as post-exertional symptom exacerbation or exercise intolerance (i.e., reduced ability to exercise) (CADTH, 2021).

pulmonary, cardiovascular, psychiatry); and 3) components (e.g., standardized symptom assessment, referral system).[69] For more details on potential models of care for long COVID, see Table 5.

- **Treatment and Management**: CADTH (September 2021) described a study on long COVID (2021) that describes treatment of minor symptoms, etiology, and follow-up:
  - Treatment of Minor Symptoms: Cough, pain, myalgia can be treated symptomatically with paracetamol (i.e., acetaminophen), cough suppressants, and oral antibiotics (if secondary bacterial infection is suspected).[70,71]
  - Etiology: Etiology behind the symptoms, (such as pulmonary embolism, cerebrovascular accident, coronary artery disease) if any, has to be treated as per the standard protocol; chest physiotherapy and neuro rehabilitation is important in patients with pulmonary and neuromuscular sequelae.[72,73]
  - Follow-up: The ideal frequency and duration of follow up is not clearly defined. In people with COVID-19 interstitial pneumonia, in the first 12 months, seven interactions with health care professionals (four face-to-face) are recommended, alongside four high-resolution CT scans, four six-minute walk tests (6MWT); four blood tests (including blood count and metabolic panel); and two SARS-CoV-2-IgG tests (i.e., antibody tests).[74,75]
  - Exercise: The CADTH report (September 2021) suggests the evidence about exercise rehabilitation for people with COVID-19 is mixed and requires further assessment. Exercise may help reduce fatigue – a common long COVID symptom – and may be helpful for people who had been bedridden (e.g., people treated in hospital or intensive care unit or people who had been hospitalized. However, limited research exists on the impact of exercise for people who had not been hospitalized.[76]
  - Vaccination: For people who have not been vaccinated and develop post-COVID-19 condition, the CADTH report (September 2021) states there is mixed evidence to suggest that receiving a COVID-19 vaccine after the acute infection phase may help to reduce their post-COVD-19 symptoms.[77] For example, a 2021 survey from the LongCOVIDSOS group reported that, of the respondents who received at least their first dose, 57% reported an overall improvement of symptoms, 25% saw no change, and 19% saw their symptoms worsen. Another preprint study reported that in a group of people with post-COVID-19 condition who had received at least one dose, 23% saw an increase in symptom resolution compared to 15% in matched unvaccinated individuals.[78]
- **Economic Impact**: The CADTH report (September 2021) suggests the economic impact and cost-effectiveness of long COVID treatment and care models are not yet established.[79] The 2021 report described a rapid systematic review (2021) that assessed the economic impact of long COVID, which was focused on health care utilization outcomes and the proportion of people who were able to return to work. The systematic review (2021) stated that the United Kingdom had announced a total investment of $230 million CAD to care for an estimated 1.1 million long COVID cases. At scale for Alberta, projections could require a $6.7million investment for the

	2021-2022 fiscal year. The review recommended additional research on the health care costs of various specialists.[80] ○ Demand for Health Care Services: A Canadian survey of 1,048 people with self-reported post-COVID-19 condition reported that nearly 50% of respondents visited a health care provider five times over the past year and nearly 30% of respondents visited more than 10 times.[81] The CADTH report (September 2021) notes that as more people develop long COVID, a number of health care services could see increases in demand (e.g., primary care; multidisciplinary rehabilitation services; prescription drugs; mental health treatments and supports).[82] ○ Health Equity: The CADTH report (September 2021) summarizes research that suggests that people experiencing vulnerabilities (e.g., diverse ethnic backgrounds, lower income households, people with disabilities) may be disproportionately impacted by long COVID, as they may be more likely to: 1) work in jobs without sick leave or extended health benefits; 2) struggle financially; 3) have challenges accessing health services; or 4) be misdiagnosed or have long COVID symptoms dismissed.[83]
Jurisdictional Evidence	• **Diagnosis**: The Mayo Clinic (2021), the National Institute for Health and Care Excellence (NICE) (November 2021),[84] and a UK-based clinical practice guideline (August 2020)[85] provide guidance on diagnosing long COVID. ○ US: The Mayo Clinic recommends looking for symptoms affecting at least two of six major organ systems (general, cardiac, respiratory, gastrointestinal, musculoskeletal, and neurologic), as well as for a decrease in functional status.[86] ○ UK: NICE (November 2021) and UK-based clinical practice guidelines (August 2020) state that suspected previous COVID-19 illness (e.g., symptoms closely linked to COVID-19 infection) is sufficient to suspect long COVID as a cause for any new or ongoing symptoms beyond four weeks; diagnosis should not depend on positive COVID-19 tests or hospitalization due to COVID-19. In addition, symptoms may vary across specific populations (e.g., children, older adults). NICE recommends that health care providers: ▪ Test those suspected of having long COVID to assess if their symptoms stem from another condition; and ▪ Use a screening questionnaire to develop a clearer understanding of each person's symptoms.[87,88,89] • **Treatment and Management**: The CADTH report (September 2021) describes the literature on treatment and management of long COVID vary across jurisdictions. [90] For example: ○ Self-Management: NICE (November 2021)[91] and a multidisciplinary clinical panel from the UK[92] recommend people with suspected long COVID be provided with education and support for self-management strategies (e.g., current information about the condition, goal setting, online support networks). ○ Exercise: Long COVID guidelines from World Physiotherapy and the CDC recommend a cautious and conservative approach to exercise; exercise may

	be useful for treating certain syndromes but not others. Further research with be needed to determine who is most likely to benefit.[93,94] ▪ Activity Management: World Physiotherapy guidelines for long COVID and the CDC's guidelines for ME/CFS recommend pacing or activity management (i.e., balancing rest with activity, and staying within personal limits) to avoid worsening symptoms.[95,96] ▪ Screening: The World Physiotherapy's report suggests that before recommending exercise, people with long COVID should be screened for post-exertional symptom exacerbation.[97] ▪ Exercise Rehabilitation: World Physiotherapy's report also recommends against exercise rehabilitation for those with cardiac impairments, exertional oxygen desaturation (i.e., low oxygen levels during exertion), or autonomic nervous system dysfunction.[98] • **Economic Impact**: The UK's National Health Service documented a nationwide investment in long COVID care. The total investment to establish 89 post-COVID clinics was CAD $58.6 million between December 2020 and April 2021.[99,e] • **Health Equity**: The CDC and health policy researchers have recommended a series of strategies for addressing health inequities that include: education, training for health service providers, and easy to navigate services. For example: ○ Allocate resources to raise awareness of long COVID among marginalized groups and increase access to needed services; ○ Provide training to health care providers surrounding sensitivity to and awareness of stigma, empathy, and the importance of completing full clinical evaluation; and ○ Use telemedicine for easier scheduling, easier collection of information including symptoms, and improving access.[100]
Canadian Evidence	• **Prevalence**: An Alberta Health Services (AHS) framework (2021) on long COVID estimates that, based on international prevalence rates, it is conceivable that there could be over 36,500 Albertans who could benefit from rehabilitation services for five or six weeks after testing positive for COVID-19 and over 14,600 persons likely require a much longer course of rehabilitation support.[101] • **Treatment and Management**: The AHS framework (2021) did not identify specific treatments for long COVID compared to similar problems that occur to patients without COVID. The AHS recommend that people with long COVID should be assessed and treated using current standards of medical care.[102] • **Rehabilitation Services**: Reports from Alberta and Quebec describe existing and recommended rehabilitation responses: ○ Alberta: Rehabilitation services vary across the five AHS Zones and there is no provincial coordination or planning. The AHS suggest a coordinated approach to rehabilitation along the continuum of care and using community care alternatives to potentially decrease emergency department visits. A multidisciplinary intervention based on personalized assessment and

[e] The report provided a figure of GBP £34 million. All Canadian Dollar (CAD) amounts were calculated using Purchasing Power Parities (PPPs) as published by the Organisation for Economic Co-operation and Development (OECD) for 2020 (1 British Pound [GBP] = 1.724 CAD). PPPs are the rates of currency conversion that eliminate the differences in price levels between countries (OECD, 2021).

	treatment might include: exercise training; education, and behavioural modification designed to improve the physical, cognitive, psychological, and social effects of long COVID.[103] ○ Quebec: Quebec's Institut national d'excellence en santé et services sociaux (2021) produced a set of guidelines for the therapeutic management of long COVID for frontline workers, including: 1) medical management; 2) functional recovery; 3) social and psychological support; and 4) self-management of signs and symptoms.[104]
Ontario Evidence	• **Prevalence**: A 2021 Ontario COVID-19 Science Advisory Table brief reported that 57,000 to 78,000 Ontarians had or are currently experiencing long COVID, although prevalence estimates can vary widely depending on the case-definition applied.[105] • **Health Care Utilization**: Ontario Health data (October 2021) suggests there were 23,260 COVID-19 cases in Ontario that required hospitalization and 22% of these cases had an ICU admission; estimates suggest that approximately 17,000 people in Ontario will require specialist supports. ○ 41% of COVID-19 inpatient cases were admitted to home and community care services in 2020 fiscal year. More analysis is needed to evaluate the rehabilitation use rate for this population. ○ Local Health Integration Networks in Central West, Central, and Toronto Central had the highest hospitalization rates within the province. These three regions are known to have growing use of acute care use and three marginalization indexes (ethnic concentration, material deprivation, income dependency).[106] • **Patient Care**: Ontario Health (October 2021) indicated that equitable and patient-centered care for long COVID would require a coordinated provincial approach that would involve various providers/sectors. They recommended nine potential actions, such as: ○ Create tools that assist primary care providers to integrate a long COVID clinical guidance document into electronic medical records applications; ○ Fund regions to plan a coordinated approach to providing long COVID care; ○ Leverage existing Primary Care and COVID-19 Community of Practice to share communications and support to primary care with the provision of long COVID care; ○ Develop service delivery model recommendations based on best evidence to date and innovative models; and ○ Develop funding calculations for ongoing future service delivery on a regional level.[107]

Methods

Individual peer-reviewed articles and review articles were identified through PubMed, and Google Scholar. The search was limited to English sources and therefore may not capture the full extent of initiatives in non-English speaking countries. Full-text results extracted were limited to those available through Open Access or studies made available to the Ministry by our partners.

The COVID-19 Evidence Synthesis Network is comprised of groups specializing in evidence synthesis and knowledge translation. The group has committed to provide their expertise to provide high-quality, relevant, and timely synthesized research evidence about COVID-19 to inform decision makers as the pandemic continues. The following members of the Network provided evidence synthesis products that were used to develop this Evidence Synthesis Briefing Note:

- Decary, S., et al. (2021). Care models for Long COVID-19: A rapid systematic review. Toronto: *SPOR Evidence Alliance. COVID-END Network*. Accessed October 20, 2021;
- Evidence Synthesis Unit. (2021). Long COVID-19 clinics (Evidence Synthesis Network briefing note). Ontario Ministry of Health, Research, Analysis and Evaluation Branch;
- Razak, F., et al. (September 2021). Understanding the Post COVID-19 Condition (Long COVID) and the Expected Burden for Ontario. *Science Briefs of the Ontario COVID-19 Science Advisory Table, 2* (44); and
- Vu, T., & McGill, S. (September 2021). CADTH Horizon Scan: An Overview of Post COVID-19 Condition (Long COVID). *Canadian Journal of Health Technologies, 1* (9), pp. 31.

For more information, please contact the Research, Analysis and Evaluation Branch (Ministry of Health).

APPENDIX

Table 2: Classifying Post COVID-19 Condition[108,f]

Symptom Duration	Sub-types or Syndromes	Other
• Timing of symptoms: A common method of describing the stages of long COVID has been the amount of time a person has had symptoms; or the time elapsed since contracting the SARS-CoV-2 infection. ○ NICE's COVID-19 rapid guideline on managing the long-term effects of COVID-19 provides the following definitions: ▪ Ongoing symptomatic COVID-19: Signs and symptoms of COVID-19 from four to 12 weeks after being infected. ▪ Post COVID-19 syndrome: Signs and symptoms that develop during or after an infection consistent with COVID-19, continuing for more than 12 weeks and are not explained by an alternative diagnosis. ▪ Long COVID: Signs and symptoms that continue or develop after acute COVID-19, including both ongoing symptomatic COVID-19 and long COVID syndrome.[109,110] ○ *Other groupings*: A research group from Spain proposed this classification that is based on relapsing/remitting nature of long COVID symptoms: ▪ Potentially infection-related symptoms (weeks four to five); ▪ Acute long COVID symptoms (weeks five to 12); ▪ Long COVID symptoms (weeks 12 to 24); and ▪ Persistent long COVID symptoms (beyond 24 weeks).[111,]	• Post-viral chronic fatigue syndrome (or myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS]). ME/CFS can occur after a viral infection and features some symptoms similar to post-COVID condition (e.g., fatigue). • Post-intensive care syndrome (PICS), also sometimes referred to as post-critical-illness syndrome. PICS is caused by medical treatment in the intensive care unit (ICU). Its symptoms may include chronically impaired pulmonary function, neuromuscular weakness, and long-term psychological impacts. • Post-traumatic stress disorder (PTSD): Acute illness and intense treatment can be deeply stressful experiences that may lead to increased risk of developing PTSD. Approximately, 9% of people hospitalized for COVID-19, or 23% of those with long COVID, may develop PTSD symptoms. • Exacerbation of a pre-existing health condition or disability: For example, a case-controlled study reported that seven months after hospital discharge for COVID-19, 53% of people who had pre-existing musculoskeletal pain reported that their pain had worsened. • A unique post-acute COVID-syndrome.[112]	• The CADTH report (2021) on post-COVID conditions suggested that other proposed classification methods are based on: ○ Symptoms: People with long COVID can be classified based on when the symptoms appear: ▪ Persistent symptoms after acute infection; ▪ New symptoms that appear after the acute phase. ○ Pathogenesis: Residual damage from acute infection versus persistent immune activation. ○ Multiple factors:[113] For example, a 2021 editorial on COVID-19 and its sequelae suggests the following subtypes: ▪ Type 1: Cases with varying lengths of recovery and rehabilitation that directly correlate with the severity of infection, target organ damage and pre-existing medical conditions at the time of infection. ▪ Type 2: Cases with mild initial symptoms, lasting >six weeks from the onset. ▪ Type 3: Cases with mild initial symptoms with a period of quiescence or near recovery, followed by a return of symptoms that persist for ≥three months or ≥six months. ▪ Type 4: Cases that are initially asymptomatic or minimally symptomatic, then develop symptoms one to three months, or ≥three months, after confirmed COVID-19 positivity, that lasts for varying periods of time.[114] ▪ Type 5: Cases that are initially asymptomatic or minimally symptomatic, who experience sudden death within 12 months.[115]

[f] This table is adapted from a CADTH horizon scan on post-COVID condition (CADTH, September 2021).

Table 3: Systematic and Narrative Reviews of Long COVID-19[g]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
• International • N=25 • Systematic Review	• Objective: Identify, systematically evaluate, and summarize the best available evidence on the frequency of long COVID-19, its clinical manifestations, and the criteria used for diagnosis. • Population: 5,440 participants. • Follow-up time: Three to 24 weeks after acute phase or hospital discharge.	• Symptoms: None of the studies assessed the duration of signs/symptoms. Most prevalent signs/symptoms across the participant group were: ○ Chest pain (up to 89%); ○ Fatigue (up to 65%); ○ Dyspnea (up to 61%); and ○ Cough and sputum production (up to 59%).	• Risk factors: Potentially associated risk factors were: ○ Old age; ○ Female sex; ○ Severe clinical status; ○ A high number of comorbidities; ○ Hospital admission; and ○ Oxygen supplementation at the acute phase.	• None reported.[116]
• International • N=36 • Living Systematic Review	• Objective: Document the prevalence of long COVID four to 12 weeks (short-term) and >12 weeks (long-term) after COVID-19 diagnosis. • Population: Participants with laboratory confirmed COVID-19. • Follow-up time: Four weeks or more from COVID-19 diagnosis.	• Four to 12 weeks after discharge, 83% of people experienced: ○ Fatigue (51%); ○ Body and muscle aches (40%); ○ Dyspnea (i.e., shortness of breath) or breathing difficulties (38%); ○ Sleep disturbances (36%); ○ Anxiety (29%); ○ Cough (28%); and ○ Ill feeling or not back to full health in the short-term (52%). • At 12 weeks after discharge, 56% of people experienced: ○ Fatigue (47%); ○ General pain or discomfort (27%); and	• The majority of studies in this review included adults or individuals who were hospitalized or treated for moderate to severe COVID-19. • Therefore, the prevalence of long-term effects in children, in individuals who were asymptomatic or who presented with mild COVID-19 symptoms in the acute stage may not be sufficiently represented in the results.	• None reported.[117]

[g] Some articles are preprints and have not been certified by peer review. They should not be relied on to guide clinical practice or health-related behaviour and should not be reported in news media as established information.

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
		○ Sleep disturbances (26%).		
• International • N=28 • Systematic Review	• Objective: To determine long-term clinical outcomes in survivors of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus infections after hospitalization or intensive care unit admission. • Population: SARS and MERS patients hospitalized or in ICU in Beijing, Hong Kong, Guangzhou, Singapore, Taiwan, Korea, and Canada the (minimum of four cases included per study); one nationwide study included. • Follow-up time: Original studies reporting clinical outcomes of adult SARS and MERS survivors three months after admission or two months after discharge were included.	• Six months after hospital discharge, participants who had SARS or MERS had symptoms similar to long COVID including: ○ Physical conditions: ▪ Impaired diffusing capacity for carbon monoxide (prevalence 27%); and ▪ Reduced exercise capacity (mean six-min walking distance 461 m). ○ Psychological conditions: ▪ Prevalence of post-traumatic stress disorder (39%); ▪ Depression (33%); and ▪ Anxiety (30%). ○ General health: ▪ Low scores on Short-Form 36 health survey;[h] and ▪ Chronic fatigue 3.5 years after being diagnosed (40%).	• None reported.	• None reported.[118]
• International • N=12 • Pragmatic review	• Objective: To understand the prevalence of and the risk factors for developing long COVID-19. • Population: COVID-19 cases in the UK or US (minimum of 250 cases included per study).	• In the first 12 weeks after the onset of COVID-19, between 5–36% of cases report still having symptoms, with those who were previously hospitalized reporting higher rates.	• Cases with long COVID are more likely to be older, suffer from pre-existing comorbidities, obesity, or psychiatric disorders and have blood type A. • A higher number of symptoms in the acute phase and specific	• In N=210 cases, the need for care assistance significantly increased (52.4%) after COVID-19 infection compared to before (7.7%), with 41.1% of cases who were not dependent previously, at

[h] The 36-Item Short Form Health Survey questionnaire (SF-36) is a popular instrument for evaluating Health-Related Quality of Life (Lins & Carvalho, 2016).

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
	• Follow-up time: ≥3 weeks after onset of acute COVID-19.	• Between 2-15% of cases report having symptoms 12 weeks or more after the onset of COVID-19. • Most commonly reported long-term symptoms: ○ Fatigue: 8 studies, 17-98%; ○ Dyspnea: 7 studies, 17-93%; and ○ Headache: 4 studies, 38-91%.	acute symptoms like fatigue, headache, dyspnea, pain with deep breath, sensitive skin, hoarse voice, and myalgia may also be risk factors for developing long COVID-19.	least partially dependent on others in the performance of daily activities subsequently.[119]
• International • N=24 post-acute; 18 acute; 10 chronic • Living rapid systematic review	• Objective: To understand the prevalence and characteristics of emerging disability after COVID-19. • Population: COVID-19 cases. • Follow up time: Not reported.	• At median 54 days post-discharge in N=384, 69% fatigue, 53% breathlessness, 34% cough, 15% depression, and 38% chest radiographs remain abnormal. • At 6 weeks post-discharge in N=200, 19.5% fatigue, 18.5% dyspnea, 18% weakness, and 14.5% activity intolerance. • In N=180 COVID-19 cases (N=8 hospitalized) with a mean follow up of 125 days after onset, 53.1% reported at least 1 symptom, 33.3% reported up to 2 symptoms, and 19.4% reported 3 more, with the most persistent symptoms being fatigue, loss of smell and taste, and arthralgias. • In N=128 COVID-19 cases (55.5% hospitalized), a median follow-up of 10 weeks after discharge or after the last day of acute COVID-19	• None reported.	• In N=1,409 COVID-19 patients discharged from hospital receiving home care, 10% were readmitted within 32 days, with the risk of readmittance being higher in male patients (hazard ratio [HR]: 1.45) and patients presenting with a comorbidity (heart failure HR 2.12; diabetes HR 1.71.)[120,121]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
		symptoms, 52.3% persistent fatigue with no association with acute COVID-19 severity. • In N=145 COVID-19 cases 100 days after onset, 36% dyspnea, 24% night-sweats, 22% sleep disorder, 19% hyposmia/anosmia. • In N=18 young mild or moderate cases, 20–100 days after recovery, 78% mild cognitive deficits.		
• International (preprint) • N=15 • Systematic review	• Objective: To identify long-term COVID-19 effects and estimate their prevalence. • Population: COVID-19 cases (minimum of 100 cases included per study). • Follow -up time: ≥2 weeks after initial symptoms.	• 80% of cases continue to have at least one COVID-19 effect beyond two weeks after the acute infection (follow up ranged from 14 to 110 days). • Most common manifestations of long COVID: ○ Fatigue: 58%; ○ Headache: 44%; ○ Attention disorder: 27%; ○ Hair loss: 25%; and ○ Dyspnea: 24%.	• Fatigue, post-activity polypnea, and alopecia was more commonly reported in females.	• None reported.[122]
• International (preprint) • N=28 • Living rapid systematic review	• Objective: Examine the frequency, profile, and duration of persistent symptoms among people with confirmed or suspected COVID-19, including previously hospitalized and never hospitalized people. • Population: The analysis included 9,442 adult COVID-19 cases (aged 37.7 to 73.9 years old) from 13 countries. • Follow-up time: 21 days post-onset or anytime post-hospital	• Most commonly reported persisting symptoms, overall: ○ Breathlessness: 13 studies; ○ Smell and taste disturbance: 12 studies; and ○ Fatigue: 11 studies. • Most commonly reported persisting psychological symptoms: ○ Anxiety: seven studies; ○ Depression: five studies; ○ Sleep disorders: four studies; and	• Risk factors could not be identified due to the limitations of the existing data.	• In N=115 patients discharged from hospital receiving rehabilitation, increased dependency in activities of daily living (ADLs; personal care and social activities) was reported on 47.5% of cases.[123]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
	discharge; longest mean follow-up period was 111 days post-hospital discharge.	○ PTSD: three studies. • Most commonly reported persisting musculoskeletal symptoms: ○ Myalgia: seven studies.		
• International • N=24 • Systematic review	• Objective: To understand the prevalence of long-term COVID-19 symptoms. • Population: COVID-19 cases. • Follow up time: 4 to 12 weeks, or after 12 weeks, from the onset of acute COVID-19.	• Most common symptoms at four to 12 weeks for previously hospitalized cases (prevalence range): ○ Shortness of breath: 32–74%; ○ Fatigue: 28–68%; ○ Cough: 7–43%; ○ Sleep disturbance: 18–57%; ○ Cognitive impairment: 18–22%; ○ Sore throat: 3–9%; ○ Loss of smell: 12–15%; and ○ Loss of taste: 9–10%. ○ In N=402 hospitalized cases, 55.7% scored in the clinical range in at least one psychopathological dimension, one month after hospital discharge. • Most common symptoms continuing past 12 weeks for previously hospitalized cases (prevalence range): ○ Shortness of breath: 6.7–94.6%; and ○ Pain: 10.5–45.9%. • Most common symptoms at four to 12 weeks for non-hospitalized cases (prevalence range): ○ Loss of smell: 7–51%;	• Consistent pattern of people who were predominantly female, most likely middle aged, and of white ethnicity. • Persisting symptoms were significantly associated with: ○ Hospital admission at symptom onset; ○ Initial clinical presentation; ○ Dyspnea; ○ Abnormal auscultation; ○ Age >40 years old; and ○ Being a health care worker.	• One study concluded that clinical abnormalities requiring action are infrequent.[124]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
		○ Lost of taste: 5–51%; ○ Shortness of breath: 8–71%; ○ Chest pain: 7–44%; ○ Joint pain: 2–31%; ○ Headache: 5–38%; ○ Fatigue: 27–87%; ○ Palpitations: 10–32%; ○ Fever: 2–11%; and ○ Cognitive impairment: 2–29%. • Most common symptoms continuing past 12 weeks for non-hospitalized cases (prevalence range): ○ Shortness of breath: 9–87%; ○ Fatigue: 21–98%; and ○ Myalgia: 7–88%. • In one study, a diagnosis of COVID-19 led to significantly more first diagnoses of psychiatric illness (HR: 1.58 to 2.24, P<0.0001).		
• International • N=40 research studies • Narrative review	• Objective: To understand the impact of long COVID on health status. • Population: COVID-19 cases. • Follow-up time: Not reported.	• Long COVID consists of dyspnea, headache, fatigue, and anosmia, and can impact the respiratory, cardiovascular, neurological, and other systems and has implications for mental health. • The most commonly reported symptoms are fatigue and dyspnea.	• Long COVID is more likely to be associated with: ○ Increasing age; ○ Increasing BMI; and ○ Female sex.	• None reported.[125]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
• International • N=43 research studies • Living review	• Objective: To understand the impact of ongoing effects of COVID-19; health and social care services responses; future research questions. • Population: COVID-19 cases. • Follow-up time: Not reported.	• Case characteristics include:[i] ○ Post-viral fatigue; ○ Viral persistence (i.e., lasting longer than two months from onset); ○ Cardiac, respiratory, other organ impairments; ○ Thromboembolism; ○ Neurological symptoms (e.g., Guillain Barré Syndrome, encephalitis) ○ Psychological aspects (e.g., depression, anxiety); ○ Cognitive difficulties (e.g., 'brain fog').	• The continuing uncertainty about the etiology of long COVID-19 means that it is difficult to predict who will experience severe consequences from it. • Estimates of long COVID vary but it seems that at least 10% of all people who contract COVID-19 have some symptoms for at least 12 weeks. • Long COVID is seen in all age groups. • COVID-19 has a disproportionate effect on certain parts of the population, including care home residents. Black and Asian communities have seen high death rates and there are concerns about other minority groups and the socially disadvantaged. These people are already seldom heard in research as well as travellers, the homeless, those in prisons, people with mental health problems or learning difficulties; each having particular and distinct needs in relation to ongoing COVID-19 that need to be understood.	• None reported.[126]

[i] Much of the evidence is speculative, based on the symptoms people with long COVID display or generalizing from conditions with similar symptoms. It is unclear whether the same pathology seen in the acute phase of COVID-19 also leads to long COVID (National Institute for Health Research, March 16, 2021).

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
• International • N=31 studies • Systematic review	• Purpose: Identify intermediate and long-term COVID-19 sequelae affecting formerly healthy adults between 18 and 50 years of age. • Population: Adult participants with confirmed SARS-CoV-2 infection. • Follow-up time: 14 days to 90 days.	• Sequelae persistence since infection spanned 14 days to three months. • Sequelae included: ○ Persistent fatigue (39–73% of assessed persons); ○ Breathlessness (39–74%); ○ Decrease in quality of life (44–69%); ○ Impaired pulmonary function, abnormal CT findings including pulmonary fibrosis (39–83%); ○ Evidence of peri-/perimyo-/myocarditis (3–26%); ○ Changes in microstructural and functional brain integrity with persistent neurological symptoms (55%); ○ Increased incidence of psychiatric diagnoses (5.8% versus 2.5–3.4% in controls); and ○ Incomplete recovery of olfactory and gustatory dysfunction (33–36% of evaluated persons).	• None reported.	• None reported.[127]
• International • The review identified 19 studies; however, none reported information of long COVID in children. ○ The author provides a case report of five Swedish children	• Purpose: Examine symptoms of long COVID in children. • Population: In the case reports, five Swedish children (4 girls) with COVID-19, with median age of 12 years (range: 9-15). • Follow-up time: Follow-up period was 35 days to two months (systematic review); follow-up	• Children in case reports: ○ Fatigue, dyspnea, heart palpitations or chest pain, headaches, difficulties concentrating, muscle weakness, dizziness, and sore throats.	• In the case reports, the children's symptoms were similar to those reported by studies of adults with long COVID. • The case reports suggest that females may be more prone to developing long COVID, as seen in adult studies.	• None reported.[128]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
• Systematic review and case report of five children	period among case reports was six months.		• Some children had improved after 6–8 months, but they all suffered from fatigue and none had fully returned to school.	
• International • N=120 studies (preprint) • Systematic scoping review	• Purpose: To synthesize what is known from literature about persistent COVID-19, its signs and symptoms, its pathophysiology, and the current management recommendations. • Population: Not reported. • Follow-up time: Not reported.	• Predominant symptoms among individuals with long COVID were: ○ Fatigue; ○ Breathlessness; ○ Arthralgia; ○ Sleep difficulties; and ○ Chest pain. • Reports also point to the risk of long-term sequelae with cutaneous, respiratory, cardiovascular, musculoskeletal, mental health, neurologic, and renal involvement in those who survive the acute phase of the illness.	• Individuals with five symptoms in the first week are more likely to develop long COVID: ○ Fatigue; headache; shortness of breath; hoarse voice; and myalgia. Illness was more prevalent among women, older people, and those with obesity. • Some prolonged COVID-19 symptoms are associated with: ○ Age 40 to 60 years; ○ Hospital admission at symptom initiation; ○ Severe COVID-19; and ○ Dyspnea or abnormal chest auscultation. • Mental health risk factors: ○ Loss of a loved one; ○ Hospitalization; ○ Containment measures such as isolation and quarantine; ○ Being in low-income regions; ○ Financial stressors; ○ Having disabilities; ○ Female gender; and ○ Older age.	• None reported.[129]
• International • N=11 • Rapid review	• Purpose: Aimed at synthesizing evidence on the long-term effects of the SARS-CoV-2 infection among survivors. • Population: Patients who had all been symptomatic during the active infection, ranging from mild	• The majority of symptoms reported were: ○ Fatigue; ○ Shortness of breath; ○ Cough; ○ Sleep disorders; and • Other symptoms reported	• Patients were all symptomatic during the active infection, ranging from mild to severe and hospitalized cases. Hospitalized patients also included those who were admitted to the ICUs.	• None reported.[130]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
	to severe and hospitalized cases; the hospitalized patients also included those who were admitted to the intensive care units (ICUs). Participants were: ○ Adults between 18 and above 60 years (ten studies); ○ Children whose average age was 12 years (one study). • Follow-up time: From seven days to 12 weeks after discharge.	were: ○ Loss of memory; ○ Muscle pain; ○ Weakness; ○ Heart palpitations; ○ Headaches; ○ Difficulties concentrating; ○ Dizziness; ○ Sore throat; ○ Loss of smell; ○ Loss of taste; ○ Skin rashes; ○ Hair loss; ○ Diarrhoea; ○ Vomiting; and ○ Mental conditions (e.g., depression, anxiety).		
• International • N=35 (preprint) • Systematic review and meta-analysis	• Purpose: To determine long-term symptoms in COVID-19 survivors after infection. • Population: 18,711 patients. • Follow-up time: None reported.	• Eight pain-related symptoms and 26 other symptoms were identified. • The highest pooled incidence among pain-related symptoms was: ○ Chest pain (17%, 95% CI, 12%-25%); ○ Headache (16%, 95% CI, 9%-27%); ○ Arthralgia (13%, 95% CI, 7%-24%); ○ Neuralgia (12%, 95% CI, 3%-38%); and ○ Abdominal pain (11%, 95% CI, 7%-16%). • The highest pooled incidence among other symptoms was: ○ Fatigue (45%, 95% CI, 32%-59%);	• Eligible studies were those reporting patients with a confirmed diagnosis of SARS-CoV-2 and who showed any symptoms persisting beyond the acute phase. • The current meta-analysis may provide a complete picture of incidence in post-acute sequelae of SARS-CoV-(PASC). It remains unclear, however, whether post-COVID symptoms progress or regress over time or to what extent PASC are associated with age or sex.	• None reported.[131]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
		○ Insomnia (26%, 95% CI, 9%-57%); ○ Dyspnea (25%, 95% CI, 15%-38%); ○ Weakness (25%, 95% CI, 8%-56%); and ○ Anosmia (19%, 95% CI, 13%-27%).		
• International • N=65 • Systematic review	• Purpose: Aim is to investigate the available evidence for long-term complications of COVID-19. • Population: Hospitalized COVID-19 patients; COVID-19 patients admitted to ICU. • Follow-up time: None reported.	• Ten potential late complications of COVID-19 were identified, including ○ Neurological injuries; ○ Lung, liver, kidney, and heart injuries; ○ Thromboembolism; ○ Cardiac/brain stroke; ○ Encephalopathy; and ○ Psychological distress. • Furthermore, some studies have pointed out other complications such as: ○ Hypoproteinemia; ○ Septic shock; and ○ Multiple organ dysfunction syndromes. • The most frequent late complications of COVID-19 included: ○ Lung injuries (N=31); ○ Venous/arterial thrombosis (N=28); ○ Heart injuries (N=26); ○ Cardiac/brain stroke (N=23); and ○ Neurological injuries (N=20).	• None reported.	• None reported.[132]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
• International • N=Not reported • Narrative review	• Purpose: To summarize the most common neurological complications and reported neurological case studies associated with COVID-19, and neurological side effects associated with COVID-19 treatments. • Population: COVID-19 patients. • Follow-up time: None reported.	• Non-specific neurological complications: o Headache; o Altered mental status; o Dizziness; o Depressed level of consciousness; o Ageusia (loss of taste); o Anosmia (loss of smell); o Myalgia; and o Fatigue. • Specific neurological complications: o Cerebrovascular complications; o Subarachnoid Hemorrhage; o Massive Cerebral Hemorrhage; o Encephalopathy; o Acute Hemorrhagic Necrotizing Encephalopathy; o Encephalitis; o Anti-N-Methyl-D-Aspartate Receptor Encephalitis; o Meningitis/Encephalitis; and o Acute Myelitis. • Demyelinating Disorders: o Guillain–Barré Syndrome; o Miller Fisher Syndrome; o Central Nervous System Demyelination; o Seizures; o Symmetrical polyneuropathy; and o Rhabdomyolysis.	• None reported.	• None reported.[133]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up Time Inclusion	Findings		
		Long-Term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
• International. • N=Not reported • Narrative review	• Purpose: To analyze various aspects of long COVID. • Population: Patients with long COVID. • Follow-up time: None reported.	• Symptoms reported in long COVID: ○ Fatigue; ○ Cough; ○ Chest tightness; ○ Breathlessness; ○ Palpitations; ○ Myalgia; and ○ Difficulty to focus. • Symptoms could be related to: ○ Organ damage; ○ Post viral syndrome; ○ Post-critical care syndrome; and ○ Others.	• Gender: The risk of long COVID is twice as common in women compared to men.[134] • Age: Increasing age is also a risk factor: ○ Patients with long COVID are around four years older than those without. ○ Presence of more than five symptoms in the acute stage of illness is associated with increased risk of developing long COVID.[135] • Co-morbidities: Presence of co-morbidities also increases the risk of developing post-COVID syndrome. Even those with mild symptoms at initial presentation were noted to develop long COVID.	• None reported.[136]

Table 4: Summary of Individual Long COVID-19 Studies

Jurisdiction, Number of Participants, and Study Type	Objective, Population, Follow-up Time	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
• Pakistan • N=158 participants • Descriptive study	• Purpose: Assess the prevalence and characteristics of post-COVID-19 manifestations and their effect on the quality of life (QoL) of COVID-19 recovered individuals. • Population: COVID-19 recovered patients with a negative-reverse transcription-polymerase chain reaction (RT-PCR) for the previous 20-90 days. • Follow-up time: 20 to 90 days.	• Symptom duration: Mean time since recovery was 38.10 ± 20 days. • Reported symptoms: An overwhelming majority (94.9%) experienced at least one post-COVID-19 symptom. • The vast majority of the population experienced, multiple symptoms, including: ○ Persistent fatigue (82.9%); ○ Poor sleep quality (56.3%); ○ Anxiety (53.2%); ○ Dyspnea (50%); ○ Joint pain (47.5%); and ○ Loss of smell and taste (47.5%).	• Findings show a significant correlation of post-COVID-19 symptoms with gender, age, and time since recovery. • COVID-19 severity was found to be significantly related to the five dimensions of the EuroQol five-dimension five-level questionnaire (EQ-5D-5L): ○ Mobility; ○ Self-care; ○ Usual activities; ○ Pain/discomfort; and ○ Anxiety/depression.	• None reported.[137]
• United States (US) • N=73,435 with confirmed COVID-19 • Comparative study	• Purpose: Use the national healthcare databases of the US Department of Veterans Affairs to identify incident sequelae of COVID-19 including diagnoses, medication use, and laboratory abnormalities. • Population: Patients with COVID-19 who survived for at least 30 days after diagnosis. • Follow-up time: Six months.	• Symptom duration: Six months after acute phase of COVID-19. • Reported symptoms: Study identifies incident sequelae at six months: ○ Respiratory conditions (e.g., respiratory failure, insufficiency, and arrest); ○ Nervous system (e.g., neurocognitive disorders); ○ Mental health disorders (e.g., anxiety and fear-related disorders, trauma- and stress-related disorders); ○ Metabolic disorders	• Findings show that a substantial burden of health loss that spans pulmonary and several extrapulmonary organ systems is experienced by patients who survive after the acute phase of COVID-19.	• None reported.[138]

Jurisdiction, Number of Participants, and Study Type	Objective, Population, Follow-up Time	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
		(e.g., disorders of lipid metabolism, diabetes mellitus, and obesity); ○ Poor general well being (e.g., malaise and fatigue); ○ Cardiovascular disorders (e.g., hypertension); ○ Gastrointestinal disorders (e.g., oesophageal disorders); ○ Other sequelae (e.g., acute pulmonary embolism).		
• United States • N=4,182 participants • Prospective observational cohort study	• Purpose: To examine long COVID-19 symptoms prevalence, risk factors, and possibility of predicting a protracted course early in the disease. • Population: 4,182 COVID-19 incident cases self-reported in COVID Symptom Study app.[j] • Follow-up time: None reported.	• Symptom duration: Participants reported symptoms lasting: ○ ≥28 days (558, 13.3%); ○ ≥8 weeks (189, 4.5%); and ○ ≥12 weeks (95, 2.3%). • Reported symptoms: Long COVID was characterized by symptoms of: ○ Fatigue; ○ Headache; ○ Dyspnea; and ○ Anosmia.	• Symptoms of long COVID-19 were more likely with increasing: ○ Age; ○ Body mass index; and ○ Female sex. • Experiencing more than five symptoms during the first week of illness was associated with long COVID (odds ratio = 3.53 (2.76–4.50)).	• None reported.[139]
• United Kingdom • N=201 participants • Observational study	• Purpose: To assess medium-term organ impairment in symptomatic individuals following recovery from acute SARS-CoV-2 infection. • Population: Community-based individuals from two UK centres between April 1 and September 14, 2020;	• Most frequently reported symptoms included: ○ Fatigue (98%); ○ Muscle aches (87%); ○ Breathlessness (88%); and ○ Headaches (83%). • Mild organ impairment was present in the: ○ Heart (26%);	• Study population was at low risk of COVID-19 mortality (obesity 20%, hypertension 7%, type 2 diabetes 2%, heart disease 5%), with only 19% hospitalized with COVID-19. • 42% of individuals had 10 or more symptoms and 60% had severe long COVID.	• Hospitalization was associated with: ○ Older age (p=0.001); ○ Non-white ethnicity (p=0.016); ○ Increased liver volume (p<0.0001); ○ Pancreatic inflammation (p<0.01); and

[j] The COVID Symptom Study smartphone-based app (previously known as COVID Symptom Tracker) was developed by Zoe Global, in collaboration with King's College London and Massachusetts General Hospital, and was launched in the United Kingdom on March 24, 2020 and in the United States on March 29, 2020 (Menni, C., et al., 2020).

Jurisdiction, Number of Participants, and Study Type	Objective, Population, Follow-up Time	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
	individuals ≥18 years with persistent symptoms following recovery from acute SARS-CoV-2 infection and age-matched healthy controls. ○ 201 individuals (mean age 45, range 21-71 years, 71% female, 88% white, 32% health care workers). • Follow-up time: An average of 141 days following SARS-CoV-2 infection, participants completed the baseline assessment.	○ Lungs (11%); ○ Kidneys (4%); ○ Liver (28%); ○ Pancreas (40%); and ○ Spleen (4%) • Organ repairment: ○ 70% single-organ impairment; and ○ 29% multiorgan impairment.	• Severe long COVID was associated with radiological evidence of cardiac damage (myocarditis).	○ Fat accumulation in the liver ($p<0.05$) and pancreas ($p<0.01$).[140]
• Spain • N=277 • Prospective cohort study	• Objectives: To analyze the incidence of post-acute COVID-19 syndrome (PCS)[k] and its components, and to evaluate the acute infection phase associated risk factors. • Population: Adult patients who had recovered from COVID-19 (February 27 - April 29, 2020). • Follow-up time: 277 patients who recovered from mild (34.3%) or severe (65.7%) forms of SARS-CoV-2 infection were evaluated 77 days (interquartile range [IQR] 72-85) after disease onset.	• PCS was detected in 141 patients (50.9%; 95%CI 45.0-56.7%). Symptoms were mostly mild. • Alterations in spirometry were noted in 25/269 patients (9.3%), while in radiographs in 51/277 (18.9%).[l]	• No baseline clinical features behaved as independent predictors of PCS development.	• None reported.[141]

[k] Post-acute COVID-19 syndrome was defined as the persistence of at least one clinically relevant symptom, or abnormalities in spirometry or chest radiology three weeks after symptom onset (Oscar Moreno-Pérez, et al., 2021).
[l] Spirometry is a common office test used to assess how well a patient's lungs work by measuring how much air they inhale and exhale, and how quickly they exhale. Spirometry is used to diagnose asthma, chronic obstructive pulmonary disease (COPD), and other conditions that affect breathing (Mayo Clinic, n.d.).

Jurisdiction, Number of Participants, and Study Type	Objective, Population, Follow-up Time	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
• China • N=1,733 • Cohort study	• Purpose: To describe the long-term health consequences of patients with COVID-19 who have been discharged from hospital and investigate the associated risk factors, in particular disease severity. • Population: Discharged patients with COVID-19; ○ Patients had a median age of 57.0 (IQR 47.0 – 65.0) years; and ○ 897 (52%) were men. • Follow-up time: Median follow-up time was 186.0 days after symptom onset.	• Six months after acute infection, COVID-19 survivors were mainly troubled with: ○ Fatigue or muscle weakness (63%, 1,038 of 1,655); ○ Sleep difficulties (26%, 437 of 1,655); and • Anxiety or depression (23%; 367 of 1,617) of patients.	• Patients who were more severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations and are the main target population for intervention of long-term recovery.	• None reported.[142]

Table 5: Potential Models of Care for Post COVID-19 Condition[143,m]

Model	Description	Strengths	Limitations
Post COVID-19 Clinics	• Specialized clinics featuring dedicated groups of health care providers, often multidisciplinary groups, to treat long COVID. These have been set up in multiple countries including Canada. ○ A pre-post study reported improved outcomes of people receiving rehabilitation at a long COVID clinic in Italy.	• May be an efficient way to develop expertise on treatment for long COVID, as providers see a higher number of people affected by the condition and can learn the effectiveness of different treatment strategies. • Coordination and continuity of care between multiple care providers may be smoother in dedicated teams.	• Potential for long waiting lists. • Difficulties with training providers. • Accessibility for those who live far from clinics. • Uncertainty about cost-effectiveness.
Primary Care-Based Model	• Primary care providers (PCPs) carry out standardized assessments of symptoms, refer to, and coordinate with specialized based on symptoms and needs, manage medications and comorbidities, and provide self-management support.	• PCPs are already familiar with their rostered patients' health and preferences. • People affected by long COVID may feel more comfortable with their regular PCPs than going to a new clinic with unfamiliar care providers.	• PCPs may feel uncomfortable treating long COVID due to a lack of training or resources., especially for complex cases. • Coordination and continuity of care across multiple specialists may be complex, which could lead to fragmented care (e.g., contradictory advice).
Hybrid Model	• A system that incorporates specialized clinics and primary care based on each person's needs. For example, in the tiered model used in Leeds, England: ○ People with mild and typical symptoms are treated in primary care. ○ People who had been hospitalized and/or have moderately complex needs are treated by community therapy teams. ○ People with symptoms at three or more months and/or have complex needs are treated by a specialized clinic.	• Could be more feasible and accessible than treating all cases of long COVID in specialized clinics. • Allows for people with complex needs to receive the intensive care that would be more difficulty to receive in a primary case-based model.	• People with complex needs living far from specialized clinics may not be able to access needed care. • Model requires effective coordination of care across multiple providers.

[m] This table is adapted from a CADTH horizon scan on post-COVID condition (CADTH, September 2021).

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