

EVIDENCE SYNTHESIS BRIEFING NOTE

TOPIC: UNDERSTANDING LONG COVID-19

Information finalized as of April 7, 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, and emerging research findings or trends.

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.

Ten systematic and narrative reviews (including three preprint studies), representing approximately 334 international studies, provided the following details:

- **Risk factors:** The identified studies suggest that 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, older age, female sex, obesity, pre-existing comorbidities, psychiatric disorders, and being a health care worker.
- **Symptomatology:** The most common symptoms reported were: fatigue, dyspnea (i.e., shortness of breath), headache, and pain (e.g., chest, joint, muscle); however, persistent symptoms have also been described for the cognitive, musculoskeletal, respiratory, gastrointestinal, cardiac, and psychological systems.

Limitations: The limited 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 seven months, there has been scant time to understand the longer-term implications of COVID-19 infection.

^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 definitions of ‘long COVID’ are provided in [Table 2](#), and reports from systematic and narrative reviews are provided in [Table 3](#).

Table 1: Summary of Emerging Research on ‘Long COVID’

Scientific Evidence	<ul style="list-style-type: none"> • ‘Long COVID’ Defined: The hashtag ‘#Long COVID’ has been frequently used in social media; however, according to the identified literature, long COVID lacks a commonly accepted case definition.¹ 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.^{2,3,b} More formal definitions have also been proposed (see Table 2). • Emerging Research Findings: Ten systematic and narrative review (including three preprint studies), representing approximately 334 international studies, provided the following details (see Table 3): <ul style="list-style-type: none"> ○ Risk factors: The identified studies suggest that 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, older age, female sex, obesity, pre-existing comorbidities, psychiatric disorders, and being a health care worker.^{4,5,6,7,8,9} ○ Symptomatology: The most common symptoms reported were: fatigue, dyspnea (e.g., shortness of breath), headache, and pain (e.g., chest, joint, muscle); however, persistent symptoms have been described for the cognitive, musculoskeletal, respiratory, gastrointestinal, cardiac, and psychological systems.^{10,11,12,13,14,15,16,17,18,19} • Limitations: The limited evidence base currently precludes a precise definition of 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 standardized way.²⁰
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^b Acute COVID-19: Signs and symptoms of COVID-19 for up to four weeks; Ongoing symptomatic COVID-19: Signs and symptoms of COVID-19 from four to 12 weeks; Post-COVID-19 syndrome: Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis ([NICE, 2020](#)).

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:

- Evidence Synthesis Unit, Research Analysis and Evaluation Branch, Ontario Ministry of Health; and
- COVID-19 Evidence Network to support Decision-making (COVID-END).

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

APPENDIX

Table 2: Proposed Definitions of Long COVID-19

National Institute for Health Care Excellence (NICE)	De Sire et al., 2020 & Ceravolo, et al., 2020	Fernández-de-las-Peñas, et al., 2021	Becker, R.C. (2021)
<ul style="list-style-type: none"> • NICE's COVID-19 rapid guideline on managing the long-term effects of COVID-19 provides the following definitions: <ul style="list-style-type: none"> ○ <u>Ongoing symptomatic COVID-19</u>: Signs and symptoms of COVID-19 from 4 to 12 weeks. ○ <u>Post-COVID-19 syndrome</u>: Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. ○ <u>Long COVID</u>: Signs and symptoms that continue or develop after acute COVID-19, including both ongoing symptomatic COVID-19 and post-COVID-19 syndrome.²¹ 	<ul style="list-style-type: none"> • <u>Post-acute</u>: Continuing from the acute phase of COVID-19 and its treatment. • <u>Late-onset</u>: Appeared as a consequence of COVID-19 but after the end of the acute phase. • <u>Chronic</u>: Definition not reported.^{22,23} 	<ul style="list-style-type: none"> • Based on relapsing/remitting nature of post-COVID symptoms, researchers proposed this classification: <ul style="list-style-type: none"> ○ <u>Potentially infection-related symptoms</u>: Up to 4–5 weeks; ○ <u>Acute post-COVID-19 symptoms</u>: From week 5 to week 12; ○ <u>Long post-COVID-19 symptoms</u>: From week 12 to week 24; and ○ <u>Persistent post-COVID-19 symptoms</u>: Lasting more than 24 weeks.²⁴ 	<ul style="list-style-type: none"> • <u>Type 1</u>: Cases with varying lengths of recovery and rehabilitation that directly correlated with the severity of infection, target organ damage and pre-existing medical conditions at the time of infection. • <u>Type 2</u>: Cases with mild initial symptoms, lasting >6 weeks from the onset. • <u>Type 3</u>: Cases with mild initial symptoms with a period of quiescence or near recovery, followed by a return of symptoms that persist for ≥3 months or ≥6 months. • <u>Type 4</u>: Cases that are initially asymptomatic or minimally symptomatic, then develop symptoms 1–3 months or ≥3 months after confirmed COVID-19 positivity, that lasts for varying periods of time. • <u>Type 5</u>: Cases that are initially asymptomatic or minimally symptomatic, who experience sudden death within 12 months.²⁵

Table 3: Systematic and Narrative Reviews of Long COVID-19^c

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
<ul style="list-style-type: none"> International N=12 Pragmatic review 	<ul style="list-style-type: none"> 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). Follow-up time: ≥3 weeks after onset of acute COVID-19. 	<ul style="list-style-type: none"> 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. Between 2-15% of cases report having symptoms 12 weeks or more after the onset of COVID-19. Most commonly reported long-term symptoms: <ul style="list-style-type: none"> Fatigue: 8 studies, 17-98%; Dyspnea: 7 studies, 17-93%; and Headache: 4 studies, 38-91%. 	<ul style="list-style-type: none"> 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 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. 	<ul style="list-style-type: none"> 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 least partially dependent on others in the performance of daily activities subsequently.²⁶
<ul style="list-style-type: none"> International N=24 post-acute; 18 acute; 10 chronic Living rapid systematic review 	<ul style="list-style-type: none"> Objective: To understand the prevalence and characteristics of emerging disability after COVID-19. Population: COVID-19 cases. Follow up time: Not reported. 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> None reported. 	<ul style="list-style-type: none"> 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.)^{27,28}

^c 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 behavior 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
		<p>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.</p> <ul style="list-style-type: none"> • 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 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. 		
<ul style="list-style-type: none"> • International (preprint) • N=15 • Systematic review 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ○ Fatigue: 58%; ○ Headache: 44%; ○ Attention disorder: 27%; ○ Hair loss: 25%; and ○ Dyspnea: 24%. 	<ul style="list-style-type: none"> • Fatigue, post-activity polypnea, and alopecia was more commonly reported in females. 	<ul style="list-style-type: none"> • None reported.²⁹

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
<ul style="list-style-type: none"> • International (preprint) • N=28 • Living rapid systematic review 	<ul style="list-style-type: none"> • 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 discharge; longest mean follow-up period was 111 days post-hospital discharge. 	<ul style="list-style-type: none"> • Most commonly reported persisting symptoms, overall: <ul style="list-style-type: none"> ○ Breathlessness: 13 studies; ○ Smell and taste disturbance: 12 studies; and ○ Fatigue: 11 studies. • Most commonly reported persisting psychological symptoms: <ul style="list-style-type: none"> ○ Anxiety: 7 studies; ○ Depression: 5 studies; ○ Sleep disorders: 4 studies; and ○ PTSD: 3 studies. • Most commonly reported persisting musculoskeletal symptoms: <ul style="list-style-type: none"> ○ Myalgia: 7 studies. 	<ul style="list-style-type: none"> • Risk factors could not be identified due to the limitations of the existing data. 	<ul style="list-style-type: none"> • 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.³⁰
<ul style="list-style-type: none"> • International • N=24 • Systematic review 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • Most common symptoms at 4–12 weeks for previously hospitalized cases (prevalence range): <ul style="list-style-type: none"> ○ 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 	<ul style="list-style-type: none"> • Consistent pattern of people who were predominantly female, most likely middle aged, and of white ethnicity. • Persisting symptoms were significantly associated with: <ul style="list-style-type: none"> ○ Hospital admission at symptom onset; ○ Initial clinical presentation; ○ Dyspnea; ○ Abnormal auscultation; ○ Age >40 years old; and ○ Being a health care worker. 	<ul style="list-style-type: none"> • One study concluded that clinical abnormalities requiring action are infrequent.³¹

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
		<p>dimension, one month after hospital discharge.</p> <ul style="list-style-type: none"> • Most common symptoms continuing past 12 weeks for previously hospitalized cases (prevalence range): <ul style="list-style-type: none"> ○ Shortness of breath: 6.7–94.6%; and ○ Pain: 10.5–45.9%. • Most common symptoms at 4–12 weeks for non-hospitalized cases (prevalence range): <ul style="list-style-type: none"> ○ Loss of smell: 7–51%; ○ Lost of taste: 5–51%; ○ Shortness of breath: 8–71%; ○ Chest pain: 6.9–44%; ○ 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): <ul style="list-style-type: none"> ○ 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 		

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		psychiatric illness (HR: 1.58 to 2.24, P<0.0001).		
<ul style="list-style-type: none"> International N=40 research studies Narrative review 	<ul style="list-style-type: none"> Objective: To understand the impact of long COVID on health status. Population: COVID-19 cases. Follow-up time: Not reported. 	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Long COVID is more likely to be associated with: <ul style="list-style-type: none"> Increasing age; Increasing BMI; and Female sex. 	<ul style="list-style-type: none"> None reported.³²
<ul style="list-style-type: none"> International N=43 research studies Living review 	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> Case characteristics include:^d <ul style="list-style-type: none"> 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'). 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> None reported.³³

^d Much of the evidence is speculative, based on the symptoms people with Long COVID display or generalising 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](#)).

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		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
			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.	
<ul style="list-style-type: none"> • International • N=31 studies • Systematic review 	<ul style="list-style-type: none"> • <u>Purpose</u>: Identify intermediate and long-term COVID-19 sequelae affecting formerly healthy adults between 18 and 50 years of age. • <u>Population</u>: Adult participants with confirmed SARS-CoV-2 infection. • <u>Follow-up time</u>: 14 days to 90 days. 	<ul style="list-style-type: none"> • Sequelae persistence since infection spanned 14 days to three months. • Sequelae included: <ul style="list-style-type: none"> ○ 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-/perimyocarditis (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 	<ul style="list-style-type: none"> • None reported. 	<ul style="list-style-type: none"> • None reported.³⁴

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
		<ul style="list-style-type: none"> ○ Incomplete recovery of olfactory and gustatory dysfunction (33–36% of evaluated persons). 		
<ul style="list-style-type: none"> • International • The review identified 19 studies; however, none reported information of long COVID in children. <ul style="list-style-type: none"> ○ The author provides a case report of five Swedish children • Systematic review and case report of five children 	<ul style="list-style-type: none"> • <u>Purpose</u>: Examine symptoms of long COVID in children. • <u>Population</u>: In the case reports, five Swedish children (4 girls) with COVID-19, with median age of 12 years (range: 9-15). • <u>Follow-up time</u>: Follow-up period was 35 days to two months (systematic review); follow-up period among case reports was six months. 	<ul style="list-style-type: none"> • Children in case reports: <ul style="list-style-type: none"> ○ Fatigue, dyspnea, heart palpitations or chest pain, headaches, difficulties concentrating, muscle weakness, dizziness, and sore throats. 	<ul style="list-style-type: none"> • 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. • Some children had improved after 6–8 months, but they all suffered from fatigue and none had fully returned to school. 	<ul style="list-style-type: none"> • None reported.³⁵
<ul style="list-style-type: none"> • International • N=120 studies (preprint) • Systematic scoping review 	<ul style="list-style-type: none"> • <u>Purpose</u>: To synthesize what is known from literature about persistent COVID-19, its signs and symptoms, its pathophysiology, and the current management recommendations. • <u>Population</u>: Not reported. • <u>Follow-up time</u>: Not reported. 	<ul style="list-style-type: none"> • Predominant symptoms among individuals with long COVID were: <ul style="list-style-type: none"> ○ 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. 	<ul style="list-style-type: none"> • Individuals with five symptoms in the first week are more likely to develop long COVID: <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ Age 40 to 60 years; ○ Hospital admission at symptom initiation; ○ Severe COVID-19; and ○ Dyspnea or abnormal chest auscultation. • Mental health risk factors: 	<ul style="list-style-type: none"> • None reported.³⁶

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
			<ul style="list-style-type: none"> ○ 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. 	

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