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CanCOVID Issue Note

Long-COVID: understanding what it means for clinical practice and research

December 21, 2021

This informational document presents a summary of the available evidence retrieved from a rapid scan of the published literature using trusted sources, and a rapid informational (grey literature, names of experts, and current research initiatives) contribution from our CanCOVID network in response to the above question. Due to the rapid timelines, it is possible that we may have missed potentially relevant evidence. Links to the source documents are included. The short summaries for each resource listed below provide an overview of the main results, usually found in the abstract and key summary/messages section. This scan does not include any further analysis or integration of results.

December 21, 2021

Input from CanCOVID Network Science Advisor, Theme Leads incorporated

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EXECUTIVE SUMMARY

Long-COVID: understanding what it means for clinical practice and research.

Question: 'Long-COVID' what we know and what it means for clinical practice and for targeted research? What is underway on establishing cohorts and other means of systematically understanding it and supplying care?

Summary of Included Resources

Our rapid search uncovered one low quality systematic review and meta-analysis focusing on severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS), five high quality guidance documents by reputable organizations, and four ongoing cohort studies, one of which is being conducted in Canada. We relied on the quality assessments reported by the study authors.

What do we know?

Studies suggest that long-term effects of COVID-19 may include, but are not limited to, heart, lung, mental health, and musculoskeletal health issues. One consistently reported estimate from survey data and the Office of National Statistics in the United Kingdom is that one in 10 people who test positive for COVID-19 have symptoms that last longer than 12 weeks, and that among children aged 2 to 10 years old, one in seven will experience symptoms beyond five weeks. In Canada, approximately 250,000 to 300,000 Canadians could currently be experiencing long-COVID as research suggests that approximately one in three COVID-19 patients can develop persistent symptoms. However, since no standardized definition exists, it remains difficult to obtain scientific-based estimates. Long-COVID care should consider multidisciplinary interventions that are based on individual patient evaluation, and that pay special attention to minority groups (i.e., Black, south Asian, and Jewish as described by the Greenhalgh et al. report). Although there is no central list, we are aware through media sources that some clinics have opened in the following places to treat individuals with long-COVID:

- The University Health Network Clinic at Toronto Western Hospital, Ontario;
- The Urgent COVID-19 Care Clinic at the London Health Science, Ontario;
- A network of three clinics including Vancouver General Hospital, St. Paul's Hospital and the Jim Pattison Outpatient Care and Surgery Centre, British Columbia;
- La Clinique Ambulatoire Post-COVID du CIUSSS-CHUS, Quebec; and
- Institut de Recherches Cliniques de Montréal (IRCM) Post-COVID Research Clinic, Quebec.

What are the notable gaps?

There is currently no standardized diagnosis or definition of long-COVID and the definition of long-COVID remains vague. Developing a diagnosis or definition should be considered to enhance access to relevant health care services and support systems, as well as identifying the true estimate of Canadians experiencing long-COVID. More research is required to inform what predisposes a person to develop long-COVID, the causality between a COVID-19 infection, and long-COVID given that many long-haulers have no proof of infection, the health outcomes, the clinical course of long-COVID among non-hospitalized patients, the effective interventions for long-COVID management, the type and model of health care services for long haulers, and the impact on the disadvantaged and vulnerable groups. As such, new research should focus on:

- developing a standardized diagnosis or definition of long-COVID;
- studies of risk factors and upstream causes of long-COVID;
- studies assessing specific biomarkers that link symptoms and a prior infection to confirm causality;
- prospective observational cohort studies of the clinical course of long-COVID in hospitalized and non-hospitalised patients;

- intervention studies;
- studies optimizing service models; and
- studies on how long-COVID impacts the disadvantaged/vulnerable (i.e., the poor, and underserved)

What is on the horizon and what are the studies that are underway to address the gaps?

Various cohort studies are being conducted to understand the long-term impacts of COVID-19 nationally and internationally through the involvement of thousands of COVID-19 patients.

Canadian studies in progress

Relevant studies conducted in Canada include:

- the Canadian COVID-19 Prospective Cohort Study (CanCOV);
- two Canadian Longitudinal Study on Aging (CLSA) studies, the Problems Coordinating and accessing Primary Care for Attached and Unattached Patients (PUPPY) Study;
- the Prospective Urban Rural Epidemiology (PURE) SARS-CoV-2 study; and
- a collaborative project by a group of neuroscientists to understand the direct and indirect effects of COVID-19 on the brain (Richard H. Swartz and Adrian Owen, Western University's Brain and Mind Institute, the Own Lab, the University of Toronto, and Sunnybrook Health Sciences Centre)

These latter studies focus on assessing the long-term health and social consequences of COVID-19, optimizing primary care access, and the impact of COVID-19 on cognition and the brain.

Studies in progress in other countries

These include the Post-Hospitalisation COVID-19 Study (PHOSP-COVID) in the United Kingdom (UK), and the Innovative Support for Patients with SARS COV-2 Infections Registry (INSPIRE) in the United States of America. UK has announced 18.5M GBP for four major studies on long-COVID, including a study of 60,000 people with and without long-COVID. UK has also announced 70 clinics commissioned to treat and manage patients with long-COVID.

Concluding statement: More research is required to understand the long-term implications of COVID-19, to define long-COVID, and to effectively manage long-COVID patients. Research is underway in Canada and internationally to address these gaps.

QUESTION

'Long-COVID' what we know and what it means for clinical practice and for targeted research? What is underway on establishing cohorts and other means of systematically understanding it and supplying care?

SUMMARY OF RESEARCH INFORMATION[1]

The following is a short summary of the available evidence regarding clinical practice for 'Long-COVID' and related ongoing research. One systematic review and meta-analysis, one international guidance, two primary care guidance documents, two professional organization guidance documents, and four single studies were found to answer this question and were used in this Rapid Evidence Summary. The comprehensiveness of this summary may be limited given the rapid timeline for our search and documents retrieved, and it is possible that we may have missed potentially relevant evidence. For additional information about each of these sources, see the appendix below.

The World Health Organization (WHO) states in its What we know about long-term effects of COVID-19 report that symptoms of COVID-19 that may persist long-term include fatigue, cough, congestion, shortness of breath, loss of taste or smell, headache, body aches, diarrhea, nausea, confusion, and chest pains [2]. The WHO also notes that more severe long-term outcomes may include: 1) heart damage and heart failure; 2) lung tissue damage and restrictive lung failure; 3) loss of smell, stroke and cognitive impairment; 4) anxiety, depression, post-traumatic stress disorder and sleep disturbance; and 5) pain in joint and muscles and fatigue [2]. One Long-term clinical outcomes in survivors of SARS and MERS coronavirus outbreaks after hospitalisation or ICU admission meta-analysis states that one should anticipate long-term outcomes similar to those observed among MERS and SARS survivors, including lung function abnormalities and mental health impacts [1].

It is recommended that COVID-19 be considered holistically, acknowledging the psychological and social long-term impacts, and international and multidisciplinary groups of researchers are needed to investigate long-term effects [4,5]. In its pre-print, Long Covid: what is it, and what is needed? report, The Royal Society emphasizes the need for a working definition of long-COVID to be established and that more large-scale cohort studies need to be established to study different aspects of long-COVID [6]. The "Long Covid": evidence, recommendations and priority research questions report recommends that a four-tier approach to organizing services for patient care should be implemented, involving 1) resources and support for self-care, 2) generalist care including therapeutic relationship in general practice and a community-based interdisciplinary rehabilitation service led by allied health professionals, 3) specialist care including system-based investigation, management and rehabilitation, and 4) specialist management of specific complications [3]. The Management of post-acute COVID-19 in primary care guidance suggests that care should emphasize a multidisciplinary intervention based directly on patient evaluation, that should include education, exercise training and behavioural modifications such as breathing techniques [4]. The National Institute for Health Research also concluded in its Living with Covid-19 review that discussion from focus groups should make clear and realistic expectations for the ongoing effects of COVID-19 and that special attention should be given to populations disproportionately affected by COVID-19 as additional support may be required [5].

[1] Disclaimer: Due to the rapid timelines, it is possible that we may have missed potentially relevant evidence. Links to the source documents are included. The short summaries for each resource listed below provide an overview of the main results, usually found in the abstract and key summary/messages section. This scan does not include any further analysis or integration of results.

Various cohort studies to understand the long-term impacts of COVID-19 are being conducted internationally including the Canadian COVID-19 Prospective Cohort Study (CANCOV) in Canada, the Post-Hospitalisation COVID-19 Study (PHOSP-COVID) in the United Kingdom, and the Innovative Support for Patients with SARS COV-2 Infections Registry (INSPIRE) in the United States of America [7,8,9]. These studies all aim to understand the impacts of COVID-19 through the involvement of thousands of COVID-19 patients.

APPENDIX

Table 1: References and brief Summaries

Type of Evidence	Author	Resource	Last Updated	Summary
(1) Systematic review and meta-analysis	Ahmed et al.	Long-term clinical outcomes in survivors of SARS and MERS coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis	May 31, 2020	• Authors conducted a systematic review and meta-analysis, and objective was 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. • Among survivors of MERS and SARS complications up to 6 months after discharge were seen included lung function abnormalities, psychological impairment, and reduced exercise capacity. • Mental health problems include stress, anxiety and depression were observed in up to one-third of survivors at 6 months post recovery. • Clinicians should therefore anticipate similar long-term outcomes for COVID-19 survivors and plan suitable and timely treatments to provide best possible recovery and quality of life.
(2) International Guidance	World Health Organization (WHO)	What we know about long-term effects of COVID-19	September 9, 2020	• People typically recover from COVID-19 after two to six weeks, although symptoms may linger for weeks or months following initial recovery. • This may occur in people with mild disease and it is thought that people are not infectious during this time. • Some symptoms that may persist are fatigue, cough, congestion, shortness of breath, loss of taste or smell, headache, body aches, diarrhea, nausea, confusion and chest pains. • COVID-19 may increase the risk of the following long-term health problems: 1) heart damage and heart failure; 2) lung tissue damage and restrictive lung failure; 3) loss of smell, stroke and cognitive impairment; 4) anxiety, depression, post-traumatic stress disorder and sleep disturbance; and 5) pain in joint and muscles and fatigue. • Among 18–34-year-old adults in good health, 20% reported prolonged symptoms.

				• Risk factors symptom persistence include high blood pressure, obesity, and mental health conditions.
(3) Expert Advice to Government	Greenhalgh et al.	"Long Covid": evidence, recommendations and priority research questions	September 23, 2020	• This guidance recommends a four-tier approach to organizing services for patient care, including: 1) resources and support for self-care; 2) generalist care including therapeutic relationship in general practice and a community-based interdisciplinary rehabilitation service led by allied health professionals; 3) specialist care including system-based investigation, management and rehabilitation; and 4) specialist management of specific complications.
(4) Primary Care Guidance	Greenhalgh et al.	Management of post-acute COVID-19 in primary care	August 11, 2020	• Authors used a pragmatic approach to locating evidence using a systematic search and own clinical experience. • Authors emphasize that they provide evidence-based recommendations that are not yet definitive. • Apart from serious ongoing complications or comorbidities, long-COVID patients should be managed pragmatically and symptomatically with emphasis on holistic support. • Care should emphasize a multidisciplinary intervention based on patient evaluation that includes education, exercise training and behavioural modification such as breathing techniques or the use of pulse oximetry to self-monitor oxygen saturation. • Weak or absent antibody response, relapse or reinfection, inflammatory and other immune reactions, deconditioning and mental factors such as post-traumatic stress may all contribute to persistent symptoms.
(5) Professional Organization Review	National Institute for Health Research	Living with Covid-19	October 15, 2020	• Authors conducted a review and worked with a steering group and patient group who provided expertise and perspectives on this topic given the small amount of published evidence on long-COVID. • COVID-19 symptoms are non-linear and appear differently for different people. • Symptoms often arise in various systems at different times (e.g., once respiratory symptoms subside, cardiovascular symptoms may arise, etc.) • COVID-19 should be considered holistically and acknowledge the psychological and social impacts in the long-term. • Discussion from focus groups suggest that clear and realistic expectations need to be set for the symptom journey and ongoing effects of COVID-19.

				• A working diagnosis that is standardized needs to be established to aid with access to services and supports. • Special attention should be given to minority populations that experience disproportionate effects of COVID-19 as they may need additional supports.
(6) Professional Organization	The Royal Society	Long Covid: what is it, and what is needed?	October 23, 2020	• This pre-print and independent overview of the science has most recent evidence up until October 23, 2020 and has not been formally peer-reviewed. • A working definition of long-COVID needs to be established. • Multiple studies suggest that long-COVID may have multi-organ effects with both persistent and recurrent symptoms. • Some studies report symptoms such as extreme fatigue and breathlessness while others report asymptomatic long-COVID. • Further research (randomized cohort studies with appropriate controls) is needed to study different aspects of long-COVID. • More public awareness is needed in understanding that COVID-19 may not always have a quick return to full health and that people of any age can develop persistent symptoms.
(7) Single Study	Brightling et al.	Long-term follow up of adults hospitalised with COVID-19	July 22, 2020	• The Post-Hospitalisation COVID-19 Study (PHOSP-COVID) is currently recruiting participants in the UK for longitudinal assessment of the long-term effects of COVID-19 and the ongoing medical, psychological and rehabilitation needs of COVID-19 patients. • The study aims to recruit 10,000 participants.
(8) Single Study	Cheung & Herridge	The Canadian COVID-19 Prospective Cohort Study		• The Canadian COVID-19 Prospective Cohort Study (CANCOV) is the first Canadian study to provide a comprehensive evaluation of early to 1-year outcomes in 2,000 patients with COVID-19 and their family caregivers. • Researchers aim to recruit individuals who were discharged from hospital following COVID-19 to study the short (0-6 months), medium (6-12 months) and long term (12 months +) effects of the disease. • The study is conducted in Quebec, Ontario, Alberta and British Columbia.
(9) Single Study	COVID INSPIRE	Innovative Support for Patients with SARS COV-2 Infections Registry		• This study, also known as INSPIRE, is a United States national collaboration which aims to assess outcomes of COVID-19 infection on various age groups over a two-year period. • The study is currently recruiting patients across the country.
	Yelin et al.			

(10) Single Study		Long-term consequences of COVID-19: research needs	October, 2020	• Long-COVID effects are not isolated to only those who experience severe symptoms of COVID-19. • Anecdotal evidence of symptoms of long-COVID include heart palpitations, intermittent brain fog, ringing in the ears, and dramatic mood swings. • International and multidisciplinary groups of researchers are needed to investigate long-term effects.
(11) Organizational Scan	The International Development Research Centre	A global cohort study to understand the risk factors and long-term health impacts of COVID-19		
(12) Organizational Scan	Cambridge Brain Sciences	Participate in the COVID-19 Brain Study		
(13) Organizational scan	Office for National Statistics	The prevalence of long COVID symptom and COVID-19 complications		

Organizational Scan

The International Development Research Centre has contributed to the funding of a project that will study 35,000 adults from 13 countries within an existing prospective cohort study to examine the risk factors of COVID-19 and the long-term cardiovascular and respiratory health effects.
A large group of neuroscientists is teaming up to understand the direct and indirect effects of COVID-19 on the brain. This is a collaborative project between Western University's Brain and Mind Institute, The Owen Lab, The University of Toronto and Sunnybrook Health Sciences Centre. Those who had COVID-19 are asked to join from all over the world to help scientists understand how to best treat the neurological impacts of COVID-19. Find the initiative here. One consistently reported estimate from survey data and the Office of National Statistics in the United Kingdom is that one in 10 people who test positive for COVID-19 have symptoms that last longer than 12 weeks, and that among children aged 2 to 10 years old one in seven will experience symptoms beyond five weeks.

What's Trending on Media and Social Media?

On November 28th, Global News describes the experience of COVID "long-haulers" who continue to face chronic symptoms after infection. Canada's first post-COVID clinic at St. Paul's Hospital in Vancouver is currently treating 160 patients who are contributing to research efforts at the hospital that aims to better understand long-term effects of COVID-19.

CanCOVID RAPID RESPONSE QUESTION POSED TO OUR NETWORK AND PATIENT PARTNERS:

'Long-COVID' – what we know, what it means for clinical practice and for targeted research. What is underway on establishing cohorts and other means of systematically understanding it and supplying care?

Network contribution date: November 30, 2020- December 4, 2020
Draft revised: December 21, 2020

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RAPID RESPONSE QUESTION

'Long-COVID' – what we know, what it means for clinical practice and for targeted research. What is underway on establishing cohorts and other means of systematically understanding it and supplying care?

OUR ASK OF THE CANCOVID COMMUNITY

On November 30th 2020, we sent the above Rapid Response Question on Long-COVID to our CanCOVID community of over 2500 members and their networks from across Canada, requesting contributions by end of day December 4th, 2020. This was shared via email and through various social media platforms including relevant CanCOVID Slack Channels and Twitter. In addition, we engaged our CanCOVID Theme Leaders to broaden our response and findings. We requested the following information:

1. **grey literature** (e.g. unpublished guidance and reports based on rigorous science);
2. **names of experts** that could be consulted; and
3. **current research initiatives** that may yield relevant evidence in the near future on Long-COVID.

SUMMARY OF GATHERED INFORMATION

The following presents the documents and information we gathered from this engagement, including grey-literature sources, a list of long-COVID experts, and a list of current/upcoming national and international research.

Grey Literature

Our scientific network found the following resources on research involving persistent and chronic symptoms after COVID-19:

- a Rapid Evidence Report by the Alberta Health Services COVID-19 Scientific Advisory Group (PDF attached to the end of this document);
    - Pohar Manhas K, Kania-Richmond A, Cunningham C, Koning C. COVID-19 Scientific Advisory Group Rapid Evidence Report Alberta, Canada November 23, 2020.

- a rapid review by the Saskatchewan Health Authority and the University of Saskatchewan (PDF attached to the end of this document);
    - Badea A, Dalidowicz, M, Fox, L. What is the post-acute covid syndrome and its implications in terms of health services? Saskatchewan 2020 Oc 13. Report No.: E0C091601.

- a British Parliamentary guidance and recommendation document by Professor Trisha Greenhalgh et al. (PDF attached to the end of this document);
    - Greenhalgh T, Ladds, E, Knight, M, Ravindran, D, Berkshire, R. 'Long Covid': evidence, recommendations and priority research questions. UK 2020 September 23. Report No.: COV0050.

- a letter in the Journal of American Medical Association by the Italian Gemelli Against COVID-19 Post-Acute Care Study Group (PDF attached to the end of this document);
    - Carfì A, Bernabei R, Landi F, for the Gemelli Against C-P-ACSG. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;324(6):603-5.

- a news article describing the United Kingdom COVID Symptom Study;

- a list of references from a PubMed, Web of Science, Google search conducted by a CanCOVID community member (see appendix, 'Additional information provided by our CanCOVID members');

Resource Update (December 21, 2020)

- a two day Long COVID form which provides a list of patient groups, researchers, research funders, public health and policy makers, who have identified research gaps on Long COVID. The two objectives of this meeting was to: 1) gain a better understanding of Long COVID: the science behind and personal impact; and 2) to define research gaps for funders and researchers to take forward.

- a Post-Acute COVID-19 Sequelae of COVID-19 Workshop agenda which outlines a list of researchers who attended and presented at this meeting. The goal of this meeting was to summarize existing knowledge on post-acute manifestations of COVID-19 and to identify key knowledge gaps.

Long-COVID Experts

Our scientific network and patient collaborators identified eight Long-COVID experts — physicians and professors — from Canada (2/8), the United States of America (3/8), and the United Kingdom (3/8). See table 1 for our collated list of experts, their research, and their contact information.

Table 1: Long-COVID list of experts, their research, and contact information

Name	Title/Affiliation	Research/involvement	Contact information
Dr. Monica Malta	Independent Scientist in the Institute for Mental Health Policy Research at CAMH	• Dr. Malta authored a Lancet commentary, titled: My journey with COVID-19, and provides personal lived experience with long-term symptoms of COVID-19	**Phone:** 519 858-5010 22135 **Email:** monica.malta@camh.ca
Dr. Kelly Burak	Associate Professor, Department of Medicine, Gastrointestinal Research Group at the University of Calgary	• Dr. Burak has/had personal lived experience with COVID-19 and long-term symptoms • Dr. Burak authored a Rapid Evidence Report with the Alberta Health Services COVID-19 Scientific Advisory Group on the mechanisms of Long COVID chronic symptoms, and high-risk populations (document attached)	**Phone:** 403 592-5049 **Email:** kwburak@ucalgary.ca
Canadian Longitudinal Study on Aging (led by three co-PIs)		• Canadian Longitudinal Study on Aging expert group (e.g. Dr. Susan Kirkland)	
Dr. David Putrino	Assistant Professor in Rehabilitation Medicine at Mount Sinai Hospital, United States of America	• Dr. Putrino established the first United States long hauler treatment center, Reba • Dr. Putrino's provides insights to his long-COVID research in his	**Phone:** 212-824-8369 **Email:** David.putrino@mountsinai.org

		interview, Unmasking Rehab Medicine During COVID	
Dr. Avindra Nath	Clinical director of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NIH)	• Dr. Nath's has authored a correspondence, a newsletter on Long-Haul COVID, and a letter on neurological issues during COVID-10 • Dr. Nath participated in two webinars on neurological complications and neurological manifestations of COVID-19	**Phone:** 301-496-1561 **Email:** natha@mail.nih.gov
Dr. Igor Koralnik	Chief of Neuro-infectious Disease and Global Neurology in the Department of Neurology at Northwestern University Feinberg School of Medicine	• Dr. Koralnik published a study on neurologic manifestations and encephalopathy associated morbidity in COVID-19 patients	**Phone:** 312-503-1345 **Email:** igor.koralnik@northwestern.edu
Dr. Nisreen Alwan	Associate Professor in Public Health at the University of Southampton	• Dr. Alwan was a Long-COVID webinar panel member, published in the British Medical Journal • Dr. Alwan published an opinion article in the Nature on defining, measuring, and recovery of mild COVID-19 infection	**Phone:** (023) 8120 4776 **Email:** N.A.Alwan@soton.ac.uk

Dr. Paul Garner	Professor at the Liverpool School of Tropical Medicine	• Dr. Garner is among patients living with Long-COVID, and organized a self-help group, Long covid and self-help pacing groups—getting by with a little help from our friends • Dr. Garner published two opinion articles on long-haul COVID-19 and COVID-19 and fatigue in the British Medical Journal	**Phone:** +44 (0)151 705 3201 **Email:** Paul.garner@lstmed.ac.uk
Trisha Greenhalgh	Professor of Primary Care Health Sciences at the University of Oxford	• Professor Greenhalgh authored a qualitative study on long-COVID patients and their symptoms, gave a talk on post-acute COVID-19 in primary care, and was an expert panelist for a British Medical Journal webinar on long-COVID diagnosis, management, prognosis	**Phone:** +44 (0)1865 289293 **Email:** Trish.greenhalgh@phc.ox.ac.uk

Current/Upcoming Research

As of December 4, 2020, we received information about 10 funded/ongoing research studies in various phases of execution related to Long-COVID in Canada (5/10) and internationally (5/10). Below is a breakdown of these results by research title and general topic.

Table 2: List of Upcoming Research and Topic Areas

Principal Investigator (country)	Title*	Topic
Simon Graham, PhD, PEng, Sunnybrook RI and UToronto (Canada)	NeuroCovid19: brain imaging of survivors	Brain Health
Theresa Liu-Ambrose, PT, PhD, UBC (Canada)	Canadian Longitudinal Study on Aging (CLSA) Covid-19 Study: Understanding the Impact of COVID-19 on Brain Health	Brain Health
Sofia Ahmed, PhD, UHN (Canada) et al	Canadian COVID-19 Prospective Cohort Study (CANCOV) – CIHR-funded	Cohort study of early to 1-year outcomes of 2,000 COVID-19 patients and caregivers
John Hirdes, PhD, UWaterloo (Canada)		
Susan Kirkland, MD, Dalhousie (Canada)	Canadian Longitudinal Study on Aging (CLSA): Building a COVID-19 Platform for Research in Canada	Long-term health and social consequences of COVID-19 and associated mitigation strategies on older adults
Melanie Wills, PhD; Vett Lloyd, PhD; Gurpreet Singh-Ranger, MD.	Chronic Complications of COVID-19	COVID-19 infection outcomes and chronic complications of COVID-19
Judd Walson, MD, UWashington (United States of America)	CHAIN cohorts for COVID-19*	Management of affected vulnerable populations
Lars Bode, MD, UCSC (United States of America)	The Power of Breast feeding and Human Milk in a Time of COVID Contagion*	Breast Milk Transmission
Mohammod Jobayer Chisti, MD (Bangladesh)	Optimising the treatment of COVID 19 affected Bangladeshi adolescents and adults with severe pneumonia and/or ARDS using adaptive version of locally made Bubble CPAP*	Treatment

Shelley McGuire, PhD, UIdaho, & National Science Foundation (United States of America)	SARS-CoV-2 in human milk: assay validation and detection in COVID-19+ women (COVID-19Lact). 2) COVID-19, human milk, and infant feeding. USA. National Science Foundation*	Breast milk and SARS-COV-2 analysis

*FOR MORE DETAILED INFORMATION ABOUT THESE STUDIES AND OTHERS INCLUDING OBJECTIVES, METHODS, SAMPLE SIZE, AND STATUS OF THE RESEARCH, PLEASE SEE THE APPENDIX, 'ADDITIONAL INFORMATION PROVIDED BY OUR CANCOVID MEMBERS'.

PDF attachments

Following this page are PDF attachments of gathered evidence from our CanCOVID community in the following order:

1. **COVID-19 Scientific Advisory Group Rapid Evidence Report**

   Pohar Manhas K, Kania-Richmond A, Cunningham C, Koning C. COVID-19 Scientific Advisory Group Rapid Evidence Report. After a diagnosis of COVID-19, which symptoms are commonly noted after 30 days, and what is the usual duration of these chronic symptoms? 2. Which patients with COVID-19 are at highest risk of developing these chronic symptoms? 3. What mechanisms are likely to be responsible for chronic symptoms? Alberta, Canada November 23, 2020.

2. **Saskatchewan Health Authority & University of Saskatchewan Rapid Review report**

   Badea A, Dalidowicz, M, Fox, L. What is the post-acute covid syndrome and its implications in terms of health services? Saskatchewan 2020 October 13. Report No.: E0C091601.

3. **Greenhalgh et al. 2020, 'Long Covid': evidence, recommendations and priority research questions**

   Greenhalgh T, Ladds, E, Knight, M, Ravindran, D, Berkshire, R. 'Long Covid': evidence, recommendations and priority research questions. UK 2020 September 23. Report No.: COV0050.

4. **Carfi et al. 2020, "Persistent Symptoms in Patients After Acute COVID-19"**

   Carfì A, Bernabei R, Landi F, for the Gemelli Against C-P-ACSG. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;324(6):603-5.

COVID-19 Scientific Advisory Group
Rapid Evidence Report

Key Research Questions:

1. **After a diagnosis of COVID-19, which symptoms are commonly noted after 30 days, and what is the usual duration of these chronic symptoms?**
2. **Which patients with COVID-19 are at highest risk of developing these chronic symptoms?**
3. **What mechanisms are likely to be responsible for chronic symptoms?**

Context

- There is growing recognition that a subset of patients recovering from COVID-19 experience symptomatology beyond the acute infection period. These “long haulers” are thought to experience a “Long Covid”, which are two hashtags increasingly prominent in social media. News media outlets are increasingly describing some of these patients’ plights, such as Nature (Marshall, 2020), Bloomberg (Gale, 2020), and CTV News (Neustaeter, 2020). Continuing medical education strategies have begun to describe and consider the long-term symptoms of COVID-19 survivors (Burak et al., 2020).
- The Post-COVID Rehabilitation Taskforce received Alberta Health Services’ leadership support on October 29, 2020 to begin implementation of a longitudinal strategy to better support patients with the post-acute symptoms of COVID-19, particularly their rehabilitation needs. This strategy includes a directive to prospectively follow-up patients recovering from COVID-19 to determine persistent symptoms and rehabilitation needs.
- To inform this initiative, and clinicians caring for patients post-COVID, in this report, we sought to determine the current best evidence regarding the nature, frequency, duration, risk factors and mechanism of these persistent, long-term, post-COVID-19 symptoms.

Key Messages from the Evidence Summary

- Although structured definitions of chronic symptoms are not yet standardized, this review found 46 unique chronic symptoms described after acute COVID-19 infection.
- The chronic symptoms noted most frequently across studies included dyspnea, fatigue, cough, headache, loss of smell (anosmia), cognitive impairment, loss of taste (ageusia), and muscle/joint pain (myalgia) (Table 1a, Figure 1). Less frequently noted was chronicity of sleep impairments, chest pain, tachycardia, GI upset, muscle weakness and anxiety.
- Based on the median [range] prevalence noted across more than one study, the three most prevalent chronic symptoms post-COVID19 at 4 to 6 weeks post-diagnosis are fatigue (55% [16.4-73%], headache (37.8%, [15-50%]), and dyspnea (33% [1.53-56%]). Based on the median [range] prevalence noted across more than one study, the three most prevalent chronic symptoms post-COVID19 at 8 to 12 weeks post-diagnosis are fatigue (42% [9.5-62%], dyspnea (39% [1.53-48%]), and sleep impairments (30.8% [10-39%]).
- The nascent nature of the illness and corresponding literature limits generalizations on the prevalence and duration of chronic symptoms. The included studies followed patients for on average 6.82 (+/- 3.16) weeks, and follow-up was often limited to a one-time follow-up, so the natural history of post COVID symptoms remains unclear. Mode of follow-up varied from rigourous, objective assessments to self-report or social media analyses, which carry a greater risk of bias.
- Of importance, the data is limited due to lack of standardized definitions of chronicity, symptomatology post-COVID-19, and an over-reliance on subjective self-report without comparator populations or objective tools.
- Given that we have only 11 months of experience with COVID 19, we do not yet understand the true duration of chronic post-COVID-19 symptoms. Few studies followed patients until complete resolution of symptoms for the majority of patients, and where such studies did, the sample sizes were quite limited.

- Current literature suggests that chronic symptoms can result in myriad symptoms and multiple functional impairments.
- Some studies have assessed risk factors for developing chronic symptoms:
    - Having dyspnea (shortness of breath) in the acute phase of the illness (defined as day 7 after symptom onset), or having a history of asthma or chronic lung disease, is associated with a higher risk for prolonged or chronic dyspnea (Carvalho-Schneider et al., 2020; Cellai & O'Keefe, 2020).
    - Younger age, being of female gender, or previous diagnosis of a psychiatric disorder (De Lorenzo et al., 2020; Halpin et al., 2020; Mazza et al., 2020; Taquet, Luciano, Geddes, & Harrison, 2020) are associated with a higher risk of persistent psychiatric symptoms, particularly PTSD.
- There is little data on long term symptoms in pediatric populations. A single study (n=25) on pediatric patients found that they did not experience chronic symptoms or laboratory abnormalities.
- The severity of the acute COVID-19 illness is associated with a higher risk of chronic post-COVID19 symptoms (Carvalho-Schneider et al., 2020), but conversely some studies find hospitalization protective (particularly against psychiatric symptoms) (De Lorenzo et al., 2020) or found no difference with respect to chronic symptoms of Intensive Care Unit (ICU) and non-ICU hospitalized patients (Garrigues et al., 2020).
- The mechanisms that may be responsible for chronic symptoms remain uncertain. The theories proposed currently describe potential pathophysiologic aspects of SARS-CoV-2 infection, including direct viral, immune and inflammatory manifestations. This includes causing 'cytokine storm,' highly inflammatory states; passing through the olfactory bulb to affect the senses; and how these may lead to both acute complications (e.g. stroke, encephalitis); and possibly transition into the experience of chronic symptoms post-acute COVID-19. Current literature focuses primarily on neurological manifestations and mechanisms although other areas are evolving and emerging in the literature.

Table 1a. Most Common Symptoms and Range of Prevalence Noted by Included Studies.

System	Symptom	# of STUDIES	Median [Range] Prevalence Range (4-6 week f/u studies)	Median [Range] Prevalence Range (8, 12 or more week f/u studies)
Respiratory	**Shortness of breath (dyspnea)**	18	**33%** [1.53% - 56%] (5 studies; 2 unclear)	**39%** [1.53% - 48%] (9 studies; 4 unclear)
	Cough	13	**18.3%** [7%-33%] (5 studies, 3 unclear)	**7.7%** [1.81% - 27%] (4 studies, 2 unclear)
	Chest pain	7	**18.0%** [n/a] (1 study, 3 unclear)	**17.1%** [13%-31%] (4 studies, 2 unclear)
Neurological	**Fatigue**	15	**55%** [16.4%-73%] (6 studies, 2 unclear)	**42%** [9.5%- 62%] (7 studies, 1 unclear)
	Headache	12	**37.8%** [15%-50%] (3 studies, 4 unclear)	**18.2%** [7%-22%] (3 studies, 2 unclear)
	Loss of smell (anosmia)	11	**12%** [5%-36%] (5 studies, 2 unclear)	**12%** [9.7%-39%] (5 studies, 1 unclear)
	Cognitive impairment	9	**18%** [12%-25.4%] (3 studies, 4 unclear)	**20%** [12%-28%] (2 studies, 2 unclear)
	Loss of taste (ageusia)	8	**28%** [9%-32%] (3 studies, 4 unclear)	**12.1%** [1.17%-23%] (2 studies, 1 unclear)
Musculoskeletal	**Muscle/joint pain**	8	**9.8%** [5%-15%] (3 studies, 3 unclear)	**16.3%** [6%-28%] (3 studies)
Mental health	**Sleep impairments**	7	**40%** [n/a] (1 study, 3 unclear)	**30.8%** [10%-39%] (3 studies)

Committee Discussion

The review was discussed by the Scientific Advisory Committee on November 18, 2020. The committee reached consensus on the following recommendations and research gaps. It was acknowledged that there was a great breadth of literature on the post-COVID-19 chronic symptoms, but that many research gaps remain. Gaps remaining include standardization of the definition of chronicity and the best methodology to study chronic symptoms post-COVID-19. The included studies were of moderate quality without any high quality studies at low risk of bias; most of the studies were observational, focused on self-report, lacked comparators and lacked objective assessments. A concern was raised that a focus on self-report and a lack of comparator or objective assessments may be as a result of paitents somaticizing their symptoms, though definitive conclusions can not be made this early in a pandemic.

While there was a focus on moderate to high quality studies, there is still a wide range on the prevalence of symptoms across the studies. There is recognition that a significant portion of COVID-19 survivors will have chronic symptoms, but less clarity on which symptoms those will be. Given the range of jurisdictions from where studies were conducted, there remain questions on whether jurisdictional or genetic differences impact chronic symptomatology. There was discussion about the importance to raise awareness on the breadth of possible long-term symptoms for patients recovering from COVID-19 amidst care providers, particularly primary care, nursing and allied health professionals. There was discussion on the importance of generating high-quality data in Alberta to inform decision-making and care planning. The related recommendation should tie to current or planned work, particularly that of the Provincial Post-COVID Rehabilitation Taskforce. The need to include hospitalized and community-only COVID-19 survivors was noted.

Recommendations

1. Strategies to support patients recovering from COVID-19 should be multidisciplinary, and should involve options for decentralized care through collaboration with primary care physicians as well as nursing and allied health professionals.
   Rationale:
   The duration and diversity of chronic symptoms post COVID-19 makes longitudinal follow-up vital to identify and support the specific needs of individual patients. Post-COVID long-term symptoms should be assessed in a systematic fashion using standard definitions, and appropriate treatment and monitoring established to support the patient.

2. For patients recovering from COVID-19 who are identified at higher risk of chronic symptoms, increased attention should be made to their general health in their long-term recovery. Particular attention should be given to patients at higher risk of mental health symptoms (current risk factors include female, younger adults, or with a history of psychiatric diagnoses) and patients at higher risk for respiratory symptoms (current risk factors include existing chronic lung disease, and/or dyspnea in the acute phase).
   Rationale:
   Patients recovering from COVID-19 should be followed clinically in a structured fashion to document incidence and duration of chronic symptoms in our population. Optimally patients may be randomized into a community-based structured care versus an intensified follow-up care stream to elucidate whether additional testing and follow-up impacts the post COVID illness experiences. In addition, assessment of therapeutic options for chronic symptoms should be preferentially offered and followed within the context of trial protocols, whether patients are in an intensive follow-up cohort or community-based cohort.

3. There should be a systematic approach, including the use of standard definitions, to monitoring and studying the chronic symptoms of Albertans with COVID-19, so that the health system can understand the local context of symptomatology and epidemiology better. It may be useful to also consider data collection in a control population (perhaps also recovering from another viral illness, or another population within primary care).
   Rationale:
   In October 2020, Alberta Health Services approved a proposed strategy by the Provincial Post-COVID Rehabilitation Taskforce (Alberta Health Services, 2020). *Part of the proposed strategy centres on*

completing longitudinal follow-up with persons recovering from COVID19, whether hospitalized or community-only experience. This follow-up should aim to ensure care continuity for patients with persistent post-COVID19 symptoms, and to provide much-needed clarity on the exact epidemiology, particularly prevalence, of chronic symptoms post-COVID-19 in Alberta. Any follow-up should consider the chronic needs of patients recovering from COVID-19 post-hospitalization as well as the needs of patients who were not admitted to hospital (for whom less information is available).

Pragmatic Considerations

Developing a care pathway focused on chronic symptoms is beyond the scope of this review, but is likely essential to support patients in their long-term recovery from COVID-19. The current Presumed/Confirmed COVID19 Positive Primary Care Pathway may represent an existing tool to update with the knowledge generated in this rapid evidence review. In particular, there may be a need to refine the current pathway to include some of these chronic symptoms. Primary care input will be needed to determine what is feasible and what support is needed.

Research Gaps

While this rapid evidence review includes 54 articles, the quality of these articles is neither abysmal nor excellent. The studies are informative and of moderate to high quality. There remain gaps in the literature that must be addressed. These include the following:

- As noted in the literature, greater clarity is required on the exact definition of chronicity in the context of COVID-19.
- The included studies varied in data collection, some studies used self-report apps, others had clinicians use de novo (or occasionally validated) surveys with patients to capture self-report, and others involved more objective physical assessments and laboratory testing to complement self-report. The committee notes a significant research gap relates to the need for a set of standard definitions on the symptomatology that is objectively chronic post-COVID-19 and for the gold standard tools to measure such symptoms.

Strength of Evidence

The body of evidence is moderate to strong. Most of the included studies were peer-reviewed (14 of the 54 studies were preprints). The risk of selection bias for forming cohorts was difficult to assess, while some studies described seeking consecutively admitted COVID-19 patients, others used social media or convenience sampling without insight on the process. Qualitative comparisons suggest that the app-based assessments (Banda et al, 2020) listed fatigue more often than other smaller clinic-based studies that mentioned mental health and dyspnea more frequently. The systematic reviews were limited but of very high quality, while the numerous observational cohorts were of moderate to high quality. None of the observational cohorts fell into the low-quality area, and all have very reasonable sample sizes. However, none of the observational cohorts stood out as of exceptionally high quality with limit risk of bias.

Limitations of this review

Chronicity of symptoms is implied to be at 30 days or longer. This was viewed as a benchmark, not a hard limit. Many studies that met the “spirit” of the research questions used a different definition for long-term follow-up or chronic post-COVID-19 symptoms (i.e. long COVID). These different definitions included using a weekly timeline that went to 4 weeks (i.e. 28 days). These studies were included to ensure comprehensive coverage. One study was highly cited (particularly by the World Health Organization), focused on long-term symptoms, but used a 2 to 3 week follow-up period (14-21 days): this study was included for Research Question 1 only (Tenforde et al., 2020). As recognized in Amenta et al. (2020), “there is no universally accepted time period that defines the beginning of the post-acute period.” But Amenta et al. (2020) suggest that chronic COVID-19 includes “… persistent symptomatology extending beyond 12 weeks after initial symptoms.”

This review limited itself to the direct language of the Research Questions, which spoke to symptoms not complications or sequelae. While the search strategy included all terms such as complications, sequelae and symptoms, the resulting studies screened did not include literature that clarified acute complications in hospital or

sought associations between particular sequelae and chronic symptoms. The symptomatology assessed in these studies considered hospitalized, non-hospitalized or both types of patients, but the detailed experiences in hospital were not discussed. A future review search strategy may be required to fully elucidate the correlation between acute complications and chronic symptoms.

The rapid turnaround time of this review introduced challenges and related workarounds, as follows:

- The second part of Research Question 2 seeks information on the duration of chronic symptoms. The included studies can only speak to duration relative to the timeline of their study, which was on average 6.93 (+/- 3.15) weeks post-diagnosis with the longest follow-up period being 15.8 weeks in one study. This evidence review cannot confirm the decisive duration of chronic post-COVID-19 symptoms. Few studies followed patients until complete resolution of symptoms for the majority of patients, and where such studies did the sample sizes were quite limited.
- The literature on the mechanism of chronic symptoms is nascent and highly hypothetical.
    - Articles were excluded if the discussion on the mechanisms focused on chronic complications that could not yet manifest given the emerging nature of this pandemic. Examples include studies that hypothesized on the pathology of neurological complications, which could lead to neurodegenerative disorders such as Alzheimer's disease, Parkinsons' disease, or cancer.
    - Articles were excluded if the discussion on mechanisms focused on acute symptomatology. Articles were included, however, if the discussion on acute symptomatology implied acute complications with long-term symptom implications. These were included for a high-level discussion (not detailed analysis). Such studies hypothesize on acute complications such as encephalitis, stroke or Guillain-Barre Syndrome.
    - Articles were included for extraction and analysis to address Research Question 3 if they approached, hypothetically or empirically, the potential mechanisms of chronic post-COVID-19 symptoms.
- The focus of this narrative review was limited to the incidence, duration and risk factors of patient symptoms or outcomes experienced post-COVID-19, and not that of medical conditions or complications which could arise as a complication of COVID-19. The former included a range of symptoms such as cough, fatigue, PTSD, and dyspnea (shortness of breath), while the latter included a range of complications such as stroke, myocardial infarction, sepsis, and post-ICU syndrome. This limit was verified by the 26 observational cohort studies that attempted to follow-up COVID-19 survivors and determine their experience. These studies measured symptoms, through self-report, lab tests or physical assessments, but did not detail patient complications or conditions.

Given the emerging nature of the pandemic and timeline since the introduction of the virus, the recommendations rely on preprints and peer-reviewed articles in equal stead. This review should be read as a rapid, emerging evidence summary, rather than a rapid evidence review.

Databases were searched for English-language evidence published in 2020, thus, evidence from outbreaks in jurisdictions where English is not common has not been included in this review.

Summary of Evidence

Literature for this review was collected from a database search covering OVID MEDLINE, CINAHL, LitCovid, PubMed, TRIP PRO, WHO COVID-19 Database, Centre for Evidence Based Medicine (CEBM), Google and Google Scholar. The search was limited by the following parameters: COVID-19, SARS-CoV-2 virus, long-term follow-up, outcomes, post-discharge, post-diagnosis, and mechanism.

One hundred and sixty-five articles (peer-reviewed and pre-prints) were identified in the initial search, alongside with citation tracking and snowball searching amongst the KRS librarian and review writers. After a title, abstract and paper review where each paper was assessed by two writers independently, 54 published articles (including 14 pre-prints) were included, based on consensus. A total of four writers were involved in screening and extraction.

The search was limited by the parameters of the questions: determining the nature, duration, risk factors and potential mechanisms for symptoms that remain with COVID-19 survivors after the acute infection stage of COVID-19. The search was limited to English articles published 2020-current. Articles were not excluded based on population. While the research questions framed chronicity as at 30 days or beyond the date of diagnosis, as discussed above, we did not limit the search strategy by specific date and sought articles that examined or considered symptoms in the non-acute infection period of COVID-19.

The majority of the included studies were observational cohorts (n=26) and unstructured review (n=11), while other studies included editorials (n=6), cross-sectional surveys (n=5), systematic reviews (n=4), case-control study (n=1) and case report (n=1). The editorials primarily described potential mechanisms, while the surveys and cohorts informed chronic symptoms prevalence and duration. The jurisdictional distribution of the studies was as follows: USA (n=19), UK (n=9), Italy (n=7), International teams (n=4), China (n=3), France (n=3), Austria (n=2), and one each from Belgium, Finland, Iran, Israel, Japan, Spain, and Switzerland.

Research Question 1: After a diagnosis of COVID-19, which symptoms are commonly noted after 30 days, and what is the usual duration of these chronic symptoms?

Evidence from secondary and grey literature

Any secondary and grey literature that was identified that addressed this question included citations to primary literature or original research. This review limited its analysis and discussion to primary literature or original research (including preprints).

Evidence from the primary literature

This synthesis is based on 38 studies that explicitly considered the nature or frequency of chronic symptoms post-COVID-19. These included 25 observational cohorts, 5 cross-sectional survey studies, 3 reviews, 3 editorials, and 1 case report. Table 3a in the Appendix section contains the information extracted from each document.

From the studies that completed follow-up, the average (standard deviation) number of weeks of follow-up was 6.82 (+/- 3.16), while the minimum and maximum follow-up periods were 2 weeks (Tenforde et al., 2020) and 15.8 weeks (Garrigues et al., 2020). Nineteen studies only included 1 time-point for follow-up, with the maximum number of follow-ups being 7 times. The included studies speak to follow-up at 30 or less days (14 studies), 42 days (11 studies), 60 days (10 studies), 90 days (6 studies), while 8 studies were unclear. Conservatively, these studies can generalize to the nature of chronic symptoms post-COVID-19 experienced by patients up to the mean of nearly 7 weeks from diagnosis. The longer-term manifestation of chronic symptoms, especially by a more formalized definition of chronic COVID-19 at 12 weeks or beyond diagnosis is unclear from the studies in this review.

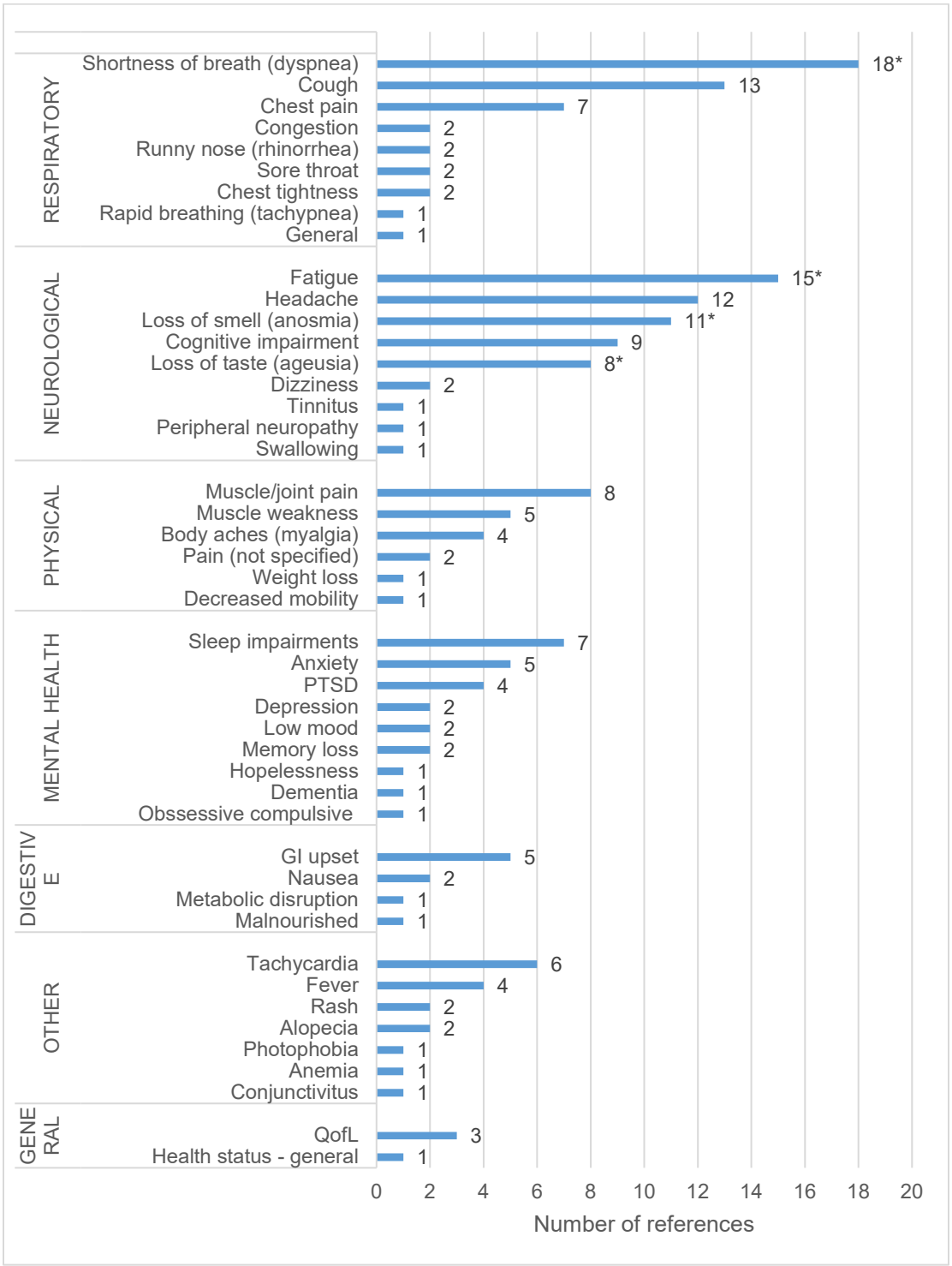
The sample size of the observational cohorts and surveys were noteworthy and wide ranging. The maximum participant sample size was 84,285 (Hampshire et al., 2020), while it is unclear how many participants took part in the Banda et al. (2020) study wherein 144,600 social media posts were analyzed. Due to outliers, the mean (SD) sample size is unclear at 4837.2 (+/- 18194.0). The median sample size for the studies was 119, while the 25th and 75th percentiles were 57 and 224, respectively. This suggest robust sample sizes, although there is less clarity on the recruitment tactics to minimize selection bias.

These studies noted that persons recovering from COVID-19 developed 46 unique chronic symptoms (Figure 1; Table 1b). The chronic symptoms noted most frequently across the included references include dyspnea (18 references), fatigue (15 references), cough (13 references), headache (12 references), loss of smell (anosmia) (11 references), cognitive impairment (11 references), myalgia (muscle/joint pain) (8 references), sleep impairments (7 references), chest pain (7 references), tachycardia (6 references), GI upset (5 references), muscle weakness (5 references) and anxiety (5 references). Based on the median [range] prevalence noted across more than one study, the five most prevalent chronic symptoms post-COVID19 at 4 to 6 weeks post-diagnosis are fatigue (55% [16.4-73%], headache (37.8%, [15-50%]), dyspnea (33% [1.53-56%]), loss of taste (ageusia) (28% [9-32%]), and cough (18.3% [7-33%]). Based on the median [range] prevalence noted across more than one study, the five most prevalent chronic symptoms post-COVID19 at 8 to 12 weeks post-diagnosis are fatigue (42%

[9.5-62%], dyspnea (39% [1.53-48%]), sleep impairments (30.8% [10-39%]), cognitive impairment (20% [12-28%]), and headache (18.2% [7-22%]).

We examined whether studies focused their aims and methods on a broad or narrow range of systems. Across the 38 studies that considered chronic symptoms, whether empirically or theoretically, 10 (26.3%) articles focused on only one system or type of symptoms (e.g. neurological, cardiovascular), while 28 (75.7%) articles took a broader approach to include more than one system. Based on the categorization of the four writers, some of the included studies had methodologies that considered neurological symptoms (64.2%), respiratory symptoms (64.2%), sensory symptoms (50.9%), functional symptoms (41.5%), cardiovascular symptoms (37.7%), fatigue-specific symptoms (45.3%), musculoskeletal symptoms (26.0%), psychiatric symptoms (26.4%), immunological and inflammatory symptoms (24.5%), and quality-of-life-related symptoms (17.3%). In most cases, the studies that assess quality of life used validated surveys, but for the other categories of symptoms the studies varied greatly on the use of validated instruments, clinical assessments or patient self-report using novel surveys.

Figure 1. Chronic Post-COVID-19 Symptoms Identified in the Primary Literature



Due to heterogeneity and time constraints, we were unable to pool studies to obtain point estimates on the frequency and duration of chronic symptoms after 30 days of diagnosis with COVID-19. Some studies were more illuminating that others in this regard. This information supplements Table 1a above:

- One study found that 43.4% of COVID-19+ cases have symptoms lasting longer than 30 days, and 24.1% still have at least one symptom after 90 days (Cirulli et al., 2020).
- Another study found that only 18 (12.6%) of participants were completely free of COVID-19-related symptoms around 8.6 weeks from diagnosis (Carfì, Bernabei, & Landi, 2020). Carfi, Bernabei & Landi (2020) also found that at follow-up, 32% of participants had 1 or 2 symptoms, and 55% had 3 or more chronic symptoms.
- At 6 weeks follow-up, a study focused on headache found it persisted for 37.8% of patients post-COVID-19, including 60.7% (17) having daily constant headache (Caronna et al., 2020).
- Cellai et al. (2020) noted that 69.2% of patients reported at least 4 concurrent symptoms at 30-day follow-up.
- Charlotte et al. (2020) found that the 30-day post-diagnosis time-point, 63% (73) patients reported persistent symptoms.
- The frequently cited, but shorter duration, study by Tenforde et al. (2020), found that 34% (59 of 175) respondents had one or more COVID-19-related chronic symptoms at follow-up.

These studies that noted symptom persistence did not distinguish on symptom severity. Few studies discussed re-hospitalization, and those that did were not explicit on which chronic symptomatology or complication caused the re-hospitalization.

Taken together, these studies suggest that a minority of patients will be without chronic symptoms at the 30-day (or 4 week) mark after COVID-19 diagnosis. However, there appears to be jurisdictional variation in the propensity for some of these symptoms.

Importantly, only one study found that no patients had clinical symptoms or laboratory test abnormalities 4-months after the study (Denina et al., 2020). Denina et al. (2020) followed 25 hospitalized children in Italy. This study may suggest that pediatric patients with COVID-19 may be less likely to experience chronic symptoms, but the small sample size and lack of corroboration limits the generalizability of this suggestion. Most of the studies included in this rapid evidence review focused on adult patients.

Table 1b. Chronic Symptoms Experienced by Patients Recovering from COVID-19.

System	Symptom	# of Studies	References
Respiratory	Shortness of breath (dyspnea)	18	Arnold DT *et al.,* 2020; Banda JM *et al*., 2020; Carfi A *et al*., 2020; Carvalho-Schneider C *et al.,* 2020; Cellai & O'Keefe, 2020; Cirulli ET *et al.*, 2020; Daher A *et al*., 2020; De Lorenzo et al., 2020; Garrigues E *et al*., 2020; Greenhalgh *et al*., 2020; Halpin SJ *et al*., 2020; Miyazato Y *et al*., 2020; Morley JE 2020; O'Keefe JB *et al*., 2020; Rogliani P *et al*., 2020; Sollini M *et al*., 2020; Wang X *et al*., 2020; Zhao YM et al., 2020
	Cough	13	Bakhoum MF *et al*., 2020; Banda JM *et al*., 2020; Blair PW *et al*., 2020; Cellai & O'Keefe, 2020; Daher A *et al*., 2020; Greenhalgh *et al*., 2020; Halpin SJ *et al*., 2020; Miyazato Y *et al*., 2020; Morley JE 2020; Klein H *et al*., 2020; O'Keefe JB *et al*., 2020; Wang X *et al*., 2020; Zhao YM et al., 2020
	Chest pain	7	Banda JM *et al*., 2020; Carfi A *et al*., 2020; Carvalho-Schneider C *et al.,* 2020; Cirulli ET *et al.*, 2020; Greenhalgh *et al*., 2020; Morley JE 2020; Sollini M *et al*., 2020
	Congestion	2	Cellai & O'Keefe, 2020; O'Keefe JB *et al*., 2020
	Runny nose (rhinorrhea)	2	Carvalho-Schneider C *et al.,* 2020; Daher A *et al*., 2020
	Sore throat	2	Daher A *et al*., 2020; Wang X *et al*., 2020
	Chest tightness	2	Cellai & O'Keefe, 2020; Wang X *et al*., 2020
	Rapid breathing (tachypnea)	1	De Lorenzo *et al*., 2020
	General	1	Charlotte P *et al*., 2020

Neurological	Fatigue	15	Arnold DT *et al.,* 2020; Banda JM *et al*., 2020; Carfi A *et al*., 2020; Cellai & O'Keefe, 2020; Charlotte P *et al*., 2020; Daher A *et al*., 2020; Garrigues E *et al*., 2020; Greenhalgh *et al*., 2020; Halpin SJ *et al*., 2020; Miyazato Y *et al*., 2020; Morley JE 2020; Savarraj JP *et al*., 2020; Sollini M *et al*., 2020; Sudre CH et al., 2020; Zhao YM et al., 2020
	Headache	12	Bakhoum MF *et al*., 2020; Banda JM *et al*., 2020; Caronna E *et al*., 2020; Cellai & O'Keefe, 2020; Cirulli ET *et al*., 2020; Daher A *et al*., 2020; Greenhalgh *et al*., 2020; Morley JE 2020; Sollini M *et al*., 2020; Sudre CH et al., 2020; Zhao YM et al., 2020; Zubair AS *et al*., 2020
	Loss of smell (anosmia)	11	Carvalho-Schneider C *et al.,* 2020; Charlotte P *et al*., 2020; Cirulli ET *et al*., 2020; Daher A *et al*., 2020; Miyazato Y *et al*., 2020; Morley JE 2020; Klein H *et al*., 2020; O'Keefe JB *et al*., 2020; Sollini M *et al*., 2020; Sudre CH et al., 2020; Zubair AS *et al*., 2020
	Cognitive impairment	9	Cirulli ET *et al*., 2020; Daher A *et al*., 2020; De Lorenzo *et al*., 2020; Garrigues E *et al*., 2020; Greenhalgh *et al*., 2020; Hamphire A *et al*., 2020; Morley JE 2020; Savarraj JP *et al*., 2020; Sudre CH et al., 2020
	Loss of taste (ageusia)	8	Carvalho-Schneider C *et al.,* 2020; Cirulli ET *et al*., 2020; Daher A *et al*., 2020; Miyazato Y *et al*., 2020; Morley JE 2020; Klein H *et al*., 2020; Sollini M *et al*., 2020; Zubair AS *et al*., 2020
	Dizziness	2	Cirulli ET *et al*., 2020; Greenhalgh *et al*., 2020
	Tinnitus	1	Sudre CH et al., 2020
	Peripheral neuropathy	1	Sudre CH et al., 2020
	Swallowing	1	Greenhalgh *et al*., 2020
Physical	Muscle/joint pain	8	Banda JM *et al*., 2020; Carfi A *et al*., 2020; Carvalho-Schneider C *et al.,* 2020; Daher A *et al*., 2020; Greenhalgh *et al*., 2020; Morley JE 2020; O'Keefe JB *et al*., 2020; Sollini M *et al*., 2020
	Muscle weakness	5	Bakhoum MF *et al*., 2020; Blair PW *et al*., 2020; Charlotte P *et al*., 2020; Greenhalgh *et al*., 2020; Morley JE 2020
	Body aches (myalgia)	4	Arnold DT *et al.,* 2020; Carvalho-Schneider C *et al.,* 2020; O'Keefe JB *et al*., 2020; Miyazato Y *et al*., 2020
	Pain (not specified)	2	Banda JM *et al*., 2020; Savarraj JP *et al*., 2020
	Weight loss	1	Carvalho-Schneider C *et al.,* 2020
	Decreased mobility	1	Morley JE 2020
Mental Health	Sleep impairments	7	Arnold DT *et al.,* 2020; Banda JM *et al*., 2020; De Lorenzo *et al*., 2020; Garrigues E *et al*., 2020; Greenhalgh *et al*., 2020; Mazza MG *et al*., 2020; Taquet M *et al*., 2020
	Anxiety	5	Daher A *et al*., 2020; De Lorenzo *et al*., 2020; Greenhalgh *et al*., 2020; Mazza MG *et al*., 2020; Taquet M *et al*., 2020
	PTSD	4	De Lorenzo *et al*., 2020; Halpin SJ *et al*., 2020; Mazza MG *et al*., 2020; Savarraj JP *et al*., 2020
	Depression	2	Daher A *et al*., 2020; Mazza MG *et al*., 2020
	Low mood	2	Greenhalgh *et al*., 2020; Taquet M *et al*., 2020
	Memory loss	2	Cirulli ET *et al*., 2020; Garrigues E *et al*., 2020
	Hopelessness	1	Greenhalgh *et al*., 2020
	Dementia	1	Taquet M *et al*., 2020
	Obsessive compulsive	1	Mazza MG *et al*., 2020
Digestive	GI upset	5	Carvalho-Schneider C *et al.,* 2020; Cellai & O'Keefe, 2020; Daher A *et al*., 2020; Greenhalgh *et al*., 2020; Zhao YM et al., 2020
	Nausea	2	Daher A *et al*., 2020; Wang X *et al*., 2020
	Metabolic disruption	1	Greenhalgh *et al*., 2020
	Malnourished	1	De Lorenzo *et al*., 2020
Other	Tachycardia	6	Banda JM *et al*., 2020; Carvalho-Schneider C *et al.,* 2020; Cellai & O'Keefe, 2020; Cirulli ET *et al*., 2020; Morley JE 2020; Sudre CH et al., 2020
	Fever	4	Banda JM *et al*., 2020; Carvalho-Schneider C *et al.,* 2020; Daher A *et al*., 2020; Greenhalgh *et al*., 2020
	Rash	2	Carvalho-Schneider C *et al.,* 2020; Greenhalgh *et al*., 2020

	Alopecia	2	Garrigues E *et al*., 2020; Miyazato Y *et al*., 2020
	Photophobia	1	Bakhoum MF *et al*., 2020
	Anemia	1	Sonnweber T *et al*., 2020
	Conjunctivitis	1	Morley JE 2020
General	QofL	3	Arnold DT *et al.,* 2020; Carfi A *et al*., 2020; Halpin SJ *et al*., 2020
	Health status - general	1	Arnold DT *et al.,* 2020

Research Question 2: Which patients with COVID19 are at highest risk of developing these chronic symptoms?

Evidence from secondary and grey literature

Any secondary and grey literature that was identified that addressed this question included citations to primary literature or original research. This review limited its analysis and discussion to primary literature or original research (including preprints).

Evidence from the primary literature

This synthesis related to risk factors is based on 17 primary articles (7 preprints, and 10 peer-reviewed articles), including 13 observational cohorts, 3 cross-sectional surveys, and 1 editorial. Table 2a one overviews the key takeaways from these articles on the risk factors for chronic symptoms post-COVID19, while Table 3a in the Appendix section contains the information extracted from each document.

There are only a few clear findings related to the types of patients with COVID19 who are at highest risk of developing certain chronic symptoms.

- First, it appears that those at higher risk of psychiatric chronic symptoms, particularly PTSD, include those:
    - of younger age (about 40-60 years) (OR 1.033 [95%CI 1.003-1.067], p=0.037, De Lorenzo et al., 2020),
    - of female gender (OR 1.76 [95% CI 0.94-3.37], p=0.085, De Lorenzo et al., 2020), (76.9% females vs. 38.5% males in ICU, Halpin et al. 2020), (2.9:1 Female: Male ratio, χ^2=54.98, p<0.001 for clinical PTSD and 3:1 M:F (χ^2=15.13, p<0.001 for clinical depression), Mazza et al. 2020).
    - with previous diagnosis of a psychiatric disorder (RR 1.65 [95% CI 1.59-1.71], p<0.001, Taquet et al. 2020)

Second, there is some support that patients with dyspnea (shortness of breath) in the acute phase, or who have a history of asthma or chronic lung disease, may be at higher risk for a chronic experience of dyspnea (OR 2.4 [1.0-5.3 95%CI, p=0.02) (Carvalho-Schneider et al., 2020; Cellai & O'Keefe, 2020). It should be noted that dyspnea is somewhat mixed as a symptom: some patients develop chronic dyspnea without any evidence of having developed a chronic lung disease, while those with prolonged COVID-19 pneumonia may have dyspnea due, in part, because they have developed a complication of the pneumonia (i.e. chronic fibrotic lung disease).

Third, the severity of the acute COVID-19 experience may lead to higher risk of chronic post-COVID19 symptoms (OR 2.8 [1.2-6.2 95% CI, p=0.017) (Carvalho-Schneider et al., 2020), but this is not irrefutable. There are studies that suggest no difference in the outcomes of ICU and non-ICU patients (Garrigues et al., 2020), while another study found hospitalization a protective factor for chronic symptoms (particularly psychiatric symptoms) (OR 1.081[95% CI 0.57-2.02], p=0.81 (De Lorenzo et al., 2020). Two of these studies are more theoretical in their attribution of severity in acute COVID-19 to chronic symptoms (Bakhoum et al., 2020; Weerahandi et al., 2020).

The remaining studies herein attempt to inform the risk factors for chronic symptoms post-COVID-19, but they do not have corroboration from other studies. For example, Pizzini et al. (2020) found that low Vitamin D was not related to chronic symptoms (no OR provided; p=0.116); Klein et al. (2020) found that severity of the olfactory change was related to chronic sensory symptoms (correlation 0.34, p=0.003); and Sonnweber et al. (2020) found that hyperferritinemia was associated with decreased 6-minute walking distance (~200m yes to hyperferritnemai versus ~400m, p=0.011).

Table 2a. Summary of Articles Informing Risk Factors for Chronic Symptoms.

Author	Study Design	Type of Article	Type of COVID patients	Noted Risk Factor	Noted Chronic Symptom
(Bakhoum et al., 2020)	Observational Cohort	Preprint	All	-Post viral inflammation	Generic[1]
(Blair et al., n.d.)	Observational Cohort	Preprint	All	-While the majority 63.7% of participant had no symptoms or only had mild symptoms during the first week of illness a substantial proportion continued to have mild or moderate symptoms for over one month.	Generic
(Caronna et al., 2020)	Observational Cohort	Peer-reviewed	All	-There were no statistically significant differences with regard to the demographic variables in patients that were not followed up.	Generic
(Carvalho-Schneider et al., 2020)	Observational Cohort	Preprint	All	-These prolonged symptoms were significantly associated with **age** 40 to 60 years old, **hospital** admission at symptom onset, **severe** COVID-19, and **dyspnea** or abnormal auscultation.	Generic
(Cellai & O'Keefe, 2020)	Observational Cohort	Peer-reviewed	Non-hospitalized	**-Asthma and chronic lung disease** (prospectively coded at intake visit) appeared more frequently in the patients identified in the persistent symptom cohort for this study.	Respiratory chronic symptoms (e.g. dyspnea, chest pain)
(Cirulli et al., 2020)	Cross-sectional Survey	Preprint	All	-We additionally observe that individuals who had an initial symptom of **dyspnea** are significantly more likely to develop long-term symptoms. -Only five factors maintained a nominal association (uncorrected $p<0.05$) with long-term symptoms in COVID-19+ cases: the initial symptoms of **dyspnea and chest pain,** and **blood type A** as well as blood **type A+** (but not blood type A-, which	Generic

[1] Generic reference to chronic symptom means articles attributes risk factor to having some type of chronic symptom, but does not specific exactly which symptom. Often the risk factor analysis focused on presence or absence (or number of) symptoms, versus type of symptoms.

				is rarer) were associated with increased risk	
(De Lorenzo et al., 2020)	Observational Cohort	Peer-reviewed	Hospitalized	-Hospitalization, instead, emerged as protective factor. -PTSD: **Decreasing age**, **female gender** and **positive psychiatric history** were significantly associated with the risk of developing PTSD after COVID-19.	Mental Health
(Garrigues et al., 2020)	Observational Cohort	Peer-reviewed	Hospitalized	No difference in persistent symptoms between ICU and non-ICU/ward groups	Generic
(Halpin et al., 2020)	Cross-sectional Survey	Peer-reviewed	Hospitalized	-Moderate or severe fatigue (rated 4 + /10) was reported more frequently by **female** patients than male patients in both groups. -PTSD symptoms were reported by a much higher proportion of **females** (10/13; 76.9%) than males (5/19; 38.5%) in the ICU, whereas in the ward group these proportions were similar (22.9% of males and 24.2% of females). -In both groups, those reporting PTSD symptoms were **younger**.	-Fatigue (for gender) -PTSD (for age, gender)
(Hampshire et al., 2020)	Observational Cohort	Preprint	All	-The observed deficits varied in scale with respiratory symptom severity, related to positive biological verification of having had the virus even amongst milder cases, could not be explained by differences in age, education or other demographic and socioeconomic variables, remained in those who had no other residual symptoms and was of greater scale than common pre-existing conditions that are associated with virus susceptibility and cognitive problems	Cognitive deficits

(Klein et al., 2020)	Cross-sectional Survey	Preprint	All	-The **severity** of **olfactory change** is associated with its recovery time.	-Loss of taste -Loss of smell
(Mazza et al., 2020)	Observational Cohort	Peer-reviewed	Hospitalized	-Despite significantly lower levels of baseline inflammatory markers, **females suffered more for both anxiety and depression**. -Patients with a **positive previous psychiatric diagnosis** showed increased scores on most psychopathological measures, with similar baseline inflammation. -**Baseline systemic immune-inflammation index (SII)** was positively associated with scores of depression and anxiety at follow-up. -**Younger patients** showed higher levels of depression and sleep disturbances	Mental Health
(Morley, 2020)	Editorial	Peer-reviewed	All	-Elevated d-dimer levels are prognostic of poor lung function at 3 months; potential for chronic sub-clinical inflammation	Respiratory symptoms
(Pizzini et al., 2020)	Observational Cohort	Peer-reviewed	Hospitalized	-Low VitD levels at disease onset or at 8-week follow up were not related to persistent symptom burden, lung function impairment, ongoing inflammation	-Generic -Respiratory symptoms
(Sonnweber et al., 2020)	Observational Cohort	Peer-reviewed	All	-Hyperferritinemia was associated with decreased 6-minute walking distance (~200m yes to hyperferritinemia versus ~400m, p=0.011).	Mobility/function
(Taquet, Luciano, Geddes, & Harrison, 2020)	Observational Cohort	Peer-reviewed	All	-Having a **diagnosis of psychiatric disorder** in the year before the COVID-19 outbreak was associated with a 65% increased risk of COVID-19 (RR 1·65, 95% CI 1·59–1·71; p<0·0001) compared with a cohort matched for established physical risk factors for	Mental Health

				COVID-19 but without a psychiatric diagnosis.	
(Weerahandi et al., 2020)	Observational Cohort	Preprint	Hospitalized	-**Increased intensive care or mechanical ventilation**, likely explaining the higher prevalence of persistent dyspnea in our study.	Dyspnea

Research Question 3: What mechanisms are likely to be responsible for chronic symptoms?

Evidence from secondary and grey literature

Any secondary and grey literature that was identified that addressed this question included citations to primary literature or original research. This review limited its analysis and discussion to primary literature or original research (including preprints).

Evidence from the primary literature

Twenty-six articles touched upon the potential mechanisms responsible for the chronic post-COVID-19 symptoms for patients. Nineteen of these articles were more hypothetical on mechanisms, and their discussion centered on mechanisms responsible for acute symptomatology or acute-phase complications (Table 2b). Seven studies were more specific in their elaboration on potential mechanisms for long-term, chronic symptoms experienced post-COVID-19 (Table 2c). The implications for chronic symptoms in Table 2b studies is more implied, while the chronic implications of proposed mechanisms are explicit in Table 2c.

The broadly hypothetical discussions speak to mechanisms involving cardiovascular, neurological, immune, gastrointestinal, and multiple systems. Often these proposed mechanisms focused on acute complications due to organ injury (especially in cardiovascular, gastrointestinal, neurological and respiratory systems), which the reader then interpreted as causing long-term consequences including chronic symptoms for that organ or system at issue. These significant complications include encephalitis, necrotizing encephalopathy, fibrotic lung disease, Guillain-Barre syndrome, hemorrhages, hepatic injury, post-infectious neurological complications, and stroke.

Two major themes from Table 2b from the 19 articles with hypothetical mechanisms are (a) hyper-inflammatory responses or heightened immune responses to the virus were proposed as manifesting in acute complications and/or chronic symptoms; and (b) the neurological activity and implications of SARS-CoV-2 is the most commonly discussed and agreed upon in theory. Chronic neurological symptoms could result from nervous system invasion by SARS-CoV-2; cytokine storms that manifest into neural injury; brain expression of SARS-CoV-2-receptors and related proteins; various routes of brain entry (including olfactory route, blood-brain barrier, and infiltration of infected immune cells); indirect brain effects from systemic factors; and a hypercoaguable state.

Table 2b. Articles Detailing Highly Hypothetical, or More Acute, Mechanisms That May Contribute to Post-COVID-19 Chronic Symptoms.

System of Focus	High-Level Summary of Proposed Mechanisms	Implicated Chronic Symptoms[2]	# Studies	Citations of Studies Included
Cardiovascular System	• Describes potential metabolic, lipid and vascular mechanisms that increase risks of SARS-CoV-2 infection susceptibility and severity, related to the role in regulation of immunity and inflammation.	-Fatigue -Chest Pain -Tachycardia -Muscle weakness -Myalgia	1	(Becker, 2020)

[2] Many of these papers were high-level and hypothetical. Often, they did not elaborate the specific chronic symptoms that would follow from these hypothetical mechanisms. This list provides potential chronic symptoms that could be implicated, but we limit to ascribing only the most-frequently cited chronic symptoms.

Neurological System	• Potential mechanisms responsible for neurological symptoms in COVID-19 infection (acute and chronic): 1) Hyperinflammatory state in some patients ('cytokine storm') that manifests into neural injury (which can lead to other potential mechanisms listed herein) 2) Nervous system invasion by SARS-CoV-2 3) Brain expression of SARS-CoV-2-receptors and related proteins 4) Various routes of brain entry (olfactory route (cribiform plate and olfactory bulb), blood-brain barrier, infiltration of infected immune cells) 5) Indirect brain effects from systemic factors 6) Hypercoaguable state	-Loss of taste (ageusia) -Loss of smell (anosmia) -Fatigue -Sleep impairments -Cognitive impairment -Anxiety -Headache	13	(Ahmed et al., 2020; Amenta et al., 2020; Caronna et al., 2020; De Lorenzo et al., 2020; Fiani, Covarrubias, Desai, Sekhon, & Jarrah, 2020; Iadecola, Anrather, & Kamel, 2020; Mazza et al., 2020; Mohammadi, Moosaie, & Aarabi, 2020; Najjar et al., 2020; Taquet, Luciano, Geddes, & Harrison, 2020; Vonck et al., 2020; F. Wang, Kream, & Stefano, 2020; Whittaker, Anson, & Harky, 2020)
Immune System	• Describe the potential link between Western diets and obesity, chronic inflammation and alveolar damage in COVID-19 pathology. Suggest the inflammation will lead to long-term symptoms, but not specific on the type of symptom.	-Unclear	1	(Butler & Barrientos, 2020)
Gastrointestinal System	• Potential mechanisms to acute liver injury in COVID-19 infection, which could lead to chronic symptoms. Includes injury due to virus, treatment, or pre-existing hepatitis.	-GI upset	1	(Kunutsor & Laukkanen, 2020)
Multiple Systems	• Activated immune response to virus may lead to neurological complications (e.g. Guillain-Barre Syndrome), hematological complications (e.g. antiphospholipid syndrome), cardiovascular complications (e.g. haemorrhagic and ischaemic stroke), and respiratory complications (e.g. lung fibrosis). These complications can lead to chronic symptoms for	-Dyspnea -Fatigue -Cough -Headache -Loss of smell (anosmia) -Cognitive impairment -Loss of taste (ageusia)	3	(Daher et al., 2020; Leung et al., 2020; Lopez, Bell, Annaswamy, Juengst, & Ifejika, 2020)

	patients (e.g. fatigue, mobility issues, chest pain, and dyspnea).	-Muscle/joint pain (myalgia) -Sleep impairments -Chest pain -Tachycardia -GI upset -Muscle weakness -Anxiety		

Seven studies more clearly, or empirically, considered the mechanisms responsible for chronic symptoms post-COVID-19 focused on the immune, respiratory or multiple systems. There is, albeit limited, empirical evidence of patients with chronic symptoms having markers of prolonged inflammation or fibrotic abnormalities in their lungs. These studies are very limited due to sample size, lack of comparison, and lack of randomization. In a review by Morley (2020), a number of mechanistic possibilities for chronic COVID-19 are postulated. These symptoms include fatigue, cough, dyspnea, loss of smell and taste, muscle weakness and chest pain. Proposed mechanisms include post-viral syndrome, and neurological and immunological mechanisms proposed for acute complications.

Table 2c. Articles Specifically Approaching Potential Mechanisms Responsible for Post-COVID-19 Chronic Symptoms

System of Focus	High-Level Summary of Proposed Mechanisms	Implicated Chronic Symptoms[3]	# Studies	Citations of Studies Included
Immune System	• Quasi-histological evidence that neuro-inflammation is present in persons who recovered from COVID19, particularly inflammatory cells in the vitreous cavity. Persons who felt that their recovery was incomplete had more inflammatory cells, which likely suggests residual inflammation elsewhere. • Vitamin D levels not associated with COVID-19 disease outcomes. • Empirical study using diagnostic imaging of patients with unexplained, persisting symptoms more than 30 days from COVID-19 diagnosis had persistent vascular inflammation.	Unclear	4	(Bakhoum et al., 2020; Galeotti & Bayry, 2020; Pizzini et al., 2020; Sollini et al., 2020)
Multiple Systems	• Connects chronic symptoms of “long COVID” to proposed hypothetical mechanisms. Symptoms recognized include fatigue, cough, dyspnea, loss of taste and smell, muscle weakness, muscle and joint pain, headache, confusion, conjunctivitis,	-Dyspnea -Fatigue -Cough -Loss of smell (anosmia) -Cognitive impairment -Loss of taste (ageusia)	1	(Morley, 2020)

[3] Many of these papers were high-level and hypothetical. Often, they did not elaborate the specific chronic symptoms that would follow from these hypothetical mechanisms. This list provides potential chronic symptoms that could be implicated, but we limit to ascribing only the most-frequently cited chronic symptoms.

	chest pain, decreased mobility and falls. • Well-recognized that post-viral syndrome usually includes chronic fatigue, which can be aggravated by immobilization during hospitalization.	-Muscle/joint pain (myalgia) -Muscle weakness -Chest pain -Decreased Mobility -Conjunctivitis		
Respiratory System	• Hypothesize that fibrotic abnormalities of the lung due to COVID-19 will manifest in pulmonary abnormalities for patients. • Hyperferritinemia was present in 38% patients in the post-acute phase of COVID-19. This was associated with functional outcomes: a decreased walking distance.	-Dyspnea -Fatigue -Cough -Chest pain	2	(Raghu & Wilson, 2020; Sonnweber et al., 2020)

Evolving Evidence

There is a rapidly evolving evidence base on the long-term impact and symptomatology of COVID-19, as researchers from the earliest affected jurisdictions publish the findings from further along the COVID-19 trajectory. There will be a need to revisit the state of the literature and understanding on the chronic symptoms and rehabilitation needs of patients recovering from COVID-19. This reassessment may be appropriate in 3 or 6 months, as we near the 1-year mark since the calling of the global pandemic.

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Authorship and Committee Members

The review was written by Kiran Pohar Manhas, Ania Kania-Richmond, Ceara Cunningham, and Cyndie Koning. It was scientifically reviewed by Brandie Walker, Chester Ho (external reviewer), Kelly W. Burak (external reviewer), Frank MacMaster (external reviewer), and Kerry Alison McBrien (external reviewer). The full Scientific Advisory Group was involved in discussion and revision of the document: Braden Manns (co-chair), Lynora Saxinger (co-chair), John Conly, Alexander Doroshenko, Shelley Duggan, Nelson Lee, Elizabeth MacKay, Andrew McRae, Melissa Potestio, Jeremy Slobodan, James Talbot, Brandie Walker, and Nathan Zelyas.

COVID-19 Scientific Advisory Group
Rapid Evidence Report

Appendix

List of Abbreviations

AHS: Alberta Health Services

COVID-19: Coronavirus Disease-2019

ICU: Intensive Care Unit

KRS: Knowledge Resource Services

PTSD: Post-Traumatic Stress Disorder

SAG: Scientific Advisory Group

Expanded Evidence Synthesis

The following tables provide most of the detailed data extracted from the included studies.

Table 3a – Data extract from literature relevant to Research Questions 1 (After a diagnosis of COVID-19, which symptoms are commonly noted after 30 days, and what is the usual duration of these chronic symptoms?) and 2 (Which patients with COVID-19 are at highest risk of developing these chronic symptoms?

Author	Study Design	Type of COVID-19 patients	Details
(Amenta et al., 2020)	Review	All	• Review article on post-acute COVID-19 • Empirical studies included in this rapid evidence review. • Length of follow-up ranged from 3 to 12 weeks. • Suggests approach to classify different manifestations of post-acute COVID-19 syndrome
(Arnold et al., 2020)	Observational Cohort (n=163)	Hospitalized	• Consecutive hospitalized patients had outcomes recorded at baseline (admission), 28 days post, and invited for follow-up at 8-12 weeks. • Focus on symptoms, radiology and pulmonary function. • 74% reported at least one ongoing symptom since discharge home. Those hospitalized with moderate or severe illness, hand at least one symptom at 28-day follow-up (75% and 89%, respectively). • Severe disease patients more symptomatic in terms of breathlessness, fatigue, myalgia and insomnia. • Study reported on co-morbidity but did not speculate on risk factors for long-term symptoms.
(Bakhoum et al., 2020)	Observational Cohort (n=15)	All	• Use of spectral domain optical coherence tomography to detect presence of inflammatory cells in vitreous cavity in persons recovered from COVID-19. • Study completed on average 10.9 weeks from COVID-19 diagnosis (range 8.7-13 weeks) • Symptoms noted in patients included cough, headache, photophobia, lower extremity weakness/numbness, post-nasal drip, dry cough.

			• Persons who felt that their recovery was incomplete had more inflammatory cells present, which likely suggests residual inflammation elsewhere.
(Banda, Singh, Alser, & PRIETO-ALHAMBRA, 2020)	Observational Cohort (n=107)	All	• Mined and manually reviewed social media data from #longcovid and #chroniccovid to select tweets related to experiences of post-COVID Twitter users. Assessed number of symptoms per tweet and person. • The 10 most commonly mentioned symptoms were: malaise and fatigue (62%), dyspnea (19%), tachycardia/palpitations (13%), chest pain (13%), insomnia/sleep disorders (10%), cough (9%), headache (7%), and joint pain, fever, and unspecified pain by 6% each.
(Becker, 2020)	Review	All	• Review article. • Discussion mostly focused on "hypothetical" symptoms that could arise due to cardiovascular injury. Only included chronic symptoms where there was evidence to support. • Viral myocarditis (7-14 days post-COVID-19) was seen typically following more severe cases of COVID-19, and had chronic symptoms.
(Blair et al., n.d.)	Observational Cohort (n=118)	All	• Prospective outpatient cohort completed measurements for symptoms, SaO2, HR, and temp at intervals up to 4 weeks. • Up to 7 follow-up data collection points. • Participants returned to their usual health a median of 20 days (IQR, 37 13 to 38) from the symptom onset, and only 65.5% of respondents were at their usual health during the fourth week of illness. • Over 28 days, 10.9% presented to the emergency department and 7.6% required hospitalization. • Individuals at the same duration of illness had a 6.1 times increased adjusted odds of subsequent hospitalization per every percent decrease in home SaO2 (95% confidence interval [CI]: 1.41 to 31.23, p=0.02). • Baseline factors of age, sex, or comorbid conditions were not associated with a delay in return to health or to usual activities with unadjusted Cox proportional hazards regression (data not shown). Notably, while the majority 63.7% of participant had no symptoms or only had mild symptoms during the first week of illness a substantial proportion continued to have mild or moderate symptoms for over one month (Figure 3C-E). During the third and fourth week of illness, only 52.6% and 65.5% of respondents had returned to their usual health, respectively.
(Carfi, Bernabei, Landi, & Gemelli Against COVID-19 Post-Acute Care Study Group, 2020)	Observational Cohort (n=143)	Hospitalized	• Assess persistent symptoms in patients who were discharged from the hospital after recovery from COVID-19 via outpatient clinic. • Patients were offered a comprehensive medical assessment with detailed history and physical examination. Data on all clinical characteristics, including clinical and pharmacological history, lifestyle factors,

			vaccination status, and body measurements, were collected in a structured electronic data collection system. • Follow-up at 60.3 days (+/- 13.6 days). • Only 18 (12.6%) were completely free of any COVID-19–related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more. • None of the patients had fever or any signs or symptoms of acute illness. • Worsened quality of life was observed among 44.1% of patients. A high proportion of individuals still reported fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%).
(Caronna et al., 2020)	Observational Cohort (n=100)	All	• This is a prospective study, comparing clinical data and inflammatory biomarkers of COVID-19 patients with and without headache, recruited at the Emergency Room/admitted to hospital. • Authors compared baseline with 6-week follow-up to evaluate disease evolution. • After 6 weeks, of the 74 headache patients, 37.8% (28/74) still had headache. Those patients whose headache had stopped had a mean duration of the symptom of 15.4-11.1 days. Then, we analyzed patients with ongoing headache after 6 weeks, observing that 50% of them (14/28) had never suffered from recurrent headache before. • A total of 60.7% of patients (17/28) had daily constant headache. • Response to acute treatment was insufficient both at baseline and follow-up, without statistically significant differences at the two time-points (32.1% vs. 28.6%; p ¼ 0.701). • RISK: There were no statistically significant differences with regard to the demographic variables in patients that were not followed up.
(Carvalho-Schneider et al., 2020)	Observational Cohort (n=150)	All	• Aimed to describe the clinical evolution and predictors of symptom persistence during 2-month follow-up in adults with non-critical COVID-19. • Patients were followed up at 7 days, 30 days and 60 days. • At D30 and D60, patients reported symptoms including dyspnea, chest pain, flu-like symptoms (aches, runny nose), digestive disorders (diarrhea), weight loss, palpitations, arthralgia, and cutaneous signs. • The most frequent symptom reported at D30 and D60 was anosmia/ageusia. • RISK: Those with prolonged symptoms were significantly associated with age 40 to 60 years old, hospital admission at symptom onset, severe COVID-19, and dyspnea or abnormal auscultation.
(Cavalagli et al., 2020)	Case Report (n=1)	Hospitalized	• This single case report expands knowledge about clinical picture about post-acute cranial nerves impairment after SARS-CoV-2 disease. • In-depth case study on one patient who presented acquired weakness and dysphagia with clinical cranial

			nerves impairment of lingual, IX, X and XII after SARS-CoV-2 infection, without electrophysiological alterations. • Speech therapy assessment showed oropharyngeal dysphagia with poor management of airway secretions with consequent persistent bubbling voice.
(Cellai & O'Keefe, 2020)	Observational Cohort (n=496)	Non-hospitalized	• Aim: To identify patients with COVID-19 in a telemedicine clinic who requested ongoing follow-up calls 6 weeks after symptom onset and assess persistent symptoms in patient population. • We identified 51 (9.4%) as receiving calls >6 weeks after symptom onset and arrived at a total of 26 (4.8%) "prolonged cases." • Respiratory symptoms were most common in week 6, and reported in 23 patients (88.5%), most frequently cough, shortness of breath with exertion, sinus congestion, and chest tightness. Other common symptoms include fatigue (17 patients, 65%) and headache (13 patients, 50%). Less commonly reported, 9 patients (34.6%) had persistent gastrointestinal symptoms, 6 patients (23%) complained of palpitations, and 3 had persistent low-grade fevers. • Of note, 18 (69.2%) reported at least 4 concurrent symptoms. Patients with persistent symptoms entered the telemedicine clinic a median (range) of 9.5 (4–39) days after symptom onset and were followed by the telemedicine clinic for a median (range) of 38 (21–49) days. The time from symptom onset to discharge from the telemedicine clinic was a median (range) of 47.5 (42–80) days. At telemedicine discharge, 24 (92.3%) patients reported significant improvement in symptoms, with only 7 (26.9%) reporting that they were at baseline health (symptom free). • RISK: Asthma and chronic lung disease (prospectively coded at intake visit) appeared more frequently in the patients identified in the persistent symptom cohort for this study.
(Charlotte et al., 2020)	Observational Cohort (n=196)	Hospitalized	• Retrospective cohort study included all inpatients hospitalized with microbiologically confirmed COVID-19 between 1 March and 12 April 2020 in the public hospital network of a Swiss area (Fribourg). Demographic data, comorbidities and outcomes were recorded. Rate of potential hospital-acquired infection, outcomes 30 days after onset of symptoms and in-hospital mortality are reported. • At D30, 73 patients (63%) reported persistent symptoms. Asthenia (67%), respiratory symptoms (56%) and anosmia/dysgeusia (10%) were the most frequently reported symptoms.
(Cirulli et al., 2020)	Cross-sectional Survey (n=233)	All	• Report the analysis of 32 self-reported short and long-term symptoms in a general adult population cohort comprised of 233 COVID-19+ cases, 3,652 SARS-CoV-2-negative controls, and 17,474 non-tested individuals. • Follow-up at 30, 60 and 90 days.

			• 43.4% of COVID-19+ cases have symptoms lasting longer than 30 days, and 24.1% still have at least one symptom after 90 days. These numbers are higher for COVID-19+ cases who were initially more ill, 59.4% at 30 days and 40.6% at 90 days, but even for very mild and initially asymptomatic cases, 14.3% have complications persist for 30 days or longer. • In contrast, only 8.6% of participants from the general untested population develop new symptoms lasting longer than 30 days due to any illness during the same study period. The long-term symptoms most enriched in those with COVID-19 are anosmia, ageusia, difficulty concentrating, dyspnea, memory loss, confusion, headache, heart palpitations, chest pain, and pain with deep breaths, dizziness, and tachycardia. • RISK: We additionally observe that individuals who had an initial symptom of dyspnea are significantly more likely to develop long-term symptoms. • RISK: After including the total number of initial symptoms as a covariate in the analysis, only five factors maintained a nominal association (uncorrected $p<0.05$) with long-term symptoms in COVID-19+ cases: the initial symptoms of dyspnea and chest pain, and blood type A as well as blood type A+ (but not blood type A-, which is rarer) were associated with increased risk.
(Daher et al., 2020)	Observational Cohort (n=33)	Hospitalized	• Hospitalized COVID-19 patients not requiring mechanical ventilation were included and followed 6 weeks after discharge to an outpatient unit. Body plethysmography, lung diffusion capacity (DLco), blood gas analysis (ABG), 6-min walk test (6MWT), echocardiography, and laboratory tests were performed. Quality of life (QoL), depression, and anxiety were assessed using validated questionnaires. • Although patients in this cohort had some respiratory symptoms, they had no significant ventilatory limitations in the PFTs and only a mild reduction in diffusing capacity of the lungs for carbon monoxide. Other Symptoms @ follow-up include: Fever 1 (3%); Cough 11 (33%); Dyspnea 11 (33%); Fatigue 15 (45%); Tiredness 15 (45%); Rhinorrhea 4 (12%); Sore throat 3 (9%); Angina pectoris 6 (18%); Myalgia 5 (15%); Headache 5 (15%); Cognitive disorders – 6 (18%); Loss of Smell 4 (12%); Loss of Taste 3 (9%); Gastrointestinal symptoms 3 (9%); Diarrhea 3 (9%); Nausea 2 (6%); Stomach pains 1 (3%). According to PHQ-9 and GAD-7 questionnaires, patients mostly suffered from mild depression and anxiety
(De Lorenzo et al., 2020)	Observational Cohort (n=185)	Hospitalized	• Setup a COVID-19 follow-up outpatient clinic to longitudinally follow patients recovered from COVID-19. Here, we report a first assessment of the information gathered on COVID-19 sequelae and propose strategies to identify patients who may benefit from continued monitoring in Milan, Italy. To investigate the relevance of

			the follow-up visit, we created a composite dichotomous outcome variable, i.e. need of follow-up, which identified patients requiring medical advice after COVID-19 recovery. • Follow-up at 4 weeks • At follow-up evaluation, 54 (29.2%) patients had shortness of breath or were tachypnoeic. 116 (62.7%) patients were malnourished or at risk for malnutrition, and approximately one quarter of patients achieved MoCA scores compatible with cognitive impairment, despite no known history of cognitive disorders. • Psychiatric disturbances including anxiety, insomnia, or PTSD were observed in 83 (44.9%) patients. • The need of follow-up, defined as the presence at follow-up evaluation of at least one among RR >20 breaths/min, uncontrolled blood pressure requiring therapeutic change, moderate to very severe dyspnea, malnutrition, or new-onset cognitive impairment, was present in 109 (58.9%) patients. • RISK: Decreasing age, female gender and positive psychiatric history were significantly associated with the risk of developing PTSD after COVID-19. • RISK: Hospitalization, instead, emerged as protective factor.
(Denina et al., 2020)	Observational Cohort (n=25)	Subpopulation	• Evaluation based - set up clinic to do follow up of discharge pediatric patients; reporting on the data they collected. • Follow-up at 35 days. • No symptom: "all of our patients showed a clinical and complete laboratory recovery about a month after discharge, without manifestation of any COVID-19-related sequelae 4 months later."
(Galeotti & Bayry, 2020)	Editorial	Subpopulation	• Discusses pediatric inflammatory multi-systemic syndrome in children with COVID19. Detailed investigations of some of these cases, including a study of 17 patients in Paris and a retrospective study of 35 patients across twelve French and one Swiss medical centre. • Revealed that in addition to gastrointestinal symptoms, skin rashes, cervical lymphadenopathy, cheilitis and high levels of inflammatory markers, myocardial involvement was common. • The increased incidence of myocarditis highlights that patients with KD-COVID-19 are more severely ill and are often hospitalized in intensive care.
(Garrigues et al., 2020)	Observational Cohort (n=120)	Hospitalized	• To assess post-discharge persistent symptoms and health-related quality of life (HRQoL) of patients hospitalized in a COVID-19 ward unit more than 100 days after their admission. • Follow-up average was 15.8 weeks (110.9 days). • The most frequently reported persistent symptoms were fatigue (55%), dyspnea (42%), loss of memory (34%),

			concentration and sleep disorders (28% and 30.8%, respectively). • Loss of hair was reported by 24 (20%) patients, including 20 women and 4 men. • Thirty-five (29%) patients had an mMRC grade ≥2 ("Walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace"). • In both group, EQ-5D (mobility, self-care, pain, anxiety or depression, usual activity) was altered with a slight difference in pain in the ICU group. No statistical significance difference between the groups. • RISK: No difference in persistent symptoms between ICU and non-ICU/ward groups.
(Greenhalgh, Knight, A'Court, Buxton, & Husain, 2020)	Editorial	All	• Post-acute covid-19 symptoms vary widely. Even so-called mild covid-19 may be associated with long term symptoms, most commonly cough, low grade fever, and fatigue, all of which may relapse and remit. • Other reported symptoms include shortness of breath, chest pain, headaches, neurocognitive difficulties, muscle pains and weakness, gastrointestinal upset, rashes, metabolic disruption (such as poor control of diabetes), thromboembolic conditions, and depression and other mental health conditions. • Skin rashes can take many forms including vesicular, maculopapular, urticarial, or chilblain-like lesions on the extremities (so called COVID toe). • Around 10% of patients who have tested positive for SARS-CoV-2 virus remain unwell beyond three weeks.
(Halpin et al., 2020)	Cross-sectional Survey (n=100)	Hospitalized	• Used C19-YRS (Yorkshire Tool) • To examine the impact of COVID-19 on survivors discharged from hospital. This study reports the first systematic assessment (in the current literature) of post-discharge symptoms and rehabilitation needs in COVID-19 survivors after hospital discharge. • Extremely high levels of fatigue were reported. The severity of the impact of this fatigue was high, with a mean rating of 4.8 out of 10 across both groups. Moderate or severe fatigue (rated 4 + /10) was reported more frequently by female patients than male patients in both groups. • New or worsened breathlessness (when compared with pre-COVID illness) was a significant symptom even several weeks post-discharge, affecting over two-fifths of ward patients and two-thirds of ICU patients. • PTSD symptoms were reported by a much higher proportion of females (10/13; 76.9%) than males (5/19; 38.5%) in the ICU, whereas in the ward group these proportions were similar (22.9% of males and • 24.2% of females). In both groups, those reporting PTSD symptoms were younger. • Symptoms relating to communication, voice, swallow, and laryngeal sensitivity (including persistent cough) were

			more common in the ICU group (12.4%) than the ward group (5.9%). • Of the 22 ICU participants experiencing new problems in mobility, self-care or usual activities, 17 had new or worsened breathlessness and 19 had new fatigue. • RISK: Moderate or severe fatigue (rated 4 + /10) was reported more frequently by female patients than male patients in both groups. • RISK: PTSD symptoms were reported by a much higher proportion of females (10/13; 76.9%) than males (5/19; 38.5%) in the ICU, whereas in the ward group these proportions were similar (22.9% of males and 24.2% of females). • RISK: In both groups, those reporting PTSD symptoms were younger.
(Hampshire et al., 2020)	Observational Cohort (n=84,285)	All	• Aim: to examine the cognitive deficits of patients with suspected or confirmed COVID at the population level (and how this differs with respiratory symptom severity and hospitalization status). • RISK: The observed deficits varied in scale with respiratory symptom severity, related to positive biological verification of having had the virus even amongst milder cases, could not be explained by differences in age, education or other demographic and socioeconomic variables, remained in those who had no other residual symptoms and was of greater scale than common pre-existing conditions that are associated with virus susceptibility and cognitive problems.
(Klein et al., 2020)	Cross-sectional Survey (n=112)	All	• Aim: to address gaps in knowledge regarding the order of symptoms appearance and their durations in RT-PCR positive patients. • 6-week follow-up • Smell and taste changes were the longest-lasting symptoms (24.3 ± 22.9 days and 19.4 ± 19.1 (mean ± SD), respectively), with longer smell recovery correlated with smell change severity. • In one third of patients who reported cough, smell and taste changes, these symptoms persisted after recovery. • 36% of patients with smell change, 32% of patients with taste change, and 27% with dry or productive cough, still had these symptoms post recovery (defined as two consecutive negative RT-PCR-test results). • RISK: The severity of olfactory change is associated with its recovery time.
(Maxwell, 2020)	Review	All	• COVID-19 is not always a linear disease with an acute phase followed by recovery or a steady state rehabilitation. It can be cyclical disease, with symptoms moving round different body systems and fluctuating in severity. • There is a lack of understanding that people living with COVID-19 can suffer from a wide range of interconnected symptoms, and that even if not individually severe they

			can collectively leave people severely debilitated. This means many are relying on peer support through social media channels.
(Mazza et al., 2020)	Observational Cohort (n=402)	Hospitalized	• The present study aims to investigate the psychopathological impact of COVID-19 in survivors at one month follow up, also considering the effect of possible risk factors. • Follow-up 4 weeks. • A significant proportion of patients self-rated in the psychopathological range: 28% for PTSD, 31% for depression, 42% for anxiety, 20% for OC symptoms, and 40% for insomnia. • COVID-19 survivors presented a high prevalence of emergent psychiatric sequelae, with 55% of the sample presenting a pathological score for at least one disorder. • RISK: Despite significantly lower levels of baseline inflammatory markers, females suffered more for both anxiety and depression. • RISK: Patients with a positive previous psychiatric diagnosis showed increased scores on most psychopathological measures, with similar baseline inflammation. • RISK: Baseline systemic immune-inflammation index (SII) was positively associated with scores of depression and anxiety at follow-up. • RISK: Younger patients showed higher levels of depression and sleep disturbances.
(Miyake & Martin, 2020)	Observational Cohort	All	• Aim: To identify competing definitions of Covid-19 through quantitative and qualitative analyses of online Long COVID narratives in the UK; to map UK Long Haulers' experiences, emotions and practices as articulated online; to encourage further dialogue between patients, doctors and researchers to reassess existing definitions of Covid-19, with the collective aim of improving care and support for Long Haulers. • Analyzed social media data posts (n=144,637 posts). • There are 'officially' recognized symptoms that are used to (self)diagnose COVID-19: at the peak of the pandemic, the UK communicated these as a 'new and continuous cough' and 'high fever'; as from 18 May,16 'loss or change to your sense of smell or taste' was also included in the criteria, as well as other secondary symptoms (Flu-like with no fever; Flu-like with fever; Gastrointestinal; Fatigue (severe level one); Confusion (severe level two); Abdominal and respiratory (severe level three). • Long COVID sufferers report a whole other range of symptoms which do not officially fall under the Covid-19 criteria, something that has also been specifically observed and highlighted in the Covid-19 'Long Hauler' Symptoms Survey Report.

(Miyazato et al., 2020)	Cross-sectional Survey (n=63)	All	• To investigate the duration of persistent symptoms and late-onset symptoms including alopecia in patients discharged from NCGM after recovery from COVID-19. • Structured 1:1 interviews. • Follow-up 4-22 weeks post-discharge. • Distinguished between prolonged symptoms (6) at 60 and 120 days after symptom onset, and late onset symptoms (anosomia= smell (n=2)); alopecia (n=14), which started 30-92 days after symptom onset; see symptom table for full details on symptoms, proportion and duration.
(Morley, 2020)	Editorial	All	• RISK: Elevated d-dimer levels are prognostic of poor lung function at 3 months; potential for chronic sub-clinical inflammation.
(O'Keefe Tong, D. C., & O'Keefe, G. A. D, 2020)	Observational Cohort (n=273)	Non-hospitalized	• Follow-up 4 weeks • We hypothesized that risk factors for covid-19 complications severity (demographics, comorbidities, symptom severity) would predict symptom duration. • Symptoms were groups into systems: upper respiratory (cough, congestion, sore throat, loss of smell or taste), systemic (body aches, chills, dizziness, headache, joint pain), lower respiratory (shortness of breath with exertion, shortness of breath at rest, chest tightness) and gastrointestinal (nausea, abdominal pain, and diarrhea).
(Pizzini et al., 2020)	Observational Cohort (n=109)	Hospitalized	• Aim: Investigate association of VitD status to COVID-19 disease presentation. • 8-week follow-up • RISK: Low VitD levels at disease onset or at 8-week follow up were not related to persistent symptom burden, lung function impairment, and ongoing inflammation.
(Rogliani et al., 2020)	Observational Cohort (n=27)	Hospitalized	• Aim: Assess the real risk of developing post-COVID-19 pulmonary fibrosis. • Follow-up 5-7 weeks • This study provides the preliminary evidence that in hospitalized patients with prevalently mild-to-moderate forms of COVID-19 pulmonary opacity was completely recovered at follow-up, with no evidence of any fibrotic abnormality. Interestingly, at follow-up also lung function and exercise capacity were in the normal range. • These findings suggest that these patients are not at risk of developing post-COVID-19 pulmonary fibrosis. However, also considering that abnormal pulmonary function was detected in COVID-19 patients at time of hospital discharge [10], the results of this study have to be confirmed in larger and longer studies, and verified also in patients with severe COVID-19.
(Savarraj et al., 2020)	Observational Cohort (n=48)	Hospitalized	• Aim: To characterize long-term neurologic outcomes (functional, cognitive, and psychiatric symptoms) after COVID-19 in a cohort of hospitalized patients who were assessed at 3-months. • Follow-up 12 weeks • Main finding is that 71% of the patients still experienced neurological symptoms at 3 months

			• The most common symptoms being fatigue (42%) and PTSD (29%), pain symptoms (64%), and cognitive symptoms (12%).
(Sonnweber et al., 2020)	Observational Cohort (n=109)	All	• Aim: To analyze for persisting alterations of iron metabolism in survivors of COVID-19. • Follow-up at 8.5 weeks (average). • 60 days after disease onset, 30% of subjects still presented with iron deficiency and 9% had anemia, mostly categorized as anemia of inflammation. • RISK: Anemia was found in ten subjects (9.2%) and was more frequent in males (12%) than females (5%). Disease severity strongly correlated with the prevalence of anemia, as 90% of anemic patients previously had severe to critical COVID-19.
(Sudre et al., 2020)	Observational Cohort (n=4182)	All	• COVID 19 Symptom Study app. app, which collects data on personal characteristics and through prospective logging of symptoms, was launched in the UK, the US and Sweden between 24th March (UK) and 30th 331 April (Sweden), and rapidly reached over 4 million users. This study focuses on 4182 users who reported testing positive to SARS-CoV2 by PCR swab test and had a disease onset between 25th March 2020 and 30th June 2020, for whom onset date matched with date of test and duration of symptoms could be estimated. • Follow-up 4 weeks. • Fatigue (97.7%) and headache (91.2%) were the most reported symptoms in those with Long- COVID, followed by anosmia and lower respiratory symptoms. Notably, while fatigue was reported continuously, other symptoms such as headache are reported intermittently. Cardiac symptoms (palpitations, tachycardia) were over-represented in the LC28 112 group (6.1%) compared to in short-COVID (0.5%) ($p<0.0005$) as were concentration or memory issues (4.1% vs 0.2%) ($p<0.0005$), tinnitus and earache (3.6% vs 0.2% $p<0.0005$) and peripheral neuropathy symptoms (pins and needles and numbness) (2% vs 0.5%) ($p=0.004$). Most of these symptoms were reported for the first time 3-4 weeks post symptom onset.
(Taquet et al., 2020)	Observational Cohort (n=62,354)	All	• QUESTION: Whether a diagnosis of COVID-19 (compared with other health events) was associated with increased rates of subsequent psychiatric diagnoses, and whether patients with a history of psychiatric illness are at a higher risk of being diagnosed with COVID-19. • RISK: Having a diagnosis of psychiatric disorder in the year before the COVID-19 outbreak was associated with a 65% increased risk of COVID-19 (RR 1·65, 95% CI 1·59–1·71; $p<0·0001$) compared with a cohort matched for established physical risk factors for COVID-19 but without a psychiatric diagnosis.
(Tenforde et al., 2020)	Cross-sectional	Non-hospitalized	• Aim: To characterize return to baseline health among outpatients with milder COVID-19 illness • Follow-up **14-21 days.**

	Survey (n=292)		• Among the 274 symptomatic outpatients, the median number of symptoms was seven of 17 listed in the interview tool (IQR = 5–10), with fatigue (71%), cough (61%), and headache (61%) those most commonly reported. • Among respondents who reported fever and chills on the day of testing, these resolved in 97% and 96% of respondents, respectively. • Symptoms least likely to have resolved included cough (not resolved in 43% [71 of 166]) and fatigue (not resolved in 35% [68 of 192]); among 90 who reported shortness of breath at the time of testing, this symptom had not resolved in 26 (29%). • The median interval to symptom resolution among those who reported individual symptoms at the time of testing but not at the time of the interview ranged from 4 to 8 days from the test date, with the longest intervals reported for loss of smell (median = 8 days; IQR = 5–10.5 days) and loss of taste (median = 8 days; IQR = 4–10 days). • Among respondents who reported returning to their usual state of health, 34% (59 of 175) still reported one or more of the 17 queried COVID-related symptoms at the time of the interview.
(X. Wang et al., 2020)	Observational Cohort (n=131)	Hospitalized	• Aim: To investigate clinical outcomes, distribution of quarantine locations, and the infection status of the contacts of COVID-19 patients after discharge (up to 4 weeks). • Follow-up weekly to 4 weeks. • Observational follow up disclosed that during the first and the second week after discharge, 63 (48.09%) patients had one or more symptoms including cough (31.3%), fatigue (5.34%), expectoration (0.76%), chest tightness (6.11%), chest pain (3.05%), palpitation (2.29%), pharyngeal pain (1.53%), nausea (1.53%), inappetence (2.29%),vomiting (0.76%), diarrhea (0.76%), myalgia (0.76%) and rhinorrhea (0.76%). • Fever (8.4%), dyspnea (7.63%) and headache (3.82%) were newly occurred. In the third and the fourth week after discharge, only 18 (13.74%) patients had one or more symptoms with the incidence of cough (9.16%), chest tightness (0.76%), dyspnea (1.53%), pharyngeal pain (1.53%) and nausea (0.76%) (Table 2). • There was no statistical difference in the percentage of each symptom between severe and non-severe patients.
(Weerahandi et al., 2020)	Observational Cohort (n=152)	Hospitalized	• Aim: to characterize overall health status and the physical and mental health of patients discharged home after severe COVID-19 (up to 6.5 weeks). • Follow-up average 6.5 weeks. • At the time of survey, a total of 113 (74.3%) participants reported some shortness of breath (median score 3 out of 10, IQR 0-5), compared to only 47 (30.9%) pre-COVID-19 infection (0, IQR 0-1), $p<0.001$.

			• The PROMIS® Global Health-10 instrument scores indicated worse general health after COVID-19 illness (3 out of 5, IQR 2-4) compared to baseline (4, IQR 3-5). Before COVID-19, participants' summary t-scores in both the physical health and mental health domains were slightly above the United States mean of 50 (54.3, standard deviation 9.3; 54.3 SD 7.8, respectively). One month after COVID-19 infection, both scores were significantly lower (physical health: 43.8, SD 9.3; mental health 47.3, SD 9.3; p<0.001 for both). Patients also reported worsened ability to carry out social activities post COVID-19. • RISK: This cohort of patients experienced increased intensive care or mechanical ventilation, likely explaining the higher prevalence of persistent dyspnea in our study.
(Zhao et al., 2020)	Observational Cohort (n=55)	Hospitalized	• Aim: To investigate the relationship between clinical characteristics and pulmonary function or CT scores. • 12-week follow-up • At the 3 month follow up, presenting symptoms included: GI symptoms (30.91%); headache (18.18%); fatigue (16.36%); dyspnea (upon exertion) (14.55%); cough and sputum (1.81%); persistent decrease in sense of taste (4%).

Table for Research Question 3 – What mechanisms are likely to be responsible for chronic symptoms?

Table 3b. Articles Detailing Highly Hypothetical Mechanisms Responsible for Post-COVID-19 Chronic Symptoms.

System of Focus	High-Level Summary of Proposed Mechanisms	# Studies	Citations of Studies Included
Cardiovascular System	• Describes potential metabolic, lipid and vascular mechanisms that increase risks of SARS-CoV-2 infection susceptibility, severity of COVID-19 infection and organ damage, and related long-term recovery. Each relate to the role in regulation of immunity and inflammation. Vascular mechanisms may relate to diffuse alveolar damage.	1	(Becker, 2020)
Neurological System	• Post-ICU syndrome might contribute to patients with post-acute COVID-19 symptoms whose hospitalization included ICU care. • Potential mechanisms responsible for neurological symptoms in COVID-19 infection (acute and chronic): 1) Hyperinflammatory state in some patients ('cytokine storm') that manifests into neural injury (which can lead to other potential mechanisms listed herein) 2) Nervous system invasion by SARS-CoV-2 3) Brain expression of SARS-CoV-2-receptors and related proteins	13	(Ahmed et al., 2020; Amenta et al., 2020; Caronna et al., 2020; De Lorenzo et al., 2020; Fiani, Covarrubias, Desai, Sekhon, & Jarrah, 2020; Iadecola, Anrather, & Kamel, 2020; Mazza et al., 2020; Mohammadi, Moosaie, & Aarabi, 2020; Najjar et al., 2020; Taquet, Luciano, Geddes, & Harrison,

	4) Various routes of brain entry (olfactory route (cribiform plate and olfactory bulb), blood-brain barrier, infiltration of infected immune cells) 5) Indirect brain effects from systemic factors 6) Hypercoaguable state • Neurological disturbances impact sleep, senses, pain sensitivity, and energy.		2020; Vonck et al., 2020; F. Wang, Kream, & Stefano, 2020; Whittaker, Anson, & Harky, 2020)
Immune System	• Describe the potential link between Western diets and obesity, chronic activation of the innate immune system, as well as lung tissue inflammation and alveolar damage in COVID-19 pathology. • Not all human studies • Hypothesizing from non-COVID-19 literature.	1	(Butler & Barrientos, 2020)
Gastrointestinal System	• Potential mechanisms to acute liver injury in COVID-19 infection, which could lead to chronic symptoms. These potential mechanisms include: 1) drug-induced hepatic injury during treatment 2) direct injury due to COVID-19 hepatitis 3) COVID-19 induced myositis 4) biding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) positive rich cholangiocytes causing liver damage 5) hepatic congestion from mechanical ventilation 6) aggravation of pre-existing viral heptatis	1	(Kunutsor & Laukkanen, 2020)
Multiple Systems	• While cardiobiological biological mechanisms are less clear, neurological disturbances noted to impact sleep, senses, pain sensitivity, and energy. • Activated immune response to virus may lead to neurological complications (e.g. Guillain-Barre Syndrome), hematological complications (e.g. antiphospholipid syndrome), cardiovascular complications (e.g. haemorrhagic and ischaemic stroke), and respiratory complications (e.g. lung fibrosis). These complications can lead to chronic symptoms for patients (e.g. fatigue, mobility issues, chest pain, and dyspnea).	3	(Daher et al., 2020; Leung et al., 2020; Lopez, Bell, Annaswamy, Juengst, & Ifejika, 2020)

Table 3c. Articles Specifically Approaching Potential Mechanisms Responsible for Post-COVID-19 Chronic Symptoms

System of Focus	High-Level Summary of Proposed Mechanisms	# Studies	Citations of Studies Included
Immune System	• Quasi-histological evidence that neuroinflammation is present in persons who recovered from COVID19, particularly inflammatory cells in the vitreous cavity. Persons who felt that their recovery was incomplete had more inflammatory cells, which likely suggests residual inflammation elsewhere. • Specific to chronic symptoms, two possible mechanisms:	4	(Bakhoum et al., 2020; Galeotti & Bayry, 2020; Pizzini et al., 2020; Sollini et al., 2020)

	1) SARS-CoV-2 acts as direct trigger of autoimmune and/or autoinflammatory conditions 2) Immune responses following SARS-CoV-2 prompt other environmental insults. • Vitamin D levels show deficiency in COVID-19 patients, but not associated with COVID-19 disease outcomes. • Empirical study using diagnostic imaging of patients with unexplained, persisting symptoms more than 30 days from COVID-19 diagnosis revealed significantly higher target-to-blood pool ratios in three vascular regions, which indicate persistent vascular inflammation.		
Multiple Systems	• Connects chronic symptoms of "long COVID" to proposed hypothetical mechanisms. Symptoms recognized include fatigue, cough, dyspnea, loss of taste and smell, muscle weakness, muscle and joint pain, headache, confusion, conjunctivitis, chest pain, decreased mobility and falls. • Well-recognized that post-viral syndrome usually includes chronic fatigue, which can be aggravated by immobilization during hospitalization. • Coronavirus can invade myocardial cells and cause destruction of heart muscle. • Elevated D-dimer levels are prognostic of poor lung function. • Discusses neurological mechanisms due to micro-structural changes in brain post-COVID-19.	1	(Morley, 2020)
Respiratory System	• Hypothesize that fibrotic abnormalities of the lung due to COVID-19 will manifest in pulmonary abnormalities for patients, but that those with pre-existing lung disease will experience severity of COVID-19 disease concomitant to severity of the pre-existing lung disease. • Hyperferritinemia was present in 38% patients in the post-acute phase of COVID-19. This was associated with functional outcomes: a decreased walking distance. This may contribute to end-organ damage in COVID-19 and chronic symptoms therein.	2	(Raghu & Wilson, 2020; Sonnweber et al., 2020)

Methods

Literature Search

A literature search was conducted by Nicole Loroff from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published from 2020 and included: Ovid MEDLINE® and In-Process & Other Non-Indexed Citations and Daily, CINAHL, PubMed, TRIP Pro, Google Scholar, medRxiv, bioRxiv, LitCOVID, WHO Global Research on COVID-19 (database), Centre for Evidence Based Medicine (CEBM), and CADTH COVID-19 Evidence Portal. Briefly, the search strategy involved combinations of keywords and subject headings including:

- "COVID-19" OR coronavirus OR SARS-CoV-2 OR "severe acute respiratory syndrome cov 2" OR SARS-Cov-2019

- Long Term Adverse Effects OR Symptom Flare Up OR symptom* OR complicat* OR consequence* OR outcome* OR effect* OR manifest* OR sequela*
- Post-covid* OR discharge* OR post-discharge* OR post-acute OR post-hospitali?ation OR aftercare OR follow-up
- Patholog* OR mechanism* OR risk* OR predispose*
- Longitudinal study OR longitudinal studies OR follow-up study OR follow-up studies
- (Long covid OR longcovid* OR long hauler* OR longhauler*) AND (covid-19 OR coronavirus OR SARS-CoV-2)

The search strategy included these terms, complemented by citation tracking and snowball searching including resources noted by the review writers and reviewers. Where possible, PowerPoint presentations were hand-searched and the published articles that were cited, not the presentations themselves, were included. The search was limited to English articles published 2020-current. Articles were not excluded based on population.

Articles identified by KRS in their search were initially screened by title against the inclusion/exclusion criteria listed in Table 4a below.165 articles were identified by KRS with references and abstracts provided for further review. 111 were excluded from the review in accordance with the inclusion/exclusion criteria stated below. Title/abstract screening and full-text screening were completed by two independent reviewers, and discrepancies were determined by discussion and consensus. The final number of included articles was 54 published articles, 40 of which were peer-reviewed and 14 were pre-prints.

Table 4a. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
- COVID-19 - Post-diagnosis (and/or post-discharge) - Long-term (or chronic) symptoms or outcomes (i.e. post-diagnosis) - Risk factors for long-term (or chronic) symptoms - Mechanism for long-term (chronic) symptoms - All COVID-19 positive populations (i.e. no limit on age, hospitalization) - 2020 to present (focus on COVID-19 outbreak) - All research methods including empirical, review, case report, editorial - English language only - All publication status: pre-print, ahead of print, accepted, published, grey literature - Any jurisdiction	- Article is not from a credible source (author or publisher) - Non-COVID-19 conditions (e.g. SARS, MERS) - Focused on solely on acute symptoms or on mechanisms leading to acute symptoms. Acute was framed as during the infectious period or acuity of experience, not by number of days post-diagnosis - Focused on the complications or conditions that may follow SARS-CoV-2 infection - Presented data/evidence is not sufficient to address the research questions

Critical Evaluation of the Evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non-peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available.

Table 4b below is a narrative summary of the body of evidence included in this review. The categories, format, and suggested information for inclusion were adapted from the Oxford Centre for Evidence-Based Medicine, the

Cochrane Library, and the AGREE Trust (Brouwers et al., 2010; Urwin, Gavinder, & Graziadio, 2020; Viswanathan et al., 2012; Wynants et al., 2020).

Table 4b. Narrative overview of the literature included in this review.

	Description
Volume	The articles examined in this narrative review included 4 systematic reviews, 11 reviews (without described methodology), 1 case-control study, 26 prospective observational cohort studies (11 were pre-review), 5 cross-sectional surveys (2 were pre-review), 1 case report (which was pre-review), and 6 editorials. The jurisdictional distribution of the studies was as follows: USA (n=19), UK (n=9), Italy (n=7), International teams (n=4), China (n=3), France (n=3), Austria (n=2), and one each from Belgium, Finland, Iran, Israel, Japan, Spain, and Switzerland. No grey literature was included in this review.
Quality	The quality of the studies was critiqued using the adapted MMAT. The four systematic reviews were generally of high quality, having undergone peer review and detailing clear research questions accompanied by relevant data. In contrast, the 11 review articles were of low to moderate quality. These articles were in stark contrast to the systematic reviews, with many lacking a clear research question (70%). Most of these review articles did not describe the methodology in collecting the data that formulated the review, and data relevance was questioned on most studies (70%). The 26 observational cohorts were of moderate to high quality. While 11 were preprints, the clarity of question and relevance of data were present in all but a minority of these articles (~15%, with 4 or 3 articles not meeting that criteria, respectively). While the MMAT permitted relatively high-quality scores, many of the observational cohort studies lacked a comparator group and relied on self-report. Their noted quality may not withstand closer scrutiny. For 24% of the studies with more than 1 follow-up data collection point, there is risk of attrition bias. While not the majority of studies, this directly influences the ability to inform the Research Question 1 interest in duration of chronic symptoms. The 5 cross-sectional survey studies were of moderate to high quality. Three of the 5 were peer-reviewed; four had clear questions; and four had relevant data. These cross-sectional surveys have methodological weaknesses inherent, particularly a reliance on subjective self-report. The sample size of the observational cohorts and surveys were noteworthy and wide ranging. The maximum participant sample size was 84285, while it is unclear how many participants took part in the Banda et al. (2020) study wherein 144,600 social media posts were analyzed. Due to outliers, the mean (SD) sample size is unclear at 4837.2 (+/- 18194.0). The median and mode sample size for the studies were 119 and 100, respectively. This suggests robust sample sizes, although no clarity on the randomization or selection of the samples. Finally, while the case-control and case report studies were of high quality according to the modified MMAT, the latter is of limited generalizability and the former lacks randomization and clarity on case matching.

Applicability	There are no Canadian (or Albertan) studies included in this review. The included primary studies were limited to the USA, Europe, and Asia. There is an over-representation of USA studies, which have had a significantly different experience in severity and mortality related to COVID-19, different COVID-19 response, and have a distinct healthcare system. The next most frequent studies from the UK and Italy have also experienced severe outbreaks, while there is more similarity in healthcare system infrastructure. This raises questions on the applicability to Alberta. Nevertheless, with respect to the Research Questions, the moderate-to-high-quality observational cohort and cross-sectional survey studies provide evidence directly applicable to the Research Questions 1 and 2 on chronic post-COVID-19 symptom nature and duration. These studies also touch upon Research Question 3 related to potential mechanisms responsible for the chronic symptoms. However, study evidence directly applicable to Research Question 3 also heavily relies on the lower-quality review articles.
Consistency	For Research Questions 1 and 2, there was consistency in some areas, particularly the most common chronic symptoms and a few of the key risk factors. However, in other areas, the findings from one study were unique and un-corroborated and should thus be considered with caution. For Research Question 3, there was relative consistency across the articles on the types and facets of the hypothesized mechanisms proposed as responsible for the chronic, post-COVID-19 symptoms.

Table 4c. Critical Quality Appraisal of Included Studies

Author	Study Design	Type of Article	Is there clear research question?	Data appropriate to research question?	Type of COVID patients
(Ahmed et al., 2020)	Systematic Review	Peer-reviewed	Yes	Yes	All
(Amenta et al., 2020)	Review	Peer-reviewed	No	No	All
(Arnold et al., 2020)	Observational Cohort	Preprint	Yes	Yes	Hospitalized
(Bakhoum et al., 2020)	Observational Cohort	Preprint	Yes	Yes	All
(Banda, Singh, Alser, & PRIETO-ALHAMBRA, 2020)	Observational Cohort	Preprint	Yes	Yes	All
(Becker, 2020)	Review	Peer-reviewed	Yes	Yes	All
(Blair et al., n.d.)	Observational Cohort	Preprint	Yes	Yes	All
(Butler & Barrientos, 2020)	Editorial	Peer-reviewed	No	No	All
(Carfi, Bernabei, Landi, & Gemelli Against COVID-19	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized

Post-Acute Care Study Group, 2020)					
(Caronna et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	All
(Carvalho-Schneider et al., 2020)	Observational Cohort	Preprint	Yes	Yes	All
(Cavalagli et al., 2020)	Case Report	Preprint	Yes	Yes	Hospitalized
(Cellai & O'Keefe, 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Non-hospitalized
(Charlotte et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Cirulli et al., 2020)	Cross-sectional Survey	Preprint	Yes	Yes	All
(Daher et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(De Lorenzo et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Del Rio, Collins, & Malani, 2020)	Review	Peer-reviewed	No	Yes	All
(Denina et al., 2020)	Observational Cohort	Peer-reviewed	No	No	Subpopulation
(Fiani et al., 2020)	Review	Peer-reviewed	Yes	No	All
(Galeotti & Bayry, 2020)	Editorial	Peer-reviewed	No	No	Subpopulation
(Garrigues et al., 2020)	Observational Cohort	Peer-reviewed	No	Yes	Hospitalized
(Greenhalgh, Knight, A'Court, Buxton, & Husain, 2020)	Editorial	Peer-reviewed	No	No	All
(Halpin et al., 2020)	Cross-sectional Survey	Peer-reviewed	Yes	Yes	Hospitalized
(Hampshire et al., 2020)	Observational Cohort	Preprint	Yes	Yes	All
(Iadecola et al., 2020)	Review	Peer-reviewed	Yes	No	All
(Klein et al., 2020)	Cross-sectional Survey	Preprint	No	No	All
(Kunutsor & Laukkanen, 2020)	Editorial	Peer-reviewed	Yes	Yes	All
(Leung et al., 2020)	Systematic Review	Peer-reviewed	Yes	Yes	All
(Lopez et al., 2020)	Review	Peer-reviewed	Yes	No	All
(Maxwell, 2020)	Review	Peer-reviewed	No	No	All
(Mazza et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Miyake & Martin, 2020)	Observational Cohort	Preprint	Yes	Yes	All

(Miyazato et al., 2020)	Cross-sectional Survey	Peer-reviewed	Yes	Yes	All
(Mohammadi et al., 2020)	Review	Peer-reviewed	Yes	No	All
(Morley, 2020)	Editorial	Peer-reviewed	No	No	All
(Najjar et al., 2020)	Review	Peer-reviewed	Yes	No	All
(O'Keefe Tong, D. C., & O'Keefe, G. A. D, 2020)	Observational Cohort	Peer-reviewed	Yes	No	Non-hospitalized
(Pizzini et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Raghu & Wilson, 2020)	Editorial	Peer-reviewed	No	No	All
(Rogliani et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Savarraj et al., 2020)	Observational Cohort	Preprint	No	No	Hospitalized
(Sollini et al., 2020)	Case-Control	Peer-reviewed	Yes	Yes	All
(Sonnweber et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	All
(Sudre et al., 2020)	Observational Cohort	Preprint	No	Yes	All
(Taquet et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	All
(Tenforde et al., 2020)	Cross-sectional Survey	Peer-reviewed	Yes	Yes	Non-hospitalized
(Vonck et al., 2020)	Review	Peer-reviewed	Yes	No	All
(F. Wang et al., 2020)	Review	Peer-reviewed	Yes	No	All
(X. Wang et al., 2020)	Observational Cohort	Preprint	Yes	Yes	Hospitalized
(Weerahandi et al., 2020)	Observational Cohort	Preprint	Yes	Yes	Hospitalized
(Whittaker et al., 2020)	Systematic Review	Peer-reviewed	Yes	Yes	All
(Zhao et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Zubair et al., 2020)	Systematic Review	Peer-reviewed	Yes	Yes	All

Search Strategy

Search Strategy

Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations and Daily 1946 to November 03, 2020

#	Searches	Results
1	exp Coronavirus/ or exp Coronavirus Infections/ or (covid or coronaviru* or corona viru* or ncov* or n-cov* or novel cov* or COVID-19 or COVID19 or COVID-2019 or COVID2019 or SARS-CoV-2 or SARSCoV-2 or	69722

	SARSCoV2 or SARSCoV19 or SARS-Cov-19 or SARSCov-19 or SARSCoV2019 or SARS-Cov-2019 or SARSCov-2019 or "severe acute respiratory syndrome cov 2" or 2019 ncov or 2019ncov).tw,kf.	
2	limit 1 to english language	66436
3	limit 2 to yr="2020 -Current"	49480
4	Long Term Adverse Effects/ or Recurrence/ or Symptom Flare Up/ or Symptom Assessment/	191000
5	((long-term or longterm or longitudinal* or chronic* or persist* or prolong* or ongoing or recurr* or lasting or long-lasting* or linger*) adj3 (symptom* or complicat* or consequence* or outcome* or effect* or manifest* or sequela*)).tw,kf.	361241
6	4 or 5	536001
7	3 and 6	742
8	Patient Discharge/ or exp Aftercare/ or Time Factors/ or Long-Term Care/ or Subacute Care/	1424418
9	(post-covid* or discharge* or post-discharge* or postdischarge* or post-acute or postacute or post-hospitali?ation or after hospitali?ation or recover* or aftercare or after care or survivor* or follow-up or duration or frequency or rehabilitat*).tw,kf.	3177887
10	8 or 9	4234711
11	7 and 10	239
12	exp Pathology/ or Risk Factors/	886026
13	(patholog* or mechanism* or risk* or predispos*).tw,kf.	5052951
14	12 or 13	5320157
15	7 and 14	311
16	exp "Signs and Symptoms"/	2088048
17	3 and 6 and 16	70
18	Longitudinal Studies/ or Follow-Up Studies/	773091
19	(longitudinal study or longitudinal studies or follow-up study or follow-up studies).tw,kf.	126939
20	18 or 19	826060
21	(symptom* or complicat* or consequence* or effect* or manifest* or sequela*).tw,kf.	9054248
22	3 and 20 and 21	230
22	(long covid* or longcovid* or long hauler* or long hauler*).tw,kf.	15
23	sequela*.tw,kf.	68653
24	3 and 23	169

CINAHL

#	Searches	Results
1	((MH "Coronavirus+") or coronavirus* or covid) AND (wuhan or beijing or shanghai)) OR (("novel coronavirus*" AND ((MH "China") or China)) OR TI coronavirus* OR (((MH pneumonia) or pneumonia) AND Wuhan) OR ((D614G or "Covid-19" or Covid19 or "2019-nCoV" or "SARS-CoV-2" or (MH Coronavirus Infections))))) AND ((MH "Coronavirus+") or coronavirus* or covid) AND (wuhan or beijing or shanghai)) OR (("novel coronavirus*" AND ((MH "China") or China)) OR TI coronavirus* OR (((MH pneumonia) or pneumonia) AND Wuhan) OR ((D614G or "Covid-19" or Covid19 or "2019-nCoV" or "SARS-CoV-2" or (MH Coronavirus Infections))))) AND DT 20191201-20300101)	26028
2	limit 1 to english language	25489
3	limit 2 to yr="2020 -Current"	25476
4	(MH “Recurrence”)	49130
5	TI ((long-term or longterm or longitudinal* or chronic* or persist* or prolong* or ongoing or recurr* or lasting or long-lasting* or linger*) n3 (symptom* or complicat* or consequence* or outcome* or effect* or manifest* or sequela*)) OR AB ((long-term or longterm or longitudinal* or chronic* or persist* or prolong* or ongoing or recurr* or lasting or long-lasting* or linger*) n3 (symptom* or complicat* or consequence* or outcome* or effect* or manifest* or sequela*))	100694
6	4 OR 5	144885

7	3 AND 6	234
8	(MH "Prospective Studies+")	453995
9	TI ((longitudinal study or longitudinal studies or follow-up study or follow-up studies)) OR AB ((longitudinal study or longitudinal studies or follow-up study or follow-up studies))	43202
10	8 OR 9	469736
11	TI ((symptom* or complicat* or consequence* or outcome* or effect* or manifest* or sequela*)) OR AB ((symptom* or complicat* or consequence* or outcome* or effect* or manifest* or sequela*))	1921345
12	3 AND 10 AND 11	304
13	TI ((long covid* or longcovid* or long hauler* or long hauler*)) OR AB ((long covid* or longcovid* or long hauler* or long hauler*))	8
14	TI sequela* OR AB sequela*	13760
15	3 AND 14	58

PubMed

#	Searches	Results
1	((Coronavirus[mh:noexp] OR Betacoronavirus[mh:noexp] OR Coronavirus Infections[mh:noexp]) AND (Disease Outbreaks[mh:noexp] OR Epidemics[mh:noexp] OR Pandemics[mh])) OR COVID-19 diagnostic testing [Supplementary Concept] OR COVID-19 drug treatment [Supplementary Concept] OR COVID-19 serotherapy [Supplementary Concept] OR COVID-19 vaccine [Supplementary Concept] OR spike glycoprotein, COVID-19 virus [Supplementary Concept] OR COVID-19 [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 [Supplementary Concept] OR nCoV[tiab] OR nCoV[tt] OR 2019nCoV[tiab] OR 2019nCoV[tt] OR 19nCoV[tiab] OR 19nCoV[tt] OR COVID19*[tiab] OR COVID19*[tt] OR COVID[tiab] OR COVID[tt] OR SARS-CoV-2[tiab] OR SARS-CoV-2[tt] OR SARSCOV-2[tiab] OR SARSCOV-2[tt] OR SARSCOV2[tiab] OR SARSCOV2[tt] OR Severe Acute Respiratory Syndrome Coronavirus 2[tiab] OR Severe Acute Respiratory Syndrome Coronavirus 2[tt] OR ((severe acute respiratory syndrome[tiab] OR severe acute respiratory syndrome[tt]) AND (corona virus 2[tiab] OR corona virus 2[tt])) OR new coronavirus[tiab] OR (new[tt] AND coronavirus[tt]) OR novel coronavirus[tiab] OR novel coronavirus[tt] OR novel corona virus[tiab] OR (novel[tt] AND corona virus[tt]) OR novel CoV[tiab] OR (novel[tt] AND CoV[tt]) OR novel HCoV[tiab] OR (novel[tt] AND HCoV[tt]) OR (("19"[tiab] OR "19"[tt] OR "2019"[tiab] OR "2019"[tt] OR Wuhan[tiab] OR Wuhan[tt] OR Hubei[tiab] OR Hubei[tt]) AND (coronavirus*[tiab] OR coronavirus*[tt] OR corona virus*[tiab] OR corona virus*[tt] OR CoV[tiab] OR CoV[tt] OR HCoV[tiab] OR HCoV[tt])) OR ((coronavirus*[tiab] OR coronavirus*[tt] OR corona virus*[tiab] OR corona virus*[tt] OR betacoronavirus*[tiab] OR betacoronavirus*[tt]) AND (outbreak*[tiab] OR outbreak*[tt] OR epidemic*[tiab] OR epidemic*[tt] OR pandemic*[tiab] OR pandemic*[tt] OR crisis[tiab] OR crisis[tt])) OR ((Wuhan[tiab] OR Wuhan[tt] OR Hubei[tiab] OR Hubei[tt]) AND (pneumonia[tiab] OR pneumonia[tt]))	73536
2	limit 1 to english language	70804
3	limit 2 to yr="2020 -Current"	68041
4	"long term adverse effects"[MeSH Terms] OR "recurrence"[MeSH Terms] OR "symptom flare up"[MeSH Terms] OR "symptom assessment"[MeSH Terms]	191090
5	"symptom*"[Title] OR "complicat*"[Title] OR "consequence*"[Title] OR "outcome*"[Title] OR "effect*"[Title] OR "manifest*"[Title] OR "sequela*"[Title]	2743001
6	"long-term"[Title] OR "longterm"[Title] OR "longitudinal*"[Title] OR "chronic*"[Title] OR "persist*"[Title] OR "prolong*"[Title] OR "ongoing"[Title] OR "recurr*"[Title] OR "lasting"[Title] OR "long lasting*"[Title] OR "linger*"[Title]	953857
7	5 and 6	141815
8	4 or 7	326254
9	3 and 8	443
10	"longitudinal studies"[MeSH Terms] OR "follow up studies"[MeSH Terms]	773544
11	“longitudinal study”[Title/Abstract] OR “longitudinal studies”[Title/Abstract] OR “follow-up study”[Title/Abstract] OR “follow-up studies”[Title/Abstract]	130122
12	10 or 11	829460

13	"symptom*"[Title/Abstract] OR "complicat*"[Title/Abstract] OR "consequence*"[Title/Abstract] OR "outcome*"[Title/Abstract] OR "effect*"[Title/Abstract] OR "manifest*"[Title/Abstract] OR "sequela*"[Title/Abstract]	10059315
14	3 and 12 and 13	312
15	"long covid*"[Title/Abstract] OR "longcovid*"[Title/Abstract] OR "long hauler*"[Title/Abstract] OR "long hauler*"[Title/Abstract]	6
16	"sequela*"[Title/Abstract]	69855
17	3 and 16	252

TRIP Pro/Google Scholar/medRxiv & bioRxiv

((long-term or longterm or longitudinal* or chronic* or persist* or prolong* or ongoing or recurr* or lasting or long-lasting or linger*) AND (symptom* or complication* or consequence* or outcome* or effect* or manifest* or sequela*)) AND (covid-19 or coronavirus or SARS-CoV-2)

(long covid or longcovid* or long hauler* or longhauler*) AND (covid-19 or coronavirus or SARS-CoV-2)

LitCOVID/WHO Global research on COVID-19 (database)/Centre for Evidence Based Medicine (CEBM)/CADTH COVID-19 Evidence Portal

((long-term or longterm or longitudinal or chronic or persist or prolong or ongoing or recurring or lasting or long-lasting or linger) adj (symptom or complication or consequence or outcome or effect or manifest or sequela or sequelae))

(long covid or longcovid* or long hauler* or longhauler*)

* The proximity string is used to demonstrate that each combination or terms was searched separately, e.g. “long-term symptom”, “long-term complication”, or “chronic symptom”, “chronic complication”, etc.).

**Citation tracking and snowball searching of key articles was conducted via Google Scholar.

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Rapid Review Report

Review Title:	What is the post acute covid syndrome and its implications in terms of health services?
Abbreviated Title:	This review will try to gauge additional resources that may be required from the health authority to treat and manage this condition.
Review ID:	EOC091601 RR
Date/Time:	October 13, 2020 13:30
Version: [to be used for updated reviews]	1
Revision History:	None
Prepared By:	Andreea Badea, CHEP, University of Saskatchewan Michelle Dalidowicz, Clinical Librarian, Saskatchewan Health Authority Library Lance Fox, Clinical Librarian, Saskatchewan Health Authority Library
Peer Reviewer:	Dr. Gary Groot, CHEP, University of Saskatchewan
Contact:	For questions specific to this review, Dr. Gary Groot gary.groot@usask.ca
Cite As:	Badea, A; Groot, G; Dalidowicz, M; Fox, L. What is the post acute covid syndrome and its implications in terms of health services? 2020 Oct 13; Document no.: EOC091601 RR. In: COVID-19 Rapid Evidence Reviews [Internet]. SK: SK COVID Evidence Support Team, c2020. 28 p. (CEST rapid review report)

Key Findings

- There is no consistent definition of the post-acute COVID syndrome.
- There is a need to distinguish between the rehabilitation needs of severe COVID patients and the persistent collection of symptoms that occur for a variable period of time in some patients.
- Individuals with severe initial infections are more likely to have ongoing symptoms
- The duration of post-covid symptoms is unclear at this point in time
- The common post-covid symptoms can be grouped as general, respiratory, cardiovascular, mental health, and neurologic sequelae.
- A follow up review is probably warranted

Limitations

- Most studies address the sequelae of hospitalized patients
- The empirical evidence on medium-and long-term health sequelae of COVID-19 is limited and still developing.
- Studies to date focus on short term sequalae (weeks to months) given the relative short experience to date

GRADE of Evidence: C - Low

A grade of "C" is assigned when further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. The review may consist of one or more studies with severe limitations.

For more information about how this rating was determined, visit
https://www.essentialevidenceplus.com/product/ebm_loe.cfm?show=grade

Background/Context

Since its discovery on December 31, 2019, the novel SARS-CoV-2 virus has infected upwards of 34 Million people, with over 1 Million infected persons dying. This means that more than 30 Million people have recovered from the infection, and are now living through the recovery process, with some experiencing persistent symptoms and other sequelae of the infection. Through the initial waves of the pandemic, much of the healthcare system was focused on rapid expansion and infection prevention control. Now as people are recovering, the system must adapt to meet the rehabilitation needs of survivors while continuing to deliver normal services to non-SARS-CoV-2 patients.

Purpose

A developing definition of the post-acute SARS-CoV-2 infection, along with the healthcare needs for these patients is prompting healthcare systems to prepare for the additional burden of survivor's ongoing healthcare needs.

Review Question(s)

- What is the post acute covid syndrome and its implications in terms of health services?

Method

For each Rapid Review, the initial question is posed by a decision-maker in the health care system seeking the evidence base for a specific policy decision. According to the subject of the question, the Evidence Task Group Intake Committee allocates this question to the appropriate Working Group. Each Working Group comprises a librarian, researcher, 1-2 clinicians, 1-2 subject matter experts, and a group leader. The Working Group and the decision-maker first discuss the question to ensure it was articulated in a clear, searchable manner. The search strategy is developed and executed by a team of medical librarians. The search is conducted in biomedical databases and also includes extensive grey literature searching. Reference lists are also reviewed for articles that may have been missed in the primary search. See Appendix for more details on the search strategies. An Evidence Search Report is thereby created. A Rapid Review of the identified literature is then performed by the researcher using the methods of a systematic review, but without a double review or meta-analysis and in a more rapid fashion. Relevant evidence is summarized in both tabular and narrative form, key findings and limitations articulated, and the quality of the body of evidence evaluated using the GRADE hierarchy. The draft Rapid Review is reviewed and edited by the Working Group clinicians, experts, and leader. Once revisions are complete, the Rapid Review is submitted to the requesting decision-maker and placed in the COVID-19 Repository. For certain topics with rapidly changing evidence, after a period of time an updated evidence search is performed, the review process repeated, and an updated Rapid Review released.

Summary of Evidence

Sequelae associated with mild-to-moderate disease

Due to the relatively short duration of the SARS-CoV-2 pandemic thus far, epidemiologic studies of recovered patients are limited to relatively short-term outcomes. A BMJ Best Practice review found that approximately 10% of patients still have symptoms 3 weeks following diagnosis[1]. Other studies of discharged patients followed up after up to 110 days found that up to 70% of patients had persistent symptoms following infection[2].

The medium to long-term sequelae of SARS-CoV-2 can be grouped as follows:

- General, including fatigue, myalgia, and insomnia
- Respiratory with associated abnormal pulmonary function tests
- Cardiovascular with documented myocardial injury
- Neurologic, including decreased olfactory, gustatory or hearing
- Mental Health, including anxiety, depression and PTSD

The most commonly reported persistent symptoms are fatigue, shortness of breath, cough, chest pain, myalgia and insominia/sleep disorders[1-11]. Psychological sequelae such as PTSD, depression and anxiety have also been reported[12-14].

The evidence on the likelihood of which patients experience persistent symptoms, and to what extent, is inconclusive, with hypotheses of both those with mild disease at an increased risk for persistent symptoms[15] due to immunological reaction differences, as well as those having experienced severe disease or presenting with comorbidities at a higher risk of persistent symptoms and likelihood of sequelae[16-18].

Sequelae associated with severe-to-critical disease

There have been several systematic analyses on the more significant sequalae faced by recovered SARS-CoV-2 patients[16,19], including myocardial injury, kidney dysfunction and cognitive sequelae, however those processes are not yet well defined in terms of prevalence and mechanism of injury. In addition to the system-wide effects of SARS-CoV-2 infection, patients who have recovered from severe-to-critical disease must also contend with the sequelae associated with mechanical ventilation, tracheostomy and/or prolonged anesthesia/immobility (commonly referred to as PICS; post intensive care syndrome)[20] which is commonly associated with acute respiratory distress independent of SARS-CoV-2 infection. The treatments for PICS are still not well defined, nor any differences between PICS experienced by COVID patients versus non-COVID patients, and the evidence for the benefits and risks of early rehabilitation is still inconclusive. What has largely been agreed upon, is that the high variability of the rehabilitation needs of SARS-CoV-2 recovered patients calls for individual assessments and the collaboration of multi-disciplinary teams, including physicians, physical therapists, speech therapists, psychologists and rehabilitation specialists[19,21-24].

Rehabilitation considerations

In addition to patient-level rehabilitation considerations, facility considerations also play an important role in considerations for post-acute COVID rehabilitation clinical decision making[24]. The fact that rehabilitation patients represent a high risk group creates a unique capacity challenge in many jurisdictions trying to simultaneously meet the needs of recovered SARS-CoV-2 patients and their regular patients.

Conclusions

Post-acute COVID-19 syndrome, an evolving concept whose definition is yet to be clarified, includes the rehabilitation needs of those COVID-19 patients who survived serious infection as well as the sequelae of COVID-19 infection that impact a yet unknown number of patients who experienced a mild to moderate COVID-19 infection.

With regards to the rehabilitation needs of severe COVID-19 patients who required mechanical ventilation and/or ICU admission, it is important to distinguish between the normally anticipated needs other ARDS patients experience and those unique to the COVID-19 viral infection such as myocardial

injury, kidney injury and complications associated with pre-existing co-morbidities. In the absence of strong empiric evidence, it is recommended that cases are assessed individually and by multidisciplinary teams including physicians, rehabilitation specialists, physical therapists, speech therapists, and psychologists.

Emerging empiric evidence suggests that people who experienced a mild-to-moderate SARS-CoV-2 infection often experience persistent symptoms such as fatigue, shortness of breath, cough, chest pain, myalgia and sleep disorders. While the emerging evidence indicates that these are not actionable medical conditions for which the acute healthcare system is frequently accessed it is likely that these sequalae will result in an increased demand for primary health care will need to be addressed.

Recovered SARS-CoV-2 patients, regardless of severity, report negative psychological outcomes upon recovery such as anxiety, depression and PTSD.

Glossary

(Optional, but useful if there are clinical/statistical terms being referenced in the document.)

Table 1: Summary of Literature

Reference	Context	Key Findings
New South Wales (Australia) COVID-19 Critical Intelligence Unit. Medium- and long-term health sequelae of COVID-19. [26 August 2020]	Rapid review of long term consequences up to 12-Sep-2020	- symptoms commonly reported 2-8 weeks after onset include fatigue, SOB, muscle or joint pain, chest pain, cough and insomnia and/or sleep disorders - discharged ICU/ward patients found that PTSD, anxiety and/or depression, voice change, laryngeal sensitivity, new continence problems and dysphagia commonly reported among recovered patients - respiratory consequences worse in patients who had severe infection - some recovered patients 5-10 weeks post-dx had cardiovascular consequences - neuro consequences that persisted among recovered pts include deterioration in hearing and/or tinnitus, olfactory dysfunction, gustatory dysfunction
New South Wales (Australia) COVID-19 Critical Intelligence Unit. Rehabilitation needs of post-acute COVID-19 patients. [4 May 2020]	Rapid review of rehab lit up to 4-May-2020	- small quasi-randomized trial of elderly COVID-19 patients found that resp rehab can improve resp function, QoL and anxiety - recommendation of early rehab after acute phase of ARDS, which is of particular value to those admitted to ICU to limit severity of ICU-acquired weakness and promote rapid functional recovery - Italian guidelines recommend rehab both with minimal clinical stability and in post-acute phase - case prioritization process that considers potential impact of not receiving immediate rehab on critical outcomes - tele-rehab tools available as well
Alberta Health Services (AHS). Rehabilitation Needs for COVID-19 Patients. Rapid Review. [19 May 2020]	Rapid review of rehab needs up to 15-May-2020	- rehab needs are potentially extensive and encompass physical, resp, cognitive and psych - ICU settings – PICS and resp rehab often focus - rehab from acute care challenging d/t diversity and high variability of issues following COVID-19

		- potential benefits of acute setting rehab need to be weighed against transmission risk to HCW - initiation of rehab earlier rather than later recommended to prevent longterm complications - primary rehab intervention recommendations for COVID-19 patients in ICU/acute care focus of resp function, physical deconditioning and urgent sequelae include dysphagia, cognitive and psych issues and prevention of complications secondary to prolonged immobilization and sedation
American Association of Medical Colleges. Post-COVID-19 Clinics Help Survivors Recover. [25 August 2020] https://www.aamc.org/news-insights/post-covid-19-clinics-help-survivors-recover	Puff piece about the Mount Sinai COVID recovery unit	- one study at a hospital in Italy found that 80% of former patients still reported symptoms two months after first feeling ill. - CDC findings more than 1 in 3 respondents were not back to their usual health 14 to 21 days after testing positive. Among young, healthy people with mild symptoms, 1 in 5 experienced longer-term issues. - a recent survey of more than 1,500 people posted by the grassroots group Survivor Corps noted some 50 lingering symptoms — 27% of which respondents said were painful. - post-recuperation study on people whose infections ranged from asymptomatic to severe found physiological changes in the hearts of 78 out of 100 of them. In another study, more than half of 60 former COVID-19 patients who had been hospitalized still had neurological symptoms such as memory loss, vision problems, and mood issues three months later.
BMJ. Long covid: How to define it and how to manage it. [7 September 2020]	Online webinar hosted by BMJ to define, diagnosis, management and prognosis of "long covid"	- "Profound fatigue" was a common symptom in most people with long covid, she said, but added that a wide range of other symptoms included cough, breathlessness, muscle and body aches, and chest heaviness or pressure, but also skin rashes, palpitations, fever, headache, diarrhoea, and pins and needles - patterns in the team's data suggested that long covid was about twice as common in women as in men and that the average age of someone presenting with it was about four

		years older than people who had what might be termed as "short covid." - data showed fatigue was the most common trait in people who had symptoms beyond three weeks. He also said that around 80% of people who had symptoms lasting more than three weeks reported "having had clear good days and bad days.
BMJ Best Practice. Coronavirus disease 2019 (COVID-19) > Complications.	Evidence for "long COVID" compiled by BMJ Best Practice	- While most patients recover within 2 weeks, approximately 10% of patients still have symptoms after 3 weeks, and some may have symptoms for months (UK monitoring app) - Nearly 90% of hospitalised patients who recovered from COVID-19 reported persistence of at least one symptom 2 months after discharge. Only 12.6% of patients had no related symptoms, 32% had one or two symptoms, and 55% had three or more symptoms - survey study of symptomatic adults, 35% had not returned to their usual state of health 2 to 3 weeks after testing. Among those aged 18 to 34 years with no underlying chronic medical conditions, 20% had not returned to their usual state of health - Common long-term symptoms include cough, low-grade fever, and fatigue. Dyspnoea, chest pain, myalgia, headaches, rashes, gastrointestinal symptoms, neurocognitive difficulties, and mental health conditions have also been reported. Blood tests should be ordered selectively and for specific clinical indications after a careful history and examination. Other investigations may include chest x-ray, urine tests, and an electrocardiogram - patients should be managed pragmatically and symptomatically
British Society for Immunology. Long-term immunological health consequences of COVID-19. [13 August 2020]	Overview of longterm immunological consequences	- One possible consequence of severe acute inflammation is scarring or fibrosis, which may be irreversible and lead to long-term health problems - A longitudinal study of SARS1 patients from 2003 to 2018 found that more than a third had reduced lung capacity.14

		Similarly, with MERS, a third of survivors had long-term lung damage - some outward similarities to chronic fatigue syndrome although we do not yet understand the underlying pathology - Defects in lipid metabolism remained 12 years after clinical recovery in a metabolomic study among 25 SARS survivors
British Society of Rehabilitation Medicine & Intensive Care Society. Responding to COVID-19 and beyond: A framework for assessing early rehabilitation needs following treatment in intensive care [National Post-Intensive Care Rehabilitation Collaborative].	Development of a "rehabilitation prescription" for post-acute COVID patients	- information from the PICUPS tools and the targeted specialist assessments by members of the multiprofessional team (see below), feed in to the development of an individualised Rehabilitation Prescription (RP) - The RP identifies each individual's need for rehabilitation and specifies how these will be met after discharge from the acute ward and as they move on to the next stage of the pathway - The RP is a free text tool that sets out the rehabilitation needs, and the recommendations / referrals that have been made to address them. The RP travels with the patient and should be reviewed and updated at appropriate intervals to record actions undertaken to implement the recommendations. - The RP is accompanied by a minimum dataset of which the key elements as follows: • Does the patient have on-going needs for rehabilitation? Yes / No • If yes, a rehabilitation needs checklist is completed to describe the needs under three categories: physical, cognitive and psychosocial • Are they being transferred to the appropriate facility? Yes / No • What type of rehabilitation does the patient need? • What is their discharge destination? • What is the reason for variance? • A brief description of further needs for rehabilitation.
COVID Symptom Study. How long does COVID-19 last? Kings College London, [2020]	Results from UK COVID Symptom Study (self-reporting app)	- But strangely, it seems that people with mild cases of the disease are more likely to have a variety of strange symptoms that come and go over a more extended period.
Department of Global Health Washington. Summary of COVID-19 Long-term Health Effects: Emerging	Summary of lit published up to 31-Aug-2020	- Among hospitalized adults (n=143) with COVID-19 in Italy who were assessed at a mean of 60 days following symptom onset, only 18/143 (12.6%) were free of symptoms. The most

Evidence and Ongoing Investigation. [1 September 2020]		commonly reported symptoms were fatigue (53%), shortness of breath (43%), joint pain (27%) and chest pain (22%). - At a median of 110 days following the date of hospitalization for COVID-19 for patients hospitalized in France (n=120), the most common symptoms were fatigue (55%) and shortness of breath (42%). - adults surveyed (n=100) at a mean of 48 days (range 29-71) following discharge from a university hospital in the UK, the most commonly reported symptoms were fatigue and breathlessness, with 72% of post-ICU patients and 60% of non-ICU patients reporting fatigue, and 66% of post-ICU patients and 43% of non-ICU patients reporting new breathlessness. - Adults with COVID-19 who had required a high level of oxygen support during their hospitalization (≥6 L/minute) in New York City (n=191) were surveyed 30-40 days after hospital discharge. They reported shortness of breath at more than twice their pre-COVID prevalence (31% affected pre-COVID-19 vs. 74% post-COVID-19). Additionally, 52/148 (35%) participants without pre-COVID supplemental oxygen requirements needed home oxygen after discharge from their COVID hospitalization, including 20 (13.5%) who still required supplemental oxygen at the time of the survey - At eight to twelve weeks after admission, among discharged patients with COVID-19 in a UK study (n=110), most (74%) reported some persistent symptoms, with breathlessness (39%), fatigue (39%), and insomnia (24%) being the most common. Sixteen (59%) patients with mild COVID-19 reported ongoing symptoms, compared to 49 (75%) with moderate COVID-19 and 16 (89%) with severe COVID-19. Chest radiographs performed at follow-up were normal in the majority of patients (n=95, 86%) - Memory loss (34%), and concentration and sleep disorders (28% and 31%, respectively) followed fatigue and breathlessness as the most commonly reported symptoms

		among people in France surveyed at a median of 110 days following the date of hospitalization - More than half of participants who had required a high level of oxygen (≥6 L/minute) during their hospitalization in New York City received visiting nurse services after their hospitalization. - Among patients with COVID-19 (n=675) discharged from hospitals in Wuhan, China who were surveyed at a mean of 37 days after discharge, 70 (10%) patients reported symptoms of moderate to severe anxiety, with another 218 (32 %) reporting mild anxiety symptoms. In the same study, 128 (19%) had symptoms of moderate to severe depression and 315 (48%) had mild depression. The researchers also found that more severe COVID-19 illness was associated with worse mental health outcomes after discharge, and that perceived discrimination by family or neighbors was a strong risk factor for PTSD, anxiety, and depression.
Lambert, N. J. & Survivor Corps. COVID-19 "Long Hauler" Symptoms Survey Report. Indiana University School of Medicine; [2020]	Data from Indiana COVID "Long Haulers" symptom survey	- coding of the participant-reported symptoms according to which caused pain revealed that 26.5% of symptoms experiences by Long Haulers are painful - body aches, nerve pain, and joint pain are frequent, and comments within the Survivor Corps group anecdotally show that this pain can be extreme and difficult to manage
Mayo Clinic. COVID-19 (coronavirus): Long-term effects. [18 August 2020]	Mayo clinic directive of long-term COVID effects	- Older people and people with many serious medical conditions are the most likely to experience lingering COVID-19 symptoms. - Organ damage may include damage to the heart, lungs and brain - increased risk of blood clots - psychological symptoms - many recovered COVID patients have gone on to develop chronic fatigue syndrome

National Health Service (NHS). Aftercare needs of inpatients recovering from COVID-19 (Version 2). [3 August 2020]	Post-acute needs of COVID inpatients	- really good over view on potential post-acute COVID healthcare needs, largely focused on inpatients/ICU patients and post-intensive care syndromes.
Pan American Health Organization (PAHO). Rehabilitation Considerations During the COVID-19 Outbreak. [2020]	Overview largely for post-ICU admission	- focuses on the rehabilitation needs of severe COVID cases that have been on ventilator support and/or extensive bedrest
Physiopedia. COVID-19: Post-Acute Rehabilitation. https://physio-pedia.com/COVID-19:_Post-Acute_Rehabilitation	Outlines need for rehabilitation	- hospitalized patients also showed associated cardiac injury (arrythmia, cardiac insufficiency, ejection fraction decline, troponin I elevation, severe myocarditis with reduced systolic dysfunction) - secondary neurological complications in patients hospitalized with COVID-19 include headaches, disturbed consciousness, seizures, absence of sense and smell, parasthesia, posterior reversible encephalopathy syndrome, viral encephalitis, increased risk for acute cerebrovascular event, reports of Guillain-Barre Syndrome associated with COVID-19 - MSK sequelae include physical deconditioning, severe muscle weakness, reduced joint mobility, neck and shoulder pain (due to prone lying), difficulty in verticalization, impaired balance and gait, CIP, CIM - pulmonary issues include impaired lung function, lung fibrosis as a sequelae of pneumonia (needing resp rehab), tough secretions requiring specific physio techniques - cognitive issues include difficulty awakening with long-lasting confusional state and psychological problems, delirium and others - Issues surrounding being ventilated/long period of immobilization and prone positioning e.g. dysphagia, impaired swallow and communication - recommend to try to do as much as possible without patient contact - randomized controlled trial from China 2x10 min sessions per week for 6 weeks for post discharge from acute care –

		significant improvement in resp function, endurance, QoL and depression
Public Health Ontario. Long-Term Sequelae and COVID-19 – What We Know So Far. [10 July 2020]	Synthesis of COVID sequelae up to 10-July-2020	- few peer-reviewed studies examining occurrence or prevalence of long-term sequelae - some evidence that olfactory and gustatory dysfunction are relatively common - multisystem inflammatory syndrome in children - cardio, pulm and other neuro may be expected based on pathophysiology - additional based on knowledge of SARS – anxiety, cardiovascular abnormalities, depression, glucose metabolism disorders, hyperlipidemia, lipid metabolism dysregulation, PTSD and reduced lung capacity
Ahmed H, Patel K, Greenwood D, et al. LONG-TERM CLINICAL OUTCOMES IN SURVIVORS OF CORONAVIRUS OUTBREAKS AFTER HOSPITALISATION OR ICU ADMISSION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF FOLLOW-UP STUDIES. medRxiv. 2020:2020.04.16.20067975. DOI: 10.1101/2020.04.16.20067975	Metaanalysis of literature up to the end of March 2020 – 28 studies	- complications commonly observed were impaired diffusing capacity for carbon monoxide (27%) - reduced exercise capacity with limited improvement beyond 6 months - increased incidence of psych disorders such as PTSD (38%), anxiety (30%), depression (33%)
to May 31st, 2020. Eur J Phys Rehabil Med. 2020;56(4):508-14. DOI: 10.23736/S1973-9087.20.06435-710.23736/S1973-9087.20.06435-7. Epub 2020 Jun 16.	Systematic review up to 31-May-2020 (58 articles)	- 5/6 studies in the category report high prevalence of nervous system involvement in COVID patients - cardiopulmonary rehab needs significant
Arnold DT, Hamilton FW, Milne A, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up; results from a prospective UK cohort. medRxiv. 2020:2020.08.12.20173526. DOI: 10.1101/2020.08.12.20173526	12 week follow up of 110 patients recruited between March-June 2020	- most (74%) had persistent symptoms (notable breathlessness and excessive fatigue) - clinical abnormalities requiring action are infrequent, especially in those without a supplementary oxygen requirement during their acute illness

Banda JM, Singh GV, Alser O, et al. Long-term patient-reported symptoms of COVID-19: an analysis of social media data. medRxiv. 2020:2020.07.29.20164418. DOI: 10.1101/2020.07.29.20164418	analysis of social media (twitter) for lingering symptoms of recovered patients	- The 10 most commonly mentioned symptoms were: malaise and fatigue (62%), dyspnea (19%), tachycardia/palpitations (13%), chest pain (13%), insomnia/sleep disorders (10%), cough (9%), headache (7%), and joint pain, fever, and unspecified pain by 6% each
Brugliera L, Spina A, Castellazzi P, et al. Rehabilitative of COVID-19 patients with acute lower extremity Ischemia and amputation. J Rehabil Med. 2020;52(9):jrm00094. DOI: 10.2340/16501977-2714 10.2340/16501977-2714.	Case study of 3 patients who underwent lower limb amputation due to COVID-related coagulopathy	- overview of rehab needs for patients who undergo amputation due to COVID-related coagulopathy
Carfi A, Bernabei R, Landi F, et al. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;324(6):603-5. DOI: 10.1001/jama.2020.12603 10.1001/jama.2020.12603.	Follow up of Italian COVID patients	- follow up ~60d POS only 12.6% free of symptoms, 32% had 1 or 2 symptoms and 55% had 3 or more - fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%)
Cheng YY, Chen CM, Huang WC, et al. Rehabilitation programs for patients with COronaVIrus Disease 2019: consensus statements of Taiwan Academy of Cardiovascular and Pulmonary Rehabilitation. J Formos Med Assoc. 2020;17:17. DOI: 10.1016/j.jfma.2020.08.015	Rehabilitation frameworks for COVID patients categorized by disease and risk level	- mild disease with no risk factors: home-based rehabilitation is recommended for this group of patients, hospital-based rehabilitation may be started only when patients have been (1) at least 10 days since symptom onset (2) at least 24 h since resolution of fever without taking antipyretic drugs and (3) without other COVID-19 related symptoms, objective of rehabilitation is primarily preventing complications of inactivity through conditioning exercises. - mild disease with epidemiological risk factors home-based outpatient programs with proper video instructions and tele-rehabilitation are still recommended to avoid COVID-19 transmission. A comprehensive exercise program including

		aerobic and resistance training, as previously mentioned, could be provided to patients with comorbidities - hospitalized with moderate to severe: promoting airway clearance and preventing complications of acute illness-related immobilization - ventilator supported patients with clear cognitive status: similar to other ventilator rehab for other viral pneumonia illnesses
Curci C, Pisano F, Bonacci E, et al. Early rehabilitation in post-acute COVID-19 patients: data from an Italian COVID-19 rehabilitation unit and proposal of a treatment protocol. A cross-sectional study. Eur J Phys Rehabil Med. 2020;15:15. DOI: 10.23736/S1973-9087.20.06339-X	Follow up of ICU admitted COVID patients in Italy (32 patients 72.6 +/- 10.9y)	post-acute COVID-19 patients suffered from dyspnoea and shortness of breath even for minimal activities, with a resulting severe disability, and only a few of them were able to perform 6-MWT with poor results
Davido B, Seang S, Barizien N, et al. Possible therapies of Post-COVID-19 chronic symptoms. Clin Microbiol Infect. 2020. DOI: 10.1016/j.cmi.2020.09.001	Letter to editor re: Miglis et al (possible pathophysiology that might be responsible for dysautonomia)	- do not require specific treatment, case by case management dependent on persistent symptoms - non-pharm therapies, including psych support and explanation of symptoms - resp education, effort re-training and relaxation - resp rehab potentially useful - targeted pharm treatment such as beta-blocker or alpha-mimetic, or even dopamine antagonist
Davido B, Seang S, Tubiana R, et al. Post-COVID-19 chronic symptoms: a postinfectious entity? Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2020:S1198-743X(20)30436-5. DOI: 10.1016/j.cmi.2020.07.028	Post-recovery follow up France	- ~30/w, mostly women around 40 with no relevant medical history, few present biological abnormalities - most likely postviral syndrome that requires no specific treatment, as described in Epstein-Barr infection - only about 30% of patients who sought care had a proven history of COVID-19 - SARS-CoV-2 could probably play the same role of an immune trigger, as already known in Gullain-Barre and other autoimmune diseases

		- in case of persistent symptoms beyond 3 months, it could be relevant to investigate deeply the possible between those chronic inflammatory symptoms and COVID-19
de Sire A, Andrenelli E, Negrini F, et al. Systematic rapid living review on rehabilitation needs due to COVID-19: update as of April 30th, 2020. Eur J Phys Rehabil Med. 2020;56(3):354-60. DOI: 10.23736/S1973-9087.20.06378-9	Rehab needs synthesis of literature up to 30-April-2020 (50 articles)	- scoping review of 32 retrospective studies reported incidence of new neuro events in 6-67% of patients hospitalized for COVID with corticospinal signs, confusion and neuromuscular injuries affecting more than half of patients - a number of papers recommending and demonstrating the value of respiratory therapy. Overall message is that in the post-acute phase telerehabilitati0on and telemonitoring were proposed as the first option while inpatient or outpatient was suggested for cases with more severe disabilities - epidemiological data regarding the disabling sequelae point to a central and peripheral nervous system involvement either as a likely consequence of virus migration to the brain or as an adverse effect of ARDS and ICU stay
Garg P, Arora U, Kumar A, et al. The "Post-COVID" Syndrome: How Deep is the Damage? J Med Virol. 2020;27:27. DOI: 10.1002/jmv.26465	Response to Halpin et al	- reason for high proportion of patients reported with residual symptoms can largely be due to age of patients (~70.5y in ward group), disease severity (67.7% among ward and all ICU receiving supplemental O2) - significant proportion of patients had comorbidities like COPD, asthma, malignancy and cardiovascular disease
Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect. 2020;25:25. DOI: 10.1016/j.jinf.2020.08.029	Follow up of 120 patients ~110 days post admission (France)	- most frequent reported persistent symptoms were fatigue (55%), dyspnea (42%), loss of memory (34%), concentration and sleep disorders (28% and 31%) - no statistical difference between ward and ICU patients - both groups had altered EQ-5D, slight difference in pain in the ICU group - average age 64, with ~1/3 having comorbidities in both groups - at the time of follow up 38% of active workers had returned to work
Goërtz YMJ, Van Herck M, Delbressine JM, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection:	2113 members of FB groups from Netherlands/Belgium	- 112 hospitalized patients and 2001 non-hospitalized patients (345 confirmed COVID, 882 symptom based COVID, 774 suspected COVID)

the post-COVID-19 syndrome? ERJ Open Research. 2020. DOI: 10.1183/23120541.00542-2020		- fatigue and dyspnea were the more prevalent symptoms during the infection and at follow up - about 3 months after symptom onset
Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol. 2020;30:30. DOI: 10.1002/jmv.26368 10.1002/jmv.26368.	Follow up of 100 post-COVID patients UK	- Participants were between 29 and 71 days (mean 48 days) postdischarge from hospital. - Thirty-two participants required treatment in intensive care unit (ICU group) and 68 were managed in hospital wards without needing ICU care (ward group). - New illness-related fatigue was the most common reported symptom by 72% participants in ICU group and 60.3% in ward group. - The next most common symptoms were breathlessness (65.6% in ICU group and 42.6% in ward group) and psychological distress (46.9% in ICU group and 23.5% in ward group). - There was a clinically significant drop in EQ5D in 68.8% in ICU group and in 45.6% in ward group
Ismael F, Bizario JCS, Battagin T, et al. Post-infection depression, anxiety and PTSD: a retrospective cohort study with mild COVID-19 patients. medRxiv. 2020:2020.08.25.20182113. DOI: 10.1101/2020.08.25.20182113	Retrospective study of psych disorders in mild COVID cases	- 895 positive cases tested in home, classified as mild - followed up ~56.6days post intake - depression (26%), anxiety (22%) and PTSD (17%) - increased number of COVID symptoms associated with depression, anxiety and PTSD
Keefe JB, Cellai M. Characterization of prolonged COVID-19 symptoms and patient comorbidities in an outpatient telemedicine cohort. medRxiv. 2020:2020.07.05.20146886. DOI: 10.1101/2020.07.05.20146886	6 week follow up of 26 patients in Atlanta	- majority female (77%), med age 47.5 - most common persistent symptoms at week 5-6 cough, shortness of breath with exertion, fatigue (65%), headache (50%) - patients had an average of 2.7 comorbid conditions (most common BMI>30, asthma, allergies and hypertension)
Li Z, Zheng C, Duan C, et al. Rehabilitation needs of the first cohort of post-acute COVID-19 patients in Hubei, China. Eur J Phys Rehabil Med.	Follow up of 280 patients	- sleep disorders (63.6%), decreased activity endurance (61.4%), and respiratory dysfunction (57.9%), while the main psychological dysfunctions included anxiety (62.1%) and fear (50.0%)

2020;56(3):339-44. DOI: 10.23736/S1973-9087.20.06298-X 10.23736/S1973-9087.20.06298-X.		- rehab requested by patients included exercise guidance, dietary instruction, traditional Chinese medicine therapy, physical therapy, and Chinese traditional health exercises
Lopez M, Bell K, Annaswamy T, et al. COVID-19 Guide for the Rehabilitation Clinician: A Review of Nonpulmonary Manifestations and Complications. Am J Phys Med Rehabil. 2020;99(8):669-73. DOI: 10.1097/PHM.0000000000001479	Summary of extrapulmonary effects of COVID	- small percentage of patients experience neuro symptoms from COVID – agitation/confusion, headache/altered consciousness - small representation of myocardial injury
Mohamed-Hussein A, Galal I, Saad M, et al. Post-COVID-19 Functional Status: Relation to age, smoking, hospitalization and comorbidities. medRxiv. 2020:2020.08.26.20182618. DOI: 10.1101/2020.08.26.20182618	Follow up of 444 recovered COVID patients (Egypt)	- 80% of COVID cases have diverse degrees of functional restrictions ranging from negligible (63%), slight (14%), moderate (2%) to severe (0.5%)
Negrini F, De Sire A, Andrenelli E, et al. Rehabilitation and COVID-19: the Cochrane Rehabilitation 2020 rapid living systematic review. Update as of July 31st, 2020. Eur J Phys Rehabil Med. 2020;09:01. DOI: 10.23736/S1973-9087.20.06539-9	Systematic review of rehab lit July 2020	- two papers studied lung function of COVID patients after discharge, one at 30d and one at 3m. - lung function abnormalities were reported in more than 50% of patients at 30d and 25% at 3m
Polastri M, Nava S, Clini E, et al. COVID-19 and pulmonary rehabilitation: preparing for phase three. The European respiratory journal. 2020;55(6). DOI: 10.1183/13993003.01822-2020	Considerations for post-COVID rehabilitation	-Post-discharge pulmonary out-patient consultations must be prepared and allow adequate early assessment of symptoms (fatigue, anxiety, depression and dysphagia), pulmonary function and exercise performance. Based on these findings, follow-up and treatment in out-patient rehabilitation or primary care with general practitioners, physiotherapists, occupational therapists and nurses can be organized - should consider physical, cognitive and psychosocial outcomes - non-COVID ARDS resulting in PICS well established but tx still under development

		- Most studies in patients after ICU discharge to enhance recovery included (home-based, mostly unsupervised) exercise training interventions. These interventions were primarily self-delivered exercise supported by diaries and regular phone calls. It is well known from studies in patients with COPD that home-based unsupervised exercise training is not improving exercise performance in comparison to a comprehensive supervised programme.
Rooney S, Webster A, Paul L. Systematic Review of Changes and Recovery in Physical Function and Fitness After Severe Acute Respiratory Syndrome-Related Coronavirus Infection: Implications for COVID-19 Rehabilitation. Phys Ther. 2020;31:31. DOI: 10.1093/ptj/pzaa129	Systematic review of physical function post SARS	- Physical function and fitness are impaired following SARS-CoV infection, and impairments may persist up to 1 to 2 years postinfection
Sheehy LM. Considerations for Postacute Rehabilitation for Survivors of COVID-19. JMIR Public Health Surveill. 2020;6(2):e19462. DOI: 10.2196/19462 10.2196/19462.		- Patients severely affected by COVID-19 are more likely to have acute kidney injury as well as secondary infection - Survivors of ARDS with mechanical ventilation have reported complications such as tracheal stenosis, heterotopic ossification, contractures, adhesive capsulitis, decubitus ulcers, hoarseness, tooth loss, sensorineural hearing loss, tinnitus, brachial plexus injuries, and entrapment neuropathies (peroneal and ulnar) - A separate unit or area is suggested for the rehabilitation of patients post–COVID-19 and other patients arriving on the unit. - Depending on need, it has been suggested that dedicated facilities should be used to treat patients post–COVID-19; examples may include underutilized rural hospitals or retrofitted unused buildings, such as university dormitories. - It may be necessary to receive patients from acute care earlier than is generally done. - Patients should stay in their rooms.

		- Group therapy and therapy in rehabilitation gyms should be prohibited; therapy should be provided one-on-one in patients' rooms. - Patients may be discharged to home sooner than usual (as soon as the family is able to take care of the patient) to free space. - It may be difficult to discharge some patients because long-term care facilities and retirement homes may not be accepting new residents. - Shared equipment must be decontaminated between patients; single-use equipment should be used where possible (eg, TheraBands rather than hand weights). Particular attention should be paid to electrode sponges, hydrocollator heat packs, gels, topical lotions, items for training manual dexterity, etc. - Plan therapeutic activities to minimize the number of personnel involved when possible (eg, one therapist with a gait aid rather than a therapist and an assistant). - Minimize the number of personnel entering a patient's room. Have a single staff member perform most (if not all) of the care and duties for a particular patient (eg, deliver food trays, make the bed, give medication, help with morning care). - Walking practice should be done in parts of the hospital that are not commonly used. - Surgical masks should be worn by the patients and the therapists. - Patients should be kept at least 2 meters apart and avoid talking or eating while facing each other - Recommendations from both China and Italy state that to avoid aggravating respiratory distress or dispersing the virus unnecessarily, respiratory rehabilitation should not begin too early - In the postacute phase, inspiratory muscle training should be included if inspiratory muscles are weak.

		- Physiotherapy should begin in the acute inpatient setting and continue after transfer to inpatient rehabilitation
Singh SM, Reddy C. An Analysis of Self-reported Longcovid Symptoms on Twitter. medRxiv. 2020:2020.08.14.20175059. DOI: 10.1101/2020.08.14.20175059	Self-reported long covid symptoms via Twitter	- most common of which were fatigue, shortness of breath, pain and brainfog/concentration difficulties. - The most common course of symptoms was episodic
Somani SS, Richter F, Fuster V, et al. Characterization of Patients Who Return to Hospital Following Discharge from Hospitalization for COVID-19. Journal of general internal medicine. 2020;19:19. DOI: 10.1007/s11606-020-06120-6	COVID discharged patients returning for emergency care within 14d @ 5 NYC hospitals	- Of 2864 discharged patients, 103 (3.6%) returned for emergency care after a median of 4.5 days, with 56 requiring inpatient readmission. - The most common reason for return was respiratory distress (50%). Compared with patients who did not return, there were higher proportions of COPD (6.8% vs 2.9%) and hypertension (36% vs 22.1%) among those who returned. - Patients who returned also had a shorter median length of stay (LOS) during index hospitalization (4.5 [2.9,9.1] vs 6.7 [3.5, 11.5] days), and were less likely to have required intensive care on index hospitalization (5.8% vs 19%). - On readmission, rates of intensive care and death were 5.8% and 3.6%, respectively.
Stierli S, Buss I, Redecker H, et al. Insights from an interprofessional POST-COVID-19 rehabilitation unit: A speech and language therapy and respiratory medicine perspective. J Rehabil Med. 2020;02:02. DOI: 10.2340/16501977-2735	Early speech therapy for intubated/tracheotomy pts	- Early intervention for dysphagia, using speech and language therapy and ventilator-compatible speaking valves, provided within an interprofessional collaborative team, can mitigate the potential negative consequences of prolonged intubation, long-term use of cuffed tracheostomy, and PICS resulting from Covid-19
Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. medRxiv. 2020:2020.07.29.20164293.	Characteristics of those presenting with persistent fatigue	- Female gender and those with a pre-existing diagnosis of depression/anxiety were over-represented in those with fatigue. Our findings demonstrate a significant burden of post-viral fatigue in individuals with previous SARS-CoV-2 infection after the acute phase of COVID-19 illness

Vaes AW, Machado FVC, Meys R, et al. Care Dependency in Non-Hospitalized Patients with COVID-19. J Clin Med. 2020;9(9). DOI: 10.3390/jcm9092946	Facebook group of patients with persistent complaints (Belgium/Netherlands)	- 1837 non-hospitalized patients - Only a small proportion of patients needed help with personal care before COVID-19, but the care need increased significantly after the infection (on average 79 +/- 17 days after the onset of symptoms; 7.7% versus 52.4%, respectively)
Weerahandi H, Hochman KA, Simon E, et al. Post-discharge health status and symptoms in patients with severe COVID-19. medRxiv. 2020;14:14. DOI: 10.1101/2020.08.11.20172742	Post-discharge follow up of severe patients 30-40d post discharge	- 152 completed survey - 113/152 (74%) participants reported shortness of breath within the prior week vs 47/152 (31%) pre-COVID-19 infection - rated their physical health and mental health as worse in their post-COVID state compared to their pre-COVID state - 52/148 (35.1%) patients without pre-COVID oxygen requirements needed home oxygen after hospital discharge; 20/148 (13.5%) reported still using oxygen at time of survey

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Appendix: Evidence Search Details

Search Strategies

Database: Ovid MEDLINE(R) ALL <1946 to September 15, 2020>

Search Strategy:

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1 exp coronavirus/ (31653)
2 exp Coronavirus Infections/ (33542)
3 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (1919)
4 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw,kf. (42133)
5 ("2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARScoronavirus2 or "SARS-coronavirus-2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2 or "SARS-coronovirus-2" or "SARScoronovirus 2" or "SARS coronovirus2").ti,ab,kw,kf. (52626)
6 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (518)
7 (("seafood market*" or "food market*" or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (1573)
8 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (300)
9 "severe acute respiratory syndrome*".ti,ab,kw,kf. (11006)
10 or/1-9 (77732)
11 Rehabilitation/ (18281)
12 rehabilitat*.ti. (64883)
13 (post-acute or postacute or post-hospital* or posthospital* or post-discharg* or postdischarg*).tw,kf. (15986)
14 (long covid or long-haulers or after-effects or ((persistent or long-term or prolonged) adj2 (symptom* or health effect* or health consequence*))).tw,kf. (13429)
15 ((covid or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARScoronavirus2 or "SARS-coronavirus-2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2 or "SARS-coronovirus-2" or "SARScoronovirus 2" or "SARS coronovirus2") adj syndrome*).tw,kf. (5)
16 or/11-15 (101090)
17 10 and 16 (382)
18 limit 17 to (english language and yr="2020 -Current") (338)
19 from 18 keep 2-3,11,14,18-19,26-27,34,38-39,44,54,72-73,75,80,82-83,94,97,109,121,123,125,128,143,151-152,163,170,172,182,192,195-197,203,216,218-219,234,239,243,252,265,284,288,290,306,318,329 (52)

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Database: Embase <1974 to 2020 September 15>

Search Strategy:

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1 exp Coronavirinae/ or exp Coronavirus infection/ (28799)
2 (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj. (46431)
3 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (1436)
4 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw. (41498)
5 ("2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARScoronavirus2 or "SARS-coronavirus-2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2 or "SARS-coronovirus-2" or "SARScoronovirus 2" or "SARS coronovirus2").ti,ab,kw. (48711)
6 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (636)
7 (("seafood market*" or "food market*" or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (1751)
8 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (141)
9 "severe acute respiratory syndrome*".ti,ab,kw. (10880)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (80081)
11 limit 10 to yr="2019 - 2020" (56049)
12 *rehabilitation/ or *pulmonary rehabilitation/ (40587)
13 rehabilitation.ti. (78400)
14 (post-acute or postacute or post-hospital* or posthospital* or post-discharg* or postdischarg*).tw. (25925)
15 (long covid or long-haulers or after-effects or ((persistent or long-term or prolonged) adj2 (symptom* or health effect* or health consequence*))).tw. (19551)
16 ((covid* or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARScoronavirus2 or "SARS-coronavirus-2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2 or "SARS-coronovirus-2" or "SARScoronovirus 2" or "SARS coronovirus2") adj1 syndrome*).tw. (114)
17 or/12-16 (143668)
18 11 and 17 (452)
19 limit 18 to english language (430)
20 from 19 keep 2,7,32,47,51,100,105,109,139,149,173,195,197,208,272,301,379-380 (18)
****

Database: Pubmed

Search Strategy:

#	Query	Results
#1	Search: (((((Coronavirus[Mesh] OR "Coronavirus Infections"[Mesh])) OR ((coronavirus*[Text Word] OR coronovirus*[Text Word] OR coronavirinae*[Text Word] OR CoV[Text Word]))) OR (("2019-nCoV"[Text Word] OR 2019nCoV[Text Word] OR nCoV2019[Text Word] OR "nCoV-	85,189

	2019"[Text Word] OR "COVID-19"[Text Word] OR COVID19[Text Word] OR "CORVID-19"[Text Word] OR CORVID19[Text Word] OR "WN-CoV"[Text Word] OR WNCoV[Text Word] OR "HCoV-19"[Text Word] OR HCoV19[Text Word] OR "2019 novel*"[Text Word] OR Ncov[Text Word] OR "n-cov"[Text Word] OR "SARS-CoV-2"[Text Word] OR "SARSCoV-2"[Text Word] OR "SARSCoV2"[Text Word] OR "SARS-CoV2"[Text Word] OR SARSCov19[Text Word] OR "SARS-Cov19"[Text Word] OR "SARSCov-19"[Text Word] OR "SARS-Cov-19"[Text Word] OR Ncovor[Text Word] OR Ncorona*[Text Word] OR Ncorono*[Text Word] OR NcovWuhan*[Text Word] OR NcovHubei*[Text Word] OR NcovChina*[Text Word] OR NcovChinese*[Text Word] OR SARS2[Text Word] OR "SARS-2"[Text Word] OR SARScoronavirus2[Text Word] OR "SARS-coronavirus-2"[Text Word] OR "SARScoronavirus 2"[Text Word] OR "SARS coronavirus2"[Text Word] OR SARScoronovirus2[Text Word] OR "SARS-coronovirus-2"[Text Word] OR "SARScoronovirus 2"[Text Word] OR "SARS coronovirus2"[Text Word])))) OR (((Wuhan*[Text Word] OR Hubei*[Text Word] OR China*[Text Word] OR Chinese*[Text Word] OR Huanan*[Text Word]) AND (respiratory symptom*[Text Word] OR respiratory disease*[Text Word] OR respiratory illness*[Text Word] OR respiratory condition*[Text Word])) OR ((Wuhan*[Text Word] OR Hubei*[Text Word] OR China*[Text Word] OR Chinese*[Text Word] OR Huanan*[Text Word]) AND ("seafood market"[Text Word] OR "food market"[Text Word] OR pneumonia*[Text Word])) OR ((Wuhan*[Text Word] OR Hubei*[Text Word] OR China*[Text Word] OR Chinese*[Text Word] OR Huanan*[Text Word]) AND (outbreak*[Text Word] OR wildlife*[Text Word] OR pandemic*[Text Word] OR epidemic*[Text Word])))) OR (severe acute respiratory syndrome*[Text Word]) Sort by: Most Recent	
#2	Search: (("immune response"[tiab] OR "immune responses"[tiab] OR "immune system"[tiab] OR immunity[tiab] OR humoral[tiab] OR antibodies[tiab] OR antibody[tiab] OR IgG[tiab] OR "immunoglobulin g"[tiab] or IgM[tiab] OR "immunoglobulin m"[tiab] OR adaptive immunity[tiab])) Sort by: Most Recent	1,317,957
#3	Search: (duration[tiab] OR time[tiab] OR timing[tiab] OR time varian*[tiab] OR time factor[tiab] OR time factors[tiab] OR phase*[tiab] OR "point in time"[tiab] OR length[tiab] OR interval*[tiab] OR stretch*[tiab] OR span*[tiab] OR period*[tiab] OR longitudinal[tiab] OR time[Mesh] or time factors[Mesh]) Sort by: Most Recent	7,449,377
#4	Search: #1 AND #2 AND #3 Sort by: Most Recent	2,519
#5	Search: #1 AND #2 AND #3 Filters: from 2020 - 2020 Sort by: Most Recent	983
#6	Search: #1 AND #2 AND #3 Filters: English, from 2020 - 2020 Sort by: Most Recent	948
#7	Search: (recover*[tw] OR protect*[tw] Filters: English Sort by: Most Recent	1,421,885
#8	Search: #6 AND #7 Filters: English Sort by: Most Recent	237

Sources

- Grey literature was searched
- Refer to the evidence search report for extensive sources

Professor Trisha Greenhalgh, Dr Emma Ladds, University of Oxford; Dr Matthew Knight, Watford General Hospital; and Dr Deepak Ravindran, Royal Berkshire Hospital – Written evidence (COV0050)

'Long Covid': evidence, recommendations and priority research questions

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Summary and recommendations

1. Long Covid is a distinct condition affecting approximately 60,000 people in the UK and characterised by persistent and fluctuating fatigue, breathlessness, cognitive blunting ("brain fog") and pain. The cause is unknown but it is likely to be due at least partly to an inflammatory reaction. Many cases remain undiagnosed, since clinicians may incorrectly require a positive test for Covid-19.
2. Most people with long Covid slowly get better over time, but a minority (perhaps 10%) are left with significant organ damage and their long-term outlook is unknown.
3. The principles of management are a) confirm the diagnosis; b) exclude serious complications; c) support and monitor the patient while avoiding over-investigation and over-referral; d) develop and supervise a rehabilitation plan and exercises; e) direct to specialist clinics if appropriate.
4. Long Covid services are currently patchy and overstretched. This is partly because funding was diverted away from rehabilitation and towards the acute sector as an emergency response to the pandemic. Specialist rehabilitation services designed for patients recovering from a hospital admission (e.g. oriented to restoring normal breathing after pneumonia) have become swamped with referrals from general practice (who often have more general symptoms such as fatigue).
5. Clinical guidance and local protocols for long Covid are currently highly variable. This is likely to be contributing to the patient experience of inconsistent and fragmented care. We recommend that the development of NICE guidelines and that these are reviewed periodically as new evidence emerges.

6. We recommend that a 4-tier clinical service be developed:
    a) Tier 1: resources and support for self-care.
    b) Tier 2: generalist care including a therapeutic relationship in general practice and a community-based interdisciplinary rehabilitation service led by allied health professionals.
    c) Tier 3: specialist care including system-based investigation, management and rehabilitation.
    d) Tier 4: specialist management of specific complications.

7. There is a significant research agenda on this new disease. We suggest five priority areas for research:
    a) Basic science studies on upstream causes, including genetics and metabolomics.
    b) Observational studies of long-term outcome, especially in non-hospitalised patients.
    c) Trials of interventions, including different rehabilitation protocols.
    d) Studies to optimise and evaluate the service model, including virtual wards and remote care.
    e) Interdisciplinary studies of how socio-economic and racial disadvantage affects the development, course and outcome of long Covid.

What is long Covid?

Long Covid is the name patients gave to Covid-19 that hasn't got better yet. A recent BMJ review defined **post-acute Covid-19** as symptoms lasting 3-12 weeks and **chronic Covid-19** as symptoms beyond 12 weeks.[1] Importantly, some people whose initial Covid-19 was mild (and who were never hospitalised) may go on to develop chronic symptoms and vice versa.

Broadly speaking, patients with long Covid fall into three groups:

A. People who were very ill (perhaps on ITU) with acute Covid-19 and now have significant long-term organ damage (e.g. lungs, heart, brain, kidneys) along with weakness and debility;
B. People who were not so ill in the acute stage but who also now have some evidence of long-term organ damage; and
C. People who have persistent symptoms after Covid-19 but who don't have persisting organ damage.

Whist the first two groups account for considerable illness and suffering, they comprise a **relatively small proportion of long Covid patients**. For example, a study of 110 patients discharged from hospital after acute Covid-19 found that three-quarters still had symptoms (usually of breathlessness and fatigue) at 12-week follow-up but only one in eight still had an abnormal chest X-ray.[2]

What are the symptoms?

People with long Covid experience a wide range of persistent (and often fluctuating) symptoms including **cough, breathlessness, fatigue, fever, sore throat, chest pains ("lung burn"), cognitive blunting ("brain fog"), muscle pains, anxiety or depression, skin rashes, and diarrhoea**.[1-5] Control of

chronic conditions such as diabetes, inflammatory bowel disease, or rheumatological conditions may deteriorate.

Relatively rarely, patients may develop thrombo-embolic complications including **heart attack, stroke and venous thrombosis** (DVT), or other serious conditions such as **heart failure or heart rhythm abnormalities**. It is, of course, important to identify (or, more commonly, exclude) these serious complications.

How common is it?
Estimates vary (e.g. those based on self-surveys of patients recruited from Facebook groups imply higher incidence,[5] presumably because people who got better didn't join a group). The figures we trust most suggest that of people who have had Covid-19:[6,7]

- **10-20%** are still unwell after 3 weeks (though many of these are in group C above and essentially 'on the mend')
- **1% are still significantly unwell** after 12 weeks

Of this 1%, the predominant symptom varies depending on which if any organs are affected (e.g. fatigue, fatigue and breathlessness, cognitive blunting, palpitations or dizziness from fluctuating blood pressure, chronic pain, depression or anxiety).

Based on these figures, approximately 60,000 people in the UK probably have long Covid. A GP practice with 20,000 patients in an area of high Covid-19 incidence (e.g. London, Leicester) is likely to have:

- Up to 2000 patients who have had Covid-19 (whether test-confirmed or not)
- Up to 200 patients whose Covid-19 required a sick note for more than 3 weeks
- Up to 100 patients with *some form of* chronic Covid-19 (i.e. not completely better by 12 weeks)
- 10-20 patients with *seriously debilitating* chronic Covid-19 (e.g. unable to work or take part in normal family life or leisure activities)

How is Long Covid diagnosed?
Long Covid is a clinical diagnosis – i.e. it's **based on a medical assessment and does not need a positive swab or antibody test** (more specifically, a positive test is helpful if present but of no value if absent or negative). This is because

a. back in March-May 2020, most people were never offered swab tests even if they had symptoms;
b. an antibody (blood) test indicates past infection – it does *not* confirm that the person's current symptoms are due to long Covid;
c. the tests aren't 100% accurate – in particular, false negative results are common (and a positive antibody test may become negative over time).

Long Covid is therefore best diagnosed by **a history consistent with acute Covid-19 followed by a prolonged recovery**. This manifests in a variety of ways but is usually dominated by fatigue and breathlessness, particularly on

minimal exertion (and therefore causing severe functional limitation). Note that other diseases (e.g. asthma) have no definitive laboratory test; they are diagnosed clinically.

What causes it?
We don't know exactly, but there is evidence that long Covid is associated with a powerful **inflammatory (immune) reaction**,[8] involving **vasculitis** (swelling of the inner lining of the blood vessels).[9]

How serious is it?
For some people, the sequelae of Covid-19 are very serious and potentially life-threatening – mostly because of **thrombo-embolic complications** (clots in the blood vessels of the brain, lungs, heart and other organs as a result of inflammatory reaction). For others, the problem is more **post-viral fatigue** (prolonged exhaustion that prevents them getting back to work and normal activities – which, while debilitating, is rarely if ever life-threatening). However, biopsy and scan studies suggest that even patients without symptoms of thrombo-embolic disease after Covid-19 may show signs of organ damage.[10] Because of this, people with long Covid need **careful monitoring and a cautious approach to rehabilitation**.

What are the risk factors?
There is remarkably little peer-reviewed data on risk factors for long Covid. People with **pre-existing conditions** are at greater risk of severe disease and more likely to require hospitalisation; these patients are likely to have a prolonged recovery time.[11,12] In one study, 87% of the hospitalised population, who had significant rates of **hypertension, thyroid disease, immune disorders, chronic obstructive pulmonary disease, and diabetes**, still exhibited some symptoms at 60 days.[11] However, many patients with long Covid had no pre-existing conditions.

The self-survey from a large online patient community found that **58% of respondents had at least one pre-existing condition**, with the commonest being asthma, vitamin D deficiency, acid reflux disease, and autoimmune disorders.[3] Of that sample, only 4.4% had been hospitalised. Medical conditions such as diabetes, heart disease and kidney disease predispose to thrombo-embolic complications after Covid-19, but previously healthy people also get them.

What is the chance of recovery?
Reassuringly, **most people seen in Covid-19 rehabilitation clinics slowly recover** (unpublished data, MK). Because Covid-19 is a new disease, the long-term outlook in the minority whose symptoms persist beyond 6 months is unknown. However, there may be parallels with other coronavirus diseases. Some patients with SARS went on to develop a **long-term illness with widespread pain, fatigue, depression and sleep disturbance**.[13,14] **Post-traumatic stress disorder** has also been described after SARS.[15]

Hence, whereas the acute and post-acute manifestations of Covid-19 were **predominantly respiratory**, the **longer-term sequelae may turn out to be more systemic** and (for some who have been traumatised) psychiatric. The

overlap with myalgic encephalomyelitis (a syndrome of profound tiredness, generalised pain and difficulty functioning, probably due to several different underlying causes) is unknown.

What do patients say?

Thousands of **people with long Covid have come together in online communities**, many of whom feel dismissed by their physicians as over-reacting to "mild" illness. They have undertaken and published their own research studies (which have informed the list of symptoms listed above).[3,16]

Research interviews by the Oxford team with over 100 people with long Covid (currently being written up for publication) have identified **five key 'touch points'** in current service provision:

a. **Dismissal:** patients are told there is nothing wrong with them or that they are just anxious (absence of positive test may be misinterpreted as evidence that the patient does not have Covid-19).
b. **Unclear lines of responsibility** – e.g. GP triage service tells patients to call NHS111 (because they have mentioned the word Covid); NHS111 says call the GP (because it's not acute).
c. **Fragmented care:** specialist services look at "one bit of me" (and confirm, for example, no heart attack) but no clinician considers the disease as a whole.
d. **Gaps in services:** patients are told there is no rehabilitation service locally or that it has exclusionary referral criteria (e.g. must have had a positive swab or antibody test, must have been admitted to hospital in the acute illness).
e. **High burden borne by the sick patient:** organising appointments and tests requires considerable effort and persistence (e.g. one patient we interviewed took 12 phone calls to secure a simple repeat prescription of an asthma inhaler).

How are patients with long Covid currently being managed?

Care of the patient with long Covid is **extremely variable** across the country. Covid-19 rehabilitation **services have typically arisen ad hoc** and in a locally path-dependent way in both secondary and community care, perhaps led by a local clinician with an interest. Referral criteria and management protocols are inconsistent and feature **both under- and over-investigation**. Whilst **paced activity**, as recommended by the Royal College of Occupational Therapists,[17] appears to be an important component of management at all levels, there is much uncertainty around who should receive what kind of rehabilitation.

General practitioners are still **operating largely remotely** in a service structure designed for infection control in the acute phase of the pandemic. All **requests for appointments are triaged** and channelled to self-care (i.e. the patient is refused a consultation), NHS111 (the patient is advised to call the NHS phone line), telephone or video call-back appointment, or a face to face appointment. In this context, **many patients fail to secure a full clinical assessment** (history, physical examination, baseline blood tests) a clear management plan, or ongoing follow-up; in some cases the GP does not accept the diagnosis of long Covid.

In our view, there is an **urgent need for interdisciplinary guidelines**, spanning both primary and secondary care, to be developed at national level, preferably by the National Institute for Health and Clinical Excellence, and for these to be reviewed and updated promptly as new evidence emerges.

How should services for long Covid be organised?

Whilst there remain many uncertainties around the diagnosis and management of long Covid, there is already considerable evidence to support a **new service model**. We propose a **4-tier service** comprising self-care, generalist care, specialist care and specialist management of specific complications. Assessment should be designed to **identify and fast-track people with severe illness** and complications while **not over-investigating or over-medicalising** the majority. Tiered care models are increasingly used (e.g. in chronic pain[18] and diabetes[19]). Patients may move between tiers as symptoms become more or less troublesome.

Almost all patients with Long Covid will require **Tier 1 support for self-care**. The YourCovidRecovery online service (https://www.yourcovidrecovery.nhs.uk) may be helpful to guide self-care.

Perhaps 80% of patients will need **Tier 2 support from a generalist team**. Patients do not just need tests on their different bodily systems; they need a **therapeutic relationship with a clinician** who recognises their diagnosis, affirms their experience and takes responsibility for their care.

Around 10% of patients will need **Tier 3 specialist care**, though this should be carefully targeted. Early thinking and planning depicted Covid-19 as a disease of the lungs (because it caused a cough and obvious acute problems like pneumonia), so **rehabilitation and follow-up services emerged mostly in respiratory clinics**. We now know that long Covid is a **multi-system disease** and that most patients recover spontaneously without extensive investigation or specific treatment.[2,6] Whilst we acknowledge that NHS England's early guidance 'Aftercare needs of inpatients recovering from Covid-19' provides important baseline recommendations in the different clinical specialties (respiratory, cardiology etc),[20] it is also the case that we need to **avoid the pitfalls seen in other comparable conditions**, where patients with multisystem Covid-19 symptoms, especially less severe cases, enter **a cycle of fragmented secondary care pathways**, sometimes leading to increasing anxiety, overdiagnosis, labels and lengthy waits to get assurance and care.

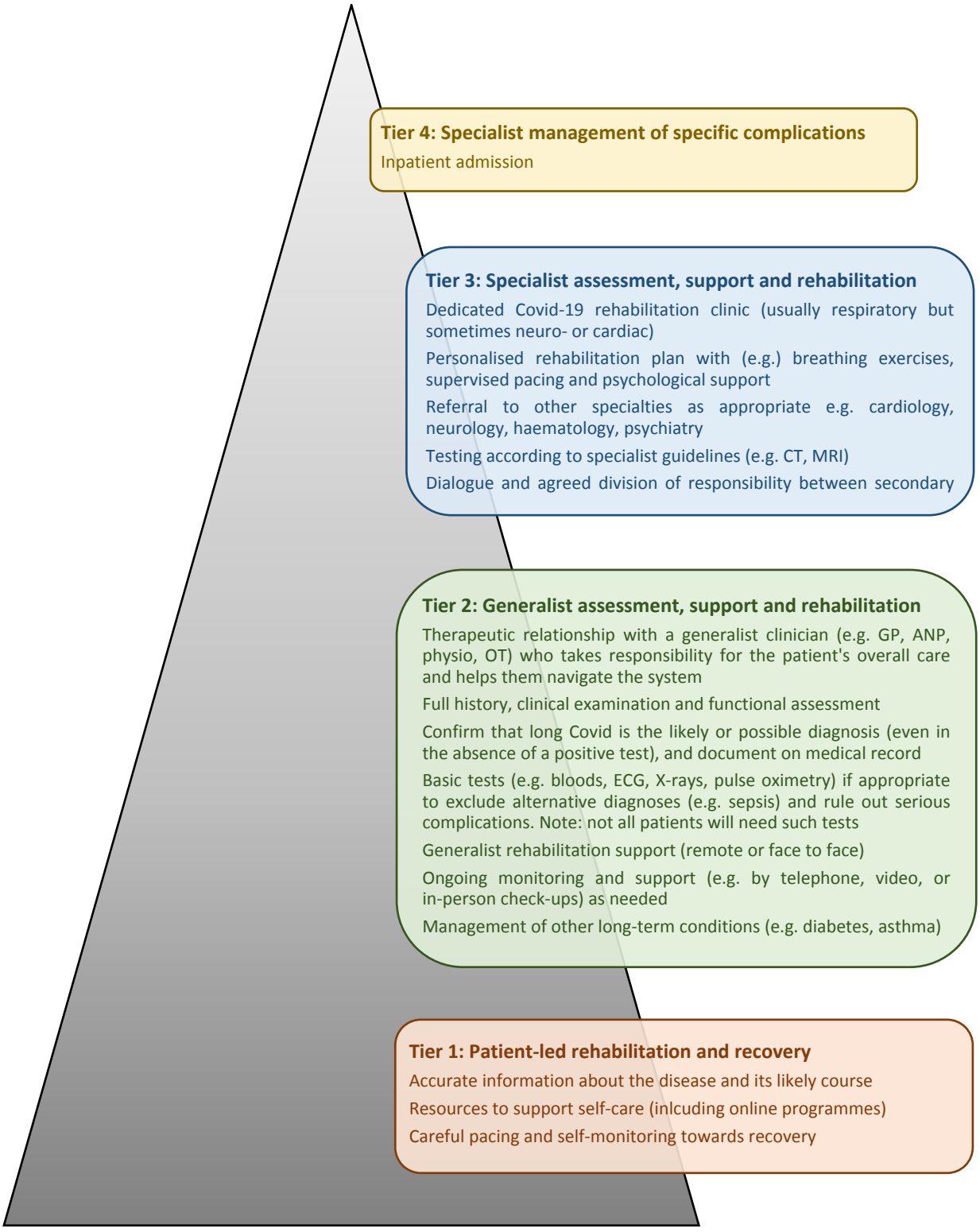

Figure: Suggested tiered approach for a long Covid service

The 1% of patients requiring **Tier 4 care for specific complications** should be readily identified by either GPs or specialist clinicians on the basis of acute (perhaps red-flag) symptoms.

In sum, we need to **retain specialist respiratory rehabilitation** for survivors of acute Covid-19 pneumonia but also supplement this with a new tier of **generalist**

(ideally, primary care based) rehabilitation and follow-up services, and provide **resources and support for self-care**.

What is needed to support a tiered long Covid service?
On the basis of the estimates in the previous section, to deliver these services, for every Clinical Commissioning Group population of 225,000, new-blood staff would be needed as follows:

- One FTE physiotherapist or equivalent (see below)
- One FTE occupational therapist
- One FTE consultant-grade clinician (e.g. sessions divided between respiratory physician, GP or advanced nurse practitioner, liaison psychiatry, rehabilitation specialist, pain specialist)
- One FTE social support (e.g. sessions divided between social prescriber, health coach, community link worker as appropriate locally) – this workforce may be linked to the new NHS Personalised Care Institute (https://www.england.nhs.uk/personalisedcare/supporting-health-and-care-staff-to-deliver-personalised-care/personalised-care-institute/) being established to train social prescribers
- Administrative support

Given that effective long Covid management will span both primary and secondary care, **integrated care pathways** will be essential. Such services are already in development.[21] However, primary care services are already stretched to breaking point and **GPs in particular are unlikely to have the capacity or the appetite** for setting up and running a new service. **New resource, and a new workforce** (perhaps drawn mainly from advanced nurse practitioners, physiotherapists and occupational therapists) is essential.

One potential source of appropriately-trained personnel for community rehabilitation clinics could include **First Contact Practitioners** (https://firstcontactpractitioner.org.uk/how-does-fcp-model-work-with-pcns/) – physiotherapists with general community and rehabilitation training – who are being trained currently to support Primary Care Networks. Those placed to provide non-medical approaches to care, such as **Social Prescribers**, may help some patients to adapt their lifestyles and address their physical and mental health needs. Patients may also benefit from financial advisers, Citizens Advice Bureau, and faith-based support.[1]

In addition to the individual components of the service, clear and efficient lines of referral between the components are crucial. A **'virtual ward' model** may be a useful technological infrastructure, particularly since many patients will have been managed on virtual wards in the acute phase.

What research is being done – and what additional research is needed?
There are three main kinds of research currently happening on long Covid:

a. **Retrospective or prospective collection of routine data** – e.g. respiratory consultants who run rehabilitation clinics for post-acute Covid-19 are analysing 3-month and 6-month follow-up data. This research is mostly unfunded (undertaken by NHS clinicians) and descriptive (i.e. it will

give a useful estimate of case mix and the clinical course of post-acute Covid-19 but was not set up to test particular hypotheses). It's hard to know how much of this kind of research is going on in the NHS, or what the quality of completed studies will be like.

b. **Prospective, independently funded research studies of particular cohorts of patients**. For example,
   - The PHOSP ('post-hospitalisation') study (www.phosp.org), led from the University of Leicester and funded by UK Research and Innovation and National Institute for Health Research (NIHR), is *"a long term research study to recruit 10,000 patients who have been hospitalised with COVID-19. Over the course of a year, clinical assessments will track patients to gain a comprehensive picture of the impact COVID-19 has had on longer term health outcomes across the UK."*
   - COVERSCAN (https://coverscan.com), funded by Innovate UK and EU Horizon 2020, seeks to map organ damage in patients with Covid-19 using serial MRI scanning.
   - University College London is leading the UK arm of an International Observational Study of Outpatients with SARS-CoV-2 Infection in adults who were not hospitalised, to estimate the rate of disease progression for adults who seek testing and test positive for SARS-CoV-2 (https://www.ucl.ac.uk/global-health/research/z-research/international-sars-cov-2-infection-observational-study-icos).

c. **Qualitative and mixed-method research**. A number of smaller studies are using mainly or exclusively qualitative methods to capture the patient experience and understand the challenges for organisation and delivery of services. For example, Remote by Default, a multi-partner study led from the University of Oxford, is exploring service provision for patients with both acute and chronic Covid-19 (https://www.phc.ox.ac.uk/covid-19/projects/remote-by-default-care). We have interviewed over 100 patients with Covid-19 for that study so far.

We have identified the following priority areas for new research:

a. **Studies of risk factors and upstream causes**. The weakest section of this report in terms of published evidence is probably the question of what predisposes a person to develop long Covid (and what could protect people from developing it). Basic science research is needed to understand the underlying causes of Long Covid, how it differs from other post-viral conditions such as Chronic Fatigue Syndrome, and what predisposing factors may predict the likelihood of developing it (eg: genetic or metabolomic studies).

b. **Prospective observational cohort studies of the clinical course of long Covid in non-hospitalised patients**. The PHOSP study has been well-designed but arguably has overly restrictive inclusion criteria, since 90% of patients with Covid-19 were never hospitalised and many (perhaps the majority) never had a positive swab. PHOSP will miss most of the patients in the long Covid support groups, for example. The Society of Rehabilitation Medicine

c. **Intervention studies**. Long Covid rehabilitation clinics are likely to be an ideal setting for clinical trials of different interventions (e.g. different kinds of breathing exercises, different treatments for fatigue and for pain).

d. **Studies of optimising the service model**. Quality improvement and co-design studies could refine and improve the outline model of tiered care described above. The role of virtual services could be explored as part of this work.

e. **Studies of how disadvantage impacts long Covid**. A condition that leads to inability to work is likely to have a disproportionate impact on the poor and disadvantaged (e.g. without full employment benefits, living in poor housing and with low health, digital and system literacy). A major finding in our qualitative research was the amount of work the patient needs to do to secure a diagnosis and a treatment package. The less articulate (including limited English speakers) and less well-connected are likely to be missing out on care. In some cases, long Covid in a family breadwinner will have major impacts (e.g. eviction, repossession).

Conclusion

We welcome the Select Committee's interest in long Covid, which is affecting tens of thousands of people across the country. There is something of a paradox that the services which were established to respond to acute Covid-19 are ill-suited to the assessment and management of this chronic, variable and fluctuating condition which needs ongoing care and support tailored to the patient's particular needs. Whilst the evidence base on this new condition is relatively sparse, we already know enough to improve current services. High on the priority list are interdisciplinary guidelines and a programme of research which incorporates basic science, epidemiology, health services research and the social sciences.

23 September 2020

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case rate of 587 per 100 000. The crude COVID-19 death rate in prisons was 39 deaths per 100 000 prisoners, which was higher than the US population rate of 29 deaths per 100 000 (**Table**). However, individuals aged 65 years or older comprised a smaller share of the prison population than of the US population (3% vs 16%, respectively) and accounted for 81% of COVID-19 deaths in the US population. The Table provides a standardized calculation showing that the adjusted death rate in the prison population was 3.0 times higher than would be expected if the age and sex distributions of the US and prison populations were equal.

The **Figure** displays the daily trends in cumulative, confirmed cases of COVID-19 in state and federal prisons and the US population from March 31, 2020, to June 6, 2020. The COVID-19 case rate was initially lower in prisons but surpassed the US population on April 14, 2020. The mean daily case growth rate was 8.3% per day in prisons and 3.4% per day in the US population.

Discussion | COVID-19 case rates have been substantially higher and escalating much more rapidly in prisons than in the US population. One limitation of the study is that it relied on officially reported data, which may be subject to inaccuracies and reporting delays, but are the only data available. Comprehensive data on testing rates were not available, and testing rates in both prisons and the overall population were uneven, with many facilities testing no prisoners or only symptomatic persons.[2,5] Mass testing in select prisons revealed wide COVID-19 outbreaks, with infection rates exceeding 65% in several facilities.[2] Reported case rates for prisoners therefore likely understated the true prevalence of COVID-19 in prisons.

A second limitation is that departments of corrections generally did not report demographic data on decedents, and therefore we could not adjust death rates to account for race/ethnicity and comorbidity. This study focused on prisons but did not include jails or other detention facilities where there have been notable COVID-19 outbreaks. Although some facilities did engage in efforts to control outbreaks, the findings suggest that overall, COVID-19 in US prisons is unlikely to be contained without implementation of more effective infection control.

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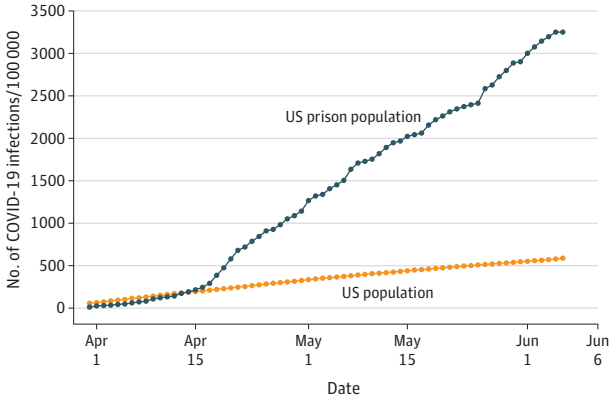
Figure. Trends in Cumulative Coronavirus Disease 2019 (COVID-19) Confirmed Case Rate per 100 000 People for Prison and US Populations



Data are from the UCLA Law COVID-19 Behind Bars Data Project and the US Centers for Disease Control and Prevention.[3,4] The US population is 327 167 439 and the US prison population is 1 295 285.

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Concept and design: Saloner, Parish, Ward.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Saloner, Parish, Ward, DiLaura.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Saloner, Parish, Ward.
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Persistent Symptoms in Patients After Acute COVID-19

In Italy, a large proportion of patients with coronavirus disease 2019 (COVID-19) presented with symptoms (71.4% of 31 845 confirmed cases as of June 3, 2020).[1] Common symptoms include cough, fever, dyspnea, musculoskeletal symptoms (myalgia, joint pain, fatigue), gastrointestinal symptoms, and anosmia/dysgeusia.[2-4] However, information is lacking on symptoms that persist after recovery. We assessed

Table. Demographic and Clinical Characteristics of the Study Sample (N = 143)

Characteristics	Value
Age, mean (SD), y	56.5 (14.6)
Female sex, No. (%)	53 (37.1)
Body mass index, mean (SD)[a]	26.3 (4.4)
Vaccination, No. (%)	
Seasonal influenza	32 (22.4)
Pneumococcus	13 (9.1)
Diagnoses, No. (%)	
Chronic heart disease	7 (4.9)
Atrial fibrillation	4 (2.8)
Heart failure	4 (2.8)
Stroke	2 (1.4)
Hypertension	50 (35)
Diabetes	10 (7)
Kidney failure	3 (2.1)
Thyroid disease	26 (18.2)
Chronic obstructive pulmonary disease	13 (9.1)
Active cancer	5 (3.5)
Immune disorders	16 (11.2)
Regular physical activity, No. (%)	90 (62.9)
Smoking status, No. (%)	
None	63 (44.1)
Active	15 (10.5)
Former	65 (45.4)
Acute COVID-19 characteristics, No. (%)	
Pneumonia diagnosed	104 (72.7)
Intensive care unit admission	18 (12.6)
Oxygen supplementation	
Oxygen therapy	77 (53.8)
Ventilation	
Noninvasive	21 (14.7)
Mechanical	7 (4.9)
Pharmacological treatments during acute COVID-19	
Antiretroviral	102 (71.3)
Hydroxychloroquine	104 (72.7)
Azithromycin	59 (41.3)
Anti-IL-6 drugs (tocilizumab)	44 (30.8)
Length of hospital stay, mean (SD), d	13.5 (9.7)
Post-acute COVID-19 follow-up characteristics	
Days since symptoms onset, mean (SD)	60.3 (13.6)
Days since discharge, mean (SD)	36.1 (12.9)
Persistent symptoms, No. (%)	
None	18 (12.6)
1 or 2	46 (32.2)
≥3	79 (55.2)
Worsened quality of life, No. (%)[b]	63 (44.1)

Abbreviation: COVID-19, coronavirus disease 2019.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Quality of life was assessed using the EuroQol visual analog scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). Worsened quality of life was defined by a 10-point difference in health status before COVID-19 vs at the time of the visit.

persistent symptoms in patients who were discharged from the hospital after recovery from COVID-19.

Methods | In the waning phase of the pandemic, beginning on April 21, 2020, the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome, Italy, established a post-acute outpatient service for individuals discharged from the hospital after recovery from COVID-19. All patients who met World Health Organization criteria for discontinuation of quarantine (no fever for 3 consecutive days, improvement in other symptoms, and 2 negative test results for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] 24 hours apart) were followed up. At enrollment in the study, real-time reverse transcriptase–polymerase chain reaction for SARS-CoV-2 was performed and patients with a negative test result were included.

Patients were offered a comprehensive medical assessment with detailed history and physical examination. Data on all clinical characteristics, including clinical and pharmacological history, lifestyle factors, vaccination status, and body measurements, were collected in a structured electronic data collection system. The COVID-19 postacute outpatient service is currently active, and further details about the patient evaluation protocol are described elsewhere.[5]

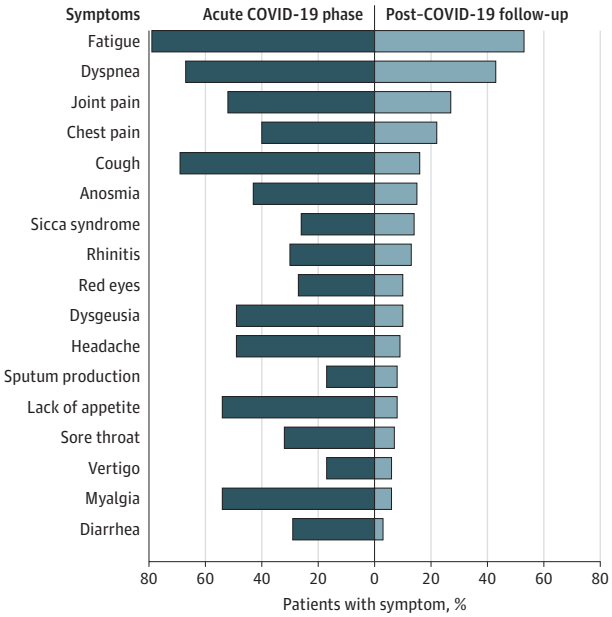
In particular, data on specific symptoms potentially correlated with COVID-19 were obtained using a standardized questionnaire administered at enrollment. Patients were asked to retrospectively recount the presence or absence of symptoms during the acute phase of COVID-19 and whether each symptom persisted at the time of the visit. More than 1 symptom could be reported. The EuroQol visual analog scale was used to ask patients to score their quality of life from 0 (worst imaginable health) to 100 (best imaginable health) before COVID-19 and at the time of the visit. A difference of 10 points defined worsened quality of life. All analyses were performed using R version 3.6.3 (R Foundation).

This study was approved by the Università Cattolica and Fondazione Policlinico Gemelli IRCCS Institutional Ethics Committee. Written informed consent was obtained from all participants.

Results | From April 21 to May 29, 2020, 179 patients were potentially eligible for the follow-up post-acute care assessment; 14 individuals (8%) refused to participate and 22 had a positive test result. Thus, 143 patients were included. The mean age was 56.5 (SD, 14.6) years (range, 19-84 years), and 53 (37%) were women. During hospitalization, 72.7% of participants had evidence of interstitial pneumonia. The mean length of hospital stay was 13.5 (SD, 9.7) days; 21 patients (15%) received noninvasive ventilation and 7 patients (5%) received invasive ventilation. The characteristics of the study population are summarized in the **Table**.

Patients were assessed a mean of 60.3 (SD, 13.6) days after onset of the first COVID-19 symptom; at the time of the evaluation, only 18 (12.6%) were completely free of any COVID-19–related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more. None of the patients had fever or any signs or symptoms of acute illness. Worsened quality of life was

Figure. COVID-19–Related Symptoms



The figure shows percentages of patients presenting with specific coronavirus disease 2019 (COVID-19)–related symptoms during the acute phase of the disease (left) and at the time of the follow-up visit (right).

observed among 44.1% of patients. The **Figure** shows that a high proportion of individuals still reported fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%).

Discussion | This study found that in patients who had recovered from COVID-19, 87.4% reported persistence of at least 1 symptom, particularly fatigue and dyspnea. Limitations of the study include the lack of information on symptom history before acute COVID-19 illness and the lack of details on symptom severity. Furthermore, this is a single-center study with a relatively small number of patients and without a control group of patients discharged for other reasons. Patients with community-acquired pneumonia can also have persistent symptoms, suggesting that these findings may not be exclusive to COVID-19.[6]

Clinicians and researchers have focused on the acute phase of COVID-19, but continued monitoring after discharge for long-lasting effects is needed.

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Author Contributions: Drs Carfì and Landi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Drafting of the manuscript: Carfì, Landi.
Critical revision of the manuscript for important intellectual content: Bernabei, Landi.
Statistical analysis: Carfì.
Supervision: Bernabei, Landi.

Conflict of Interest Disclosures: None reported.

Additional Information: The members of the Gemelli Against COVID-19 Post-Acute Care Study Group are listed in reference 5.

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Trends in Daily Use of Biotin Supplements Among US Adults, 1999-2016

Over-the-counter biotin supplements, especially in high dosages (≥5 mg/d, or 166-fold greater than the dietary recommendation of 30 µg/d), are widely available and marketed as having health benefits such as stimulating growth of hair and nails. The US Food and Drug Administration (FDA) issued a safety communication in 2017 warning that high-dosage biotin supplement use may interfere with laboratory test accuracy.[1] To understand the potential clinical implications of high-dosage biotin supplement use, we characterized the prevalence and trends in use of 1 mg/d or greater and 5 mg/d or greater of biotin among US adults from 1999 to 2016. A biotin dosage of 1 mg/d or greater was chosen because lower dosages (<1 mg/d) are unlikely to interfere with laboratory tests; a dosage of 5 mg/d or greater was studied because biotin supplements for hair and nail growth often contain 5 mg/d or more.

Methods | Repeated cross-sectional surveys from the nationally representative National Health and Nutrition Examination Survey (NHANES) were used to assess trends in self-reported biotin supplement use of 1 mg/d or greater and 5 mg/d or greater from 1999 to 2016 (9 survey cycles). In each cycle, NHANES sampled noninstitutionalized US residents through a complex, stratified, multistage probability sampling design with certain populations overrepresented (overall response, 74%).[2] Participants provided informed consent.[2] Because the data are publicly available and anonymized, the

APPENDIX

Additional information contributed by our CanCOVID members

List of references

Databases searched: PubMed, Web of Science, Google, Dimensions.ai
Search strategy: (long OR post-acute OR chronic OR haul) AND COVID*

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WHO MNCAH Covid-19 research network _ Research abstracts_Last updated 29th June 2020						
#	Title, Site, PI, Organisation, Funder	Objectives	Methods	Sample size	Current status	Results expected (mm/yyyy)
1	CHAIN cohorts for COVID-19. Kenya. Judd Walson. University of Washington and James Berkley, KEMRI Wellcome Trust/Oxford University. Funded by Bill & Melinda Gates Foundation	(1). To establish capacity for facility-based surveillance of SARS CoV-2 . (2). To detail clinical presentation, course and outcomes. (3). To develop clinical protocols for effective utilization of a respiratory care bundle and referral. (4). To determine risk of death by age and risk group. (5). To determine the contribution of faecal shedding in high risk populations. (6). To develop protocols for sample collection to ensure lack of compromise by SARS-CoV-2. (7). To determine indirect effects on other health services.	Enhance surveillance at the KEMRI/Wellcome Trust Research Programme Clinical Information Network (CIN) participating sites to include adults, peripheral facilities and ongoing surveillance of health resources . We will answer targeted research questions that will have immediate impact on the understanding, surveillance and management of SARS-CoV-2 affected vulnerable populations. We will also expand to additional sites based on a review of initial data and epidemiologic status.	TBD	Ongoing	TBD
2	The Power of Breast feeding and Human Milk in a Time of COVID Contagion. US, Canada, China, Australia, Switzerland, UK, Japan, Uganda, South Africa, Brazil, Peru, Switzerland, UK, Germany. Lars Bode. University of California, San Diego, Mother-Milk-Infant Center of Research Excellence (MOMI CORE). Funded by unrestricted gift from the Family Larsson-Rosenquist Foundation, Switzerland; community philanthropic support; grant from Yankelovich Center for Social Science Research at UC San Diego	(1) To confirm that the virus is not transmitted through breastfeeding. (2) To discover antiviral components in human milk. (3) To synthesize antiviral components for people of all ages. (4) To evaluate effective science communication by tracking social media and other platforms to ensure that accurate messaging reaches the population at large.	(1) Human cohort study to confirm absence of SARS-CoV-2 from human milk and, more importantly, (2) combination of preclinical efficacy testing in tissue culture and animal models to identify antiviral components in human milk, (3) synthesize identified antiviral components in bioengineered microbes, (4) use of social networking theory and message tracking to evaluate communication dissemination and diffusion with particular emphasis on social media platforms.	(1) Initially 100 mother-infant dyads, (2,3) n/a, (4) global	(1) human cohort study ongoing; (2,3) preclinical efficacy testing ongoing; (4) pilot project completed and recently published in Maternal & Child Nutrition; scaling up ongoing	First results are already available and either published or in preparation for publication

3	Optimising the treatment of COVID 19 affected Bangladeshi adolescents and adults with severe pneumonia and/or ARDS using adaptive version of locally made Bubble CPAP. Bangladesh. Mohammod Jobayer Chisti, Icddr,b.	To describe the proportion of patients developing treatment failure or death among adolescent and adult COVID-19 patient with severe pneumonia receiving adult bubble CPAP contrasting to WHO standard oxygen therapy	(1) Test device in healthy individuals to assess whether appropriate nasal sealing is achieved, and adequacy of the oxygen flow and the desired pressure is maintained (measured by manometer). (2) Test safety in 30-40 COVID-19 patients (age ≥18 years) with severe pneumonia and hypoxemia. (3) Cluster RCT to test effectiveness.The study population will be hospitalized adult COVID-19 patients excluding those who will not have adequate respiratory drive such as gasping respiration or requiring cardiopulmonary resuscitation.	Safety phase: 30-40 participants; Testing phase: 100 participants	Ongoing	Dec-20
4	(1). SARS-CoV-2 in human milk: assay validation and detection in COVID-19+ women (COVID-19Lact). USA. Shelley McGuire, University of Idaho, Funded by the Bill and Melinda Gates Foundation. (2). COVID-19, human milk, and infant feeding. USA. National Science Foundation	(1). Cross-validate a RT-qPCR for SARS-CoV-2 in human milk in 2 human milk laboratories (2). Evaluate whether milk produced by COVID-19+ women (as tested by nasopharyngeal or oropharyngeal swab specimens) contains SARS-CoV-2 RNA. (3). Examine immunological profiles (SARS-CoV-2 specific IgG, IgA) in milk and blood collected from COVID-19+ women in the 2 months after diagnosis	Using standardized and optimized methods, we will collect milk, blood spots, and breast swab samples from COVID-19+ women during the 2 months following diagnosis. We will also study nonbreastfeeding women. Milk will be analyzed for the virus and antibodies to the virus using methods validated/optimized for human milk (also part of this project).	50 breastfeeding dyads and 25 nonbreastfeeding dyads	Currently enrolling	End of summer or fall for finalized data for BMGF grant; 2021 for NSF grant

5	Maternal and perinatal outcomes of coronavirus disease (COVID-19) in pregnancy in the UK. United Kingdom. Marian Knight, National Perinatal Epidemiology Unit, University of Oxford, UK. Funded by the National Institute for Health Research Health Technology Assessment Programme (NIHR HTA)	(1). To determine: i. incidence of hospitalisation with COVID-19 in pregnancy; ii. the outcomes of COVID-19 in pregnancy for mother and infant. (2). To investigate: i. influence of demographic and pregnancy characteristics on outcomes; ii. timing of delivery and use of extracorporeal membrane oxygenation. iii. influence of other variations in management on outcomes. (3). To inform guidance on the management of coronavirus (COVID-19) infection in pregnancy	National prospective observational cohort study using the national UK Obstetric Surveillance System (UKOSS). UKOSS collects information about severe maternal morbidity through > 500 collaborating clinicians in all 194 UK hospitals with consultant-led maternity units throughout the UK. Reporting clinicians report all pregnant women with confirmed COVID-19 admitted to their unit using a web-based rapid reporting system. Data on comparison women will be obtained from the existing UKOSS system.	Population level (1000+)	Ongoing - data collection commenced from 1st March 2020	Interim results planned by May 2020; final results Feb 2021
6	Neonatal complications of coronavirus disease (COVID-19) in the UK. United Kingdom. Chris Gale Imperial College London, Jenny Kurinczuk National Perinatal Epidemiology Unit, University of Oxford. Funded by the NIHR Policy Research Unit in Maternal and Neonatal Health and Care, UK.	(1). Incidence of hospitalised neonatal COVID-19? (2). Clinical presentation of neonatal COVID-19? (3) clinical treatments used for neonatal COVID-19? (4). Incidence of nosocomial spread of neonatal COVID-19. (5) Characteristics of infants with nosocomially acquired neonatal COVID-19. (6). Outcome of neonatal COVID-19. (7) Rate of reported vertical transmission of COVID-19. (8) Secondary neonatal impacts of maternal COVID-19 infection in the context of staff protection	Active surveillance will be undertaken through the British Paediatric Surveillance Unit (BPSU) which asks all UK paediatricians to report any baby that is affected by COVID-19 weekly. A response is requested even if no cases were encountered. This will link with ongoing obstetric surveillance for maternal cases, surveillance of neonatal deaths and stillbirths, confirmed cases notified through relevant public health agencies and routinely recorded neonatal and paediatric intensive care data.	Population level (currently unknown)	Ongoing - data collection commenced from 1st March 2020 for 1 year initially	Interim results planned by June 2020

7	COVID-19: Harnessing AMANHI Infrastructure to assess direct impact on MNCH. Fyezah Jehan Aga Khan University (Karachi, Pakistan site), Sunil Sazawal Center for Public Health Kinetics and Public Health Laboratory-IDC, Pemba, (Pemba, Tanzania site), Abdullah Baqui, Johns Hopkins University and Projahnmo Research Foundation (Sylhet, Bangladesh site). Funded by Bill and Melinda Gates Foundation	(1) Determine Covid-19 age-specific cumulative incidence in age 1-4 years and women of reproductive age. (2) Determine proportion with moderate/severe disease. (3) Investigate risk factors. (4). Evaluate impact on subsequent infection and severity risk. (5). Evaluate clinical presentation, treatment, clinical course to 8 weeks postpartum. (ii) Evaluate outcomes in Covid positive women and identify high risk subgroups. (iii). Collect harmonized data, contribute to pooled analyses. (6). Document health care utilization.	(1) In phase 1 (epidemic phase) weekly telephonic surveillance will be conducted to collect information about both mother and child on respiratory and non- respiratory illnesses including confirmed COVID diagnosis, hospitalization, pregnancy status of the mother and telephonic follow-up for well-being of the newborns. (2) In phase 2 (post epidemic phase) we will continue with morbidity surveillance using household visits and perform Rapid COVID-19 Antibody Testing on all women and their children.	10,000	In planning and approval phase. Expected to start by end of May 2020	Apr-21
8	A prospective cohort study of the effects of COVID-19 in pregnancy and the neonatal period. Pakistan. Shabina Ariff Aga Khan University Karachi Jose Villar Oxford Maternal and Perinatal Health Institute (OMPHI). Funded by Oxford University (Intergrowth 21st consortium)	Provide high-quality evidence regarding the effects of COVID-19 on maternal, fetal and neonatal outcomes	This will be a case –control study with 2 controls for each case. Women will be recruited both in the antenatal wards as well as in labor suits 'Exposed' cases will be defined as a pregnant women with either: a) laboratory confirmed COVID-19; b) radiological pulmonary findings suggestive of COVID-19; c) maternal symptoms compatible with COVID-19 according to a predefined list, or d) absence of symptoms, whilst in close interaction with a person(s) with confirmed COVID-19	Total 500 exposed and 1000 controls	Ethical approval submitted. Recruitment expected to commence mid May 2020	Dec-20

9	Understanding COVID-19 infections in pregnant women and their babies in The Gambia, Malawi, Mozambique, Kenya and Uganda (periCOVIDAfrica) and UK (periCOVID). Kirsty LeDoare St George's University UK. Funded by EDCTP/PREPARE and Wellcome Trust/PRECISE	Develop a programme to monitor pregnant women for COVID-19; determine the impact of COVID-19 infection in pregnancy on health outcomes 3 months after delivery; examine immune responses to SARS-CoV-2 in pregnant women and their babies; determine whether protective immunity can be passed from mother to infant inutero by examining umbilical cord blood; work with communities to understand how infections like COVID-19 can be spread and prevented during pregnancy	Embed COVID-19 surveillance into the ongoing PREPARE and PRECISE studies; create a longitudinal biobank of samples collected at different time points in asymptomatic women and between diagnosis, delivery and 4-10 weeks postpartum to measure immunity to COVID-19; measure antibody concentrations in recruited mothers and babies; embed COVID-19 public engagement into existing PREPARE work	Up to 45,000 women	Protocol development	Mar-21
10	Containing COVID-19 in rural Africa: Can symptom checks replace testing in the Test-Trace-Isolate (TTI) paradigm? The Gambia, West Kiang Region. Andrew Prentice LSHTM The Gambia	To test whether a Symptoms-Trace-Isolate approach to COVID-19 containment can replace Test-Trace-Isolate in rural African communities.	Thrice-weekly telephone questionnaire to 1650 family heads enquiring about symptoms in each family member. PCR testing of indicative cases. Family isolation advice and Community Care Packages for any family with a positive case. Retrospective antibody testing of all ~15,000 family members once peak of epidemic has passed. Additional social science and GWAS/EWAS investigations will be embedded.	15,000 people of all ages living in 1650 households in 36 villages covered by our West Kiang Demographic & Health Surveillance Survey.	Not yet started	Mid 2021

12	French-Covid cohort. Pregnancy and pediatric sub-studies. French national study. Olivier Picone Hospital Louis Mourier Colombes France, François Angoulvant Hopital Necker-Enfants Malades Université de Paris France, Yazdan Yazdanpannah Inserm reacting France, Funded by Inserm reacting, France	Pregnant women cohort study: Follow up of pregnant women with proven Covid-19 infection. To gather data on consequences of covid-19 infection during pregnancy. Pediatric cohort study: Follow up of children with proven Covid-19 infection. To gather data on consequences of covid-19 infection in children. To obtain samples from infected children to perform genetic, immunologic, serologic, and transcriptomic lab tests	Prospective cohort study. Inclusion criteria in the pregnancy study: proven covid-19 infection during pregnancy; hospitalization. Inclusion criteria in the pediatric study: age < 18 years; proven covid-19 infection; hospitalisation		Recruiting	Jul-20
12	Prevalence and impact of the COVID-19 disease in young children at high risk of mortality. Côte d'Ivoire, Cameroon, Uganda, Mozambique, Zambia, Cambodia. Maryline Bonnet. Institut de Recherche pour le Développement. TB-Speed COVID. Funded by ANRS with co-funding from UNITAID and the 5% initiative	Using the opportunity of the TB-Speed project set-up, our primary objective is to assess the prevalence of COVID-19 in children below 5 years old at high risk of mortality: i) children severe pneumonia and in hospitalized: ii) hospitalized children with severe acute malnutrition.	Nested observational studies.Children will be tested for SARS-Cov-2 at the time of enrolment and data collected in the TB-Speed Pneumonia and TB-Speed SAM studies will be used to document their clinical presentation, medical history, laboratory and radiological characteristics and outcomes. Gr1 Children with severe pneumonia. Children 2-59 months. Severe pneumonia defined using WHO criteria. Gr2. Hospitalized children without SAM. Children 2-59 months. Hospitalized with SAM	We propose to enrol all consecutive children included in the TB-Speed Pneumonia study (Group 1, N=940) and the TB-Speed SAM study (Group 2, N=210) over a 6 months period	Protocol writing	Apr-21

13	Covid-19 Pediatric Observatory (PANDOR). French National study. François Angoulvant. Hopital Necker-Enfants Malades Université de Paris France. Funded by ACTIV. Supported by the French Pediatric Society	To describe the clinical phenotypes of hospitalized pediatric patients with Covid19 in France, according to age groups. This includes Kawasaki Syndrome and Kawasaki like induced by COVID-19	Prospective cohort study. Inclusion criteria: age < 18 years, proven covid-19 infection, hospitalisation https://clinicaltrials.gov/ct2/show/NCT04336956	Over 400 children were already included from March 1st to May 12th , 2020	Recruiting	May-20
14	COVIME : Assessment of a routine screening strategy of SARS-CoV-2 in health professionals and delivering women at the maternity hospital of Yalgago Ouedraogo Hospital, Ouagadougou, Burkina Faso: acceptability, prevalence and six-week outcomes of the mother-child pairs. Valériane Leroy, Inserm 1027, Toulouse, France. Séni Kouanda, IRSS, Ouagadougou, Burkina Faso. Yalgado Ouédraogo University Hospital maternity ward, Ouagadougou, Burkina Faso. Funded by ANRS	To implement and evaluate a routine screening strategy for SARS-CoV-2 infection with triage of healthcare workers and parturient women at the Yalgado Ouédraogo University Hospital maternity ward, in Ouagadougou in Burkina Faso, including a 6-week follow-up of mother-infant pairs.	Cross-sectional study including a SARS-CoV-2 diagnostic test by rt-PCR to all healthcare workers, and to parturient women presenting symptoms in line with probable COVID-19 cases, followed by an observational prospective cohort comprised of delivering women at the Yalgado Ouédraogo University Hospital maternity ward and followed-up with their newborn until 6 weeks post-partum, and according to their exposure to SARS-CoV-2.	200 healthcare workers and 3150 mother-infants pairs at birth, of whom 1225 possible cases requiring SARS-CoV-2 diagnosis.	Preparation	May-21

15	COroFet. Assessment of obstetric, fetal, neonatal and vertical transmission risk of SARS-CoV-2 during the COVID-19 pandemic. Creation of a clinical, biological and tissue database of pregnancy outcomes. France. CHU Toulouse. Charlotte Dubuc, Marion Groussolles CHU Toulouse. Funded by PHRC	Describe 4 groups of women at the time of pregnancy termination: symptomatic COVID-19 positive (C + S), asymptomatic COVID-19 positive (C + A), immune COVID-19 negative (CIA), COVID negative -19 not immunized (NINI) - Compare the occurrence of an unfavorable pregnancy outcome (early miscarriage before 14 weeks or late after 14 weeks, fetal death in utero, abnormal course of pregnancy, premature delivery). Document vertical mother-to-child transmission of COVID-19 if found	Monocentric observational epidemiological study (CHU Toulouse). The study scheme is inspired by a case-cohort design. The study will take place in 2 phases: an inclusion and data collection phase, and an analysis phase of the samples taken	3920	Recruitment commenced 27th April 2020	Jun-21
16	Knowledge, attitudes, and risk behaviour practices related to Covid-19, in women of reproductive age in rural Bangladesh. Mymensingh, Bangladesh. Camille Raynes-Greenow, University of Sydney.	What are the knowledge, attitudes and practices of understanding risk of SAR-CoV-2/covid-19 in women of reproductive age in rural Bangladesh?	Household surveillance of women of reproductive age, cross sectional design, data collected via telephone interview electronically.	Population surveillance system, total households 93045, total population 380510, currently married women of reproductive age 70325, 3000 identified pregnant women	Finalising the data collection form	Dec-20

17	Covid-19 infection and movement restrictions impact on health service use and pregnancy outcomes. Mymensingh, Bangladesh. Camille Raynes-Greenow, University of Sydney.	Have movement restrictions reduced health service use and pregnancy outcomes?	A cohort study (embedded into a cluster randomised controlled trial) of women who were recently pregnant or who became pregnant during the covid-19 movement restriction in Bangladesh. Telephone interviews (or face to face pending movement restrictions) of birth outcomes and health service use.	2200	Designing the data collection form. Cohort already assembled	Dec-21
18	Rapid monitoring surveys to inform response to the COVID-19 crisis across sub-Saharan Africa. PI Wafaie Fawzi, Harvard T.H. Chan School of Public Health. Partner organizations: Africa Research Implementation Science and Education (ARISE) Network, Africa Academy for Public Health (Tanzania), Muhimbili University of Health and Allied Sciences (Tanzania), University of Dodoma (Tanzania), Addis Continental Institute of Public Health (Ethiopia), Haramya University (Ethiopia), Nouna Health Research Center (Burkina Faso) , University of Ibadan (Nigeria).	Establish a mobile survey platform across Ethiopia, Burkina Faso, Tanzania and Nigeria to rapidly generate longitudinal data from adults and adolescents in urban and rural households, and separately from healthcare workers, to inform policy efforts and prioritize areas for intervention to mitigate direct and indirect health consequences of the COVID-19 epidemic.	This longitudinal study will assess knowledge, attitudes, practices and perceptions related to COVID-19 prevention and management as well as the impact of the outbreak on other health domains including nutrition, food security and hunger; mental health; access to medications, curative services and preventive services such as antenatal care and immunization; and impact of school closures on adolescent health and wellbeing. 10-15 minute surveys will be administered monthly using computer-assisted telephone interviewing (CATI) methods.	2400 adults aged 20 or over from the general population; 2400 adolescents aged 10-19; 1200 healthcare workers	In planning and approval phase. Expected to start by June 2020.	Jun-20

19	LAKANA COVID-19 Surveillance Study - Impact on health systems. Mali. Per Ashorn and Samba Sow. Tampere University and the Center for Vaccine Development, Mali. The Bill & Melinda Gates Foundation.	To measure the impact of the epidemic on health service delivery at 12 health facilities in the Kayes and Kita regions of Mali.	A number of service delivery indicators will be collected on a weekly basis for the duration of the study. The collected indicators will be compared to historical data sourced from health facility records to understand the change in the delivery of services and functioning of the health system over the course of the epidemic.	12 health facilities near Kita, Mali.	Preparing to start enrollment.	June 2021 (preliminary results sooner).
20	LAKANA COVID-19 Surveillance Study - Community survey of infection and exposure. Mali. Per Ashorn and Samba Sow. Tampere University and the Center for Vaccine Development, Mali. The Bill & Melinda Gates Foundation.	To estimate the population-level prevalence of acute Covid-19 infections and exposure to Covid-19 infection in rural and semi-urban settings, separately in four age strata and (under 5, 5 to 14, 15 to 60, and over 60 years), and to describe the risk factors of Covid-19 infection in the general population.	A population-based sample survey will be conducted. All members of selected households will be given the opportunity to enroll and provide blood and NPS samples.Data will be collected on physical signs, comorbidities, symptoms and disease severity to understand how the infection affects different sub-groups.	3000 participants.	Preparing to start enrollment.	September 2020.

21	SARS-CoV-2 and the immune system in early life. France. Dr Nabila SEDDIKI, INSERM. Funded by ANR (Agence Nationale de la Recherche)	To use a non-human primate (NHP) model in collaboration with IDMIT (headed by Dr Roger Le Grand) in order to 1) understand the basis of the interaction(s) between SARS-CoV-2 and the immune system in early life, and 2) To uncover potential transfer of the virus from infected neonates to their mothers during breast-feeding and nursing period.	Pregnant Rhesus animals are currently available at IDMIT for developing a longitudinal newborn study for COVID-19. We propose to expose the newborn with SARS-CoV-2 at birth and follow them up longitudinally for up to 3 months. The primary aim is to perform virological follow up, cellular and molecular immunological assays. In addition samples from mucosal sites will be collected for microbiota analyses.	Cohorts of 10 pregnant animals will be included.	Birth is scheduled for July 2020. All assays are being miniaturized and nursing facilities ready for Mother and child well-being for longitudinal follow-up.	The first results are expected for begining of August 2020.
22	Using ongoing RTSS malaria vaccine evaluation to understand any connection between COVID-19 and malaria among hospitalised children in Ghana. Site: Ghana, PI: Dr Kwaku Poku Asante, Organisation: Kintampo Health Research Centre, Ghana Health Health Service	1. To determine the burden of COVID-19 among children in Ghana. 2. To determine the burden of COVID-19 morbidity and its association with careseeking, 3. To estimate the coinfection of COVID-19, malaria and its influence on presentation of illness among children, 4. To describe clinical features of COVID-19 among hospitalised children with or without malaria comorbidity, 5. To identify appropriate treatment guidelines in the context of COVID-19	The proposed research will be nested within an ongoing evaluation of the pilot implementation of RTS,S/AS01 new malaria vaccine within routine health system in Ghana by the Ghana Health Service. Children receive their first dose of RTS,S/AS01 vaccine at 6 months, second dose at 7 months and third dose delivered at 9 months alongside existing vaccines, measles and yellow fever vaccinations. The fourth dose is administered in 24 months. The pilot implementation is a cluster-randomized design, with some districts implementing the RTS,S/AS01 vaccine and other districts acting as comparison districts. Similar	10,000	The malaria vaccine pilot evaluation is ongoing. The COVID-19 sub study will start once ethical is received on the amended protocol	Dec-21

23	Spanish Registry Epidemiology Children with COVID-19 in Spain (EPICO) Cohort hospitalized children. PIs: Alfredo Tagarro, Cinta Moraleda. Site: SERMAS-Fundacion para la Investigación Biomédica 12 de Octubre. Funder: Asked for funds to several funders, currently not directly funded.	To determine the incidence of SARS-CoV-2 in children, evaluating if it can generate epidemic peaks similar to respiratory syncytial virus (RSV) and influenza virus. To describe the spectrum of the disease, including the contagion time, associated with SARS-CoV-2 infection in the different pediatric age ranges. To describe the mortality and complication rate in pediatric patients with respiratory infection by 2019- nCoV. To predict the risk of mortality and complications based on the clinical, epidemiological and analytical characteristics and the treatment received. To analyze the implications of co-infections in the	Type of study. Multicenter prospective, observational (currently, 50 centers). Population Pediatric patients from 1 month to 17 years attended in hospitals with SARS-CoV-2. Duration of recruitment 24 months. Start of recruitment. March 2020. The registry is is at the secure server of Fundación para la Investigación Biomédica del Hospital 12 de Octubre. The CRF is English-based and set in an electronic format (RedCap) worldwide extended so they can be harmonized with other cohorts, with other registries as WHO registry or PREPARE/ISARIC, and the information and data dictionaries can be easily	Currently, 324 participants.	Enroling.	A first analysis of the 3 first months of epidemics is ongoing. Currently doing database cleaning, analysis will be done in the next 2-3 weeks. A first letter about multisystemic inflammatory syndrome will be released likely next week. A complete analysis will be send likely in the first fortnight of June. We attach some slides of first results.
24	Baby-Friendly Practices and Breastfeeding Rates in Mississippi Hospitals during the COVID epidemic. Anne Merewood. Community Health Sciences, Boston University School of Public Health	(1)Via survey: Assess maternity unit service changes made in 39 birthing hospitals in Mississippi during the COVID epidemic; (2) Assess breastfeeding rates, and rates of skin to skin and rooming in in 39 birthing hospitals in Mississippi, by data from the medical records.	Survey has been sent on Qualtrix to the cohort of hospitals. Data collection is being submitted monthly also by Qualtrxi.	39 Mississippi hospitals with birthing units	Survey has been sent. Data collection is ongoing.	Sep-20

25	Global review of COVID-19 guidelines for postpartum maternal and newborn care identifies the need for better alignment with evidence-based recommendations from the World Health Organization, collborators from Alive and Thrive, no external funding. Karleen Gribble. Western Sydney University, Australia	To assess COVID-19 guidance for alignment with the WHO Guidance regarding post-natal care	National guidance was collected and analysed for alignment with WHO guidance regarding skin-to-skin, early initiation of breastfeeding, direct breastfeeding, rooming in and psychological support	33 countries	Process of writing up	Hopefully will be submitted by end of June
26	Concerns of mothers regarding COVID-19 raised with breastfeeding counsellors in Australia, partner with the Australian Breastfeeding Association, no external funding. Karleen Gribble. Western Sydney University, Australia	To identify how mother's infant feeding concerns have been impacted by COVID-19 in Australia	ABA counsellors completed an online survey after their shift on the National Breastfeeding Helplne describing the COVID-19 related concerns raised with them	211 breastfeeding counsellors	Process of writing up	Hopefully will be submitted by early july

27	Title: Understanding Breastfeeding Practices Among ECHO Cohort Participants Before and During/After the COVID-19 Pandemic; Site PI: Jean Kerver; Org: Michigan State University; Funder: NIH (under review); Proposal is for an Administrative Supplement to the parent ECHO Pediatric Cohort grant (Environmental influences on Child Health Outcomes) for post-doctoral training and research. Jean M Kerver, Michigan State University, Traverse City Campus	Aim 1 (not relevant to COVID-19): To determine if the duration of exclusive breastfeeding protects children born to women with pre-pregnancy obesity from risk for childhood overweight/obesity; Aim 2: To determine if breastfeeding initiation and duration rates among ECHO cohort participants differ prior to and during/after the COVID-19 pandemic; Aim 3: In a COVID-19 hotspot (Detroit, MI) as well as other areas of Michigan, use semi-structured interviews to explore the decision-making experiences regarding infant feeding practices (breastfeeding initiation and duration) of ECHO participants who	First, using data from multiple ECHO cohorts, we aim to determine if the duration of exclusive breastfeeding protects against risk for childhood obesity among those exposed to maternal obesity while in utero. Second, we will estimate, both quantitatively and qualitatively, the impact of the SARS-CoV-2 pandemic on women's breastfeeding practices and experiences. The combination of quantitative and qualitative approaches will enable a more comprehensive understanding of the determinants of breastfeeding before and during/after the pandemic.	unsure at this point, but n= approximately 4,000 pre-COVID-19; n=approximately 700 during/after COVID-19	Administrative Supplement grant is under review at NIH, but parent grant is in year 4 of a 7 year grant	If funded, project dates are 9/1/2020 to 8/31/2022
28	International Pediatric COVID-19 Dara Aggregation Consortium Florence Bourgeois, MD, MPH Boston Children's Hospital and Harvard Medical School, Boston, USA	To build a platform that will provide an integrated database and analytics hub to promote the secure sharing of existing de-identified patient-level data and encourage the standardization of new data collection	Data aggregation across sites and organizations for pooling into a secure cloaud-based database.	unkown	Initiating	Oct-20

29	SARS-CoV-2 in pregnant women and their infants in Fiji, Fiona Russell, MCRI, not funded. If funding available have interested sites in Timor Leste, Ethiopia, Indonesia, PNG	The primary objectivei is to determine if infection with SARS-CoV-2 during pregnancy is a risk factor for poor perinatal outcomes. The secondary objectives are to: 1. Describe the perinatal epidemiology of SARS-CoV-2 in pregnant women; 2. Determine whether pregnant women with maternal diabetes and infection with SARS-CoV-2 during pregnancy is a risk factor for poor perinatal outcomes compared with pregnant women not infected with SARS-CoV-2 during pregnancy, without maternal diabetes;	Prospectve cohort study	2400 pregnant women; 1400 controls	Not started	Dec-21
30	THE ADVERSE RISK OF MATERNAL ANTENATAL SARS-COV-2 INFECTION ON CHILD NEURODEVELOPMENT AND HEALTH OUTCOMES Brown Univeristy, Sean Deoni, NIH / Self	Specific Aim 1: Determine the effect of maternal antenatal Covid-19 infection on fetal and infant neurodevelopment; Specific Aim 2: Determine the impact of outbreak-related environmental stressors on infant neurodevelopment	Neuroiumaging (MRI), neurocognitie assessments (Mullens, CSBS, etc.)	50 infants with Covid-19 mothers; 50 without recruited at same time; 1500 pre-Covid outbreak infants and children	Enrolling new mothers/newborns	Ongoing

31	LONGITUDINAL IMPACT OF THE COVID-19 ENVIRONMENT ON CHILD NEURODEVELOPMENT Brown Univeristy, Sean Deoni, NIH / Self	Examine the longitudinal trajectors of neurodevelopment in children across the age spectrum (infant, young, child, older child and adolescent)	Neuroimaging, Neurocognitive assessments (battery depending on age),	1500+	On-going	On-going
32	Comprehensive assessment of SARS-CoV-2-reactive antibodies in human milk to determine their potential as a COVID-19 therapeutic and as a means to prevent infection of breastfed babies; Icahn School of Medicine at Mount Sinai, PI: R.Powell; New York, NY, USA, Internally funded at the moment, some support from Medela/Milk Stork, other funding pending	Aim 1: To evaluate SARS-CoV-2 Ab binding titers in human milk. Aim 2: To evaluate the neutralization capacity of SARS-CoV-2-specific milk Abs. Aim 3: To evaluate the non-neutralizing, Fc-mediated anti-viral functions of SARS-CoV-2-specific milk Abs. The overarching objective of this study is to reliably estimate the proportion of all COVID-19-recovered milk donors that would have significantly potent SARS-CoV-2-reactive Abs their milk, and the durability of this response.	Milk samples will be assayed by high-throughput Luminex assay against the SARS-CoV-2 Spike protein for IgA, IgG, IgM, and secretory-type Ab reactivity. Samples will be obtained longitudinally for up to 2 years to examine the durability of this response. A subset of milk samples identified as 'high positive' (≥5x the positive cutoff endpoint dilution) will be further analyzed for neutralization, ADCP, and C3 complement pathway activation.	1000 COVID-19-recovered participants	90% enrolled, prelim work published, pilot studies ongoing, awaiting full funding	see https://www.medrxiv.org/content/10.1101/2020.05.04.20089995v1

33	Title: Feasibility of implementing Essential Coaching for Every Mother during COVID-19 Site: IWK Health Centre (Halifax, NS, Canada) PI: Justine Dol (Dalhousie University), Dr. Marsha Campbell-Yeo (Dalhousie University) Funder: Canadian Institutes of Health Research Doctoral Award held by Ms. Justine Dol	To determine the feasibility and acceptability of providing Essential Coaching for Every Mother during the coronavirus pandemic	Cohort study	75	Development stage completed May 2020; Waiting on ethical approval for Phase II (June 29, 2020)	12/2020
34	Title: Mothers' experience of postnatal adjustment during the first six-months of caring for a newborn during COVID-19: A survey with postnatal mothers in the Maritimes Site: Halifax, NS, Canada PI: Justine Dol (Dalhousie University), Brianna Richardon (Dalhousie University), Dr. Marsha Campbell-Yeo (Dalhousie University) Funder: Canadian Institutes of Health Research Doctoral Award held by Ms. Brianna Richardson	The purpose of this study is to explore the relationship between mothers' confidence, social support, anxiety, depression, newborn pain management knowledge, and health information seeking behaviour during COVID-19.	Online survey	500+	Under development, to be launched October 1, 2020	44348

35	Title: Direct and indirect effects of COVID-19 on pregnant women, children and the elderly Site: MRC-RMPRU, Johannesburg, South Africa. PI Shabir Madhi, Portia Mutevedzi	To determine the direct and indirect effects of COVID-19 and the control measures thereof on general health, access to health services, vaccinationa, antenatal services, chronic disease care, nutrition and access to food on a cohort of pregnant women	Leveraging on the health and demographic surveillance system that RMPRU has been running for the last 3 years, a prospective cohort study of pregnant women will be set up to monitor direct and indirect effects of COVID-19	1200 pregnancies expected within the HDSS; 12 000 children followed up twice yearly and ~13000 aged 50+yrs	data collection due to start in July 2020	August 2020 onwards
36	Title: COVID-19 household transmission dynamics; MRC-RMPRU, Johannesburg, South Africa. PI Shabir Madhi, Portia Mutevedzi, Sunday Adedini, Nellie Myburgh	Establish the extent of transmission within a household by estimating the secondary infection rate for household contacts at an individual level, and factors associated with any variation in the secondary infection risk.	prospective cohort study	150 households	protocol developed	Sep-20

37	Title: Understanding community perceptions and experiences of COVID-19 and national COVID-19 control measures and response strategies. MRC-RMPRU, Johannesburg, South Africa. PI Shabir Madhi, Portia Mutevedzi, Sunday Adedini, Nellie Myburgh	To understand community perceptions and experiences of COVID-19 and national COVID-19 control measures and response strategies. - To understand behavioral and cultural factors influencing (positive and negative) compliance with control measures, infection prevention and response strategies instituted by government - To explore issues around stigma, denial, knowledge (knowledge about COVID-19 and source of information) acceptance, community myths and rumors.	qualitative research methods	775 households	data collection due to start in July 2020	Oct-20
38	National pregnancy exposure registry - multi-site in Southa Africa. RMPRU sire PI Portia Mutevedzi	assess the imapct of medical including HIV and ART, environmental and other risk exposures during pregancy on pregnancy outcomes	prospective cohort recruited at antinatal clinics	~25 000 pregnancies per year	funding obtained, awaiting ethics clerance	Mar-21

39	Global review of COVID-19 guidelines for postpartum maternal and newborn care identifies the need for better alignment with evidence-based recommendations from the World Health Organization, collborators from Alive and Thrive, no external funding	To assess COVID-19 guidance for alignment with the WHO Guidance regarding post-natal care	National guidance was collected and analysed for alignment with WHO guidance regarding skin-to-skin, early initiation of breastfeeding, direct breastfeeding, rooming in and psychological support	33 countries	Process of writing up	Hopefully will be submitted by end of June
40	Concerns of mothers regarding COVID-19 raised with breastfeeding counsellors in Australia, partner with the Australian Breastfeeding Association, no external funding	To identify how mother's infant feeding concerns have been impacted by COVID-19 in Australia	ABA counsellors completed an online survey after their shift on the National Breastfeeding Helplne describing the COVID-19 related concerns raised with them	211 breastfeeding counsellors	Process of writing up	Hopefully will be submitted by early july

41	Title: Understanding Breastfeeding Practices Among ECHO Cohort Participants Before and During/After the COVID-19 Pandemic; Site PI: Jean Kerver; Org: Michigan State University; Funder: NIH (under review); Proposal is for an Administrative Supplement to the parent ECHO Pediatric Cohort grant (Environmental influences on Child Health Outcomes) for post-doctoral training and research	Aim 1 (not relevant to COVID-19): To determine if the duration of exclusive breastfeeding protects children born to women with pre-pregnancy obesity from risk for childhood overweight/obesity; Aim 2: To determine if breastfeeding initiation and duration rates among ECHO cohort participants differ prior to and during/after the COVID-19 pandemic; Aim 3: In a COVID-19 hotspot (Detroit, MI) as well as other areas of Michigan, use semi-structured interviews to explore the decision-making experiences regarding infant feeding practices (breastfeeding initiation and duration) of ECHO participants who	First, using data from multiple ECHO cohorts, we aim to determine if the duration of exclusive breastfeeding protects against risk for childhood obesity among those exposed to maternal obesity while in utero. Second, we will estimate, both quantitatively and qualitatively, the impact of the SARS-CoV-2 pandemic on women's breastfeeding practices and experiences. The combination of quantitative and qualitative approaches will enable a more comprehensive understanding of the determinants of breastfeeding before and during/after the pandemic.	unsure at this point, but n= approximately 4,000 pre-COVID-19; n=approximately 700 during/after COVID-19	Administrative Supplement grant is under review at NIH, but parent grant is in year 4 of a 7 year grant	If funded, project dates are 9/1/2020 to 8/31/2022
42	Baby-Friendly Practices and Breastfeeding Rates in Mississippi Hospitals during the COVID epidemic.	(1)Via survey: Assess maternity unit service changes made in 39 birthing hospitals in Mississippi during the COVID epidemic; (2) Assess breastfeeding rates, and rates of skin to skin and rooming in in 39 birthing hospitals in Mississippi, by data from the medical records.	Survey has been sent on Qualtrix to the cohort of hospitals. Data collection is being submitted monthly also by Qualtrxi.	39 Mississippi hospitals with birthing units	Survey has been sent. Data collection is ongoing.	Sep-20

43	COVID Mothers Study; Melissa Bartick,Harvard Medical School/Harvard TH Chan School of Public Health, no funding Collaborators include Cooper Medical School, Boston Medical Center, Italian National Institute of Health (ISS)	a) To see if separation of mothers and infants causes harm or benefits to mothers and Infants (outcomes include difficults with bresatfeeding, or symptomatic COVID infection) b) If direct breastfeeding in the perinatal period causes harm to infants, c) if rooming in causes harm toinfant, and if breastfeeding is associated with prtecdtion from symptomatic COVID less severe disease in older infants	Worldwide survey of mothers with COVID or suspsected COVID, or mothers of infants who have had COVID or suspsected COVID. Inclusion criteria are that mothers must be biological mother of an infant who is <12 moths old at the time of the event; mother cannot complete the survey until after infant is at least 1 month old; either mother or infant had to have had COVID or suspected COVID.	Original goal was for 1000 mothers, but we would need much fewer than that to show significant differences, depending on effect size.	Survey was launched on May 4 to everywhere except GDPR-affected countries (EU plus UK 4 other European countries, as we are awaiting IRB approval for those countries). As of June 21, 2020, 560 respondents have taken the survey, but only 117 have been eligible,	10/2020 or sooner.
44	COVID Lactation Study; Maria Carmen Collado (IATA-CSIC), Cecilia Martinez-Costa (INCLIVA)	Our objective is to determine the presence of SARS-COV2 by PCR in breast milk samples from positive mothers and also, to determine the presence of antibodies in milk. As a secondary objectives, we aimed to identify the impavct of maternal infection on milk immunological and metabolomic profile as well as in the infant microbiota.	National multicentric study (n=10 hospital institutions). Mothers PCR positive and/or antibodies positive . Inclusion criteria are that mothers who are following breastfeeding practises . Breast milk samples and infant feces are collected at 2 time points (early lactation <7d and later, >1month).	100 mothers (SARS-Cov2 positive and/or seropositive) -2 time points	Applied funding (3 national calls)	end 2020

45	**Title:** The COVID-19 Ontario Pregnancy Event (COPE) Network: Assessing the impact of COVID-19 in pregnancy on maternal, fetal and newborn health **Site:** Ontario, Canada **PI:** Darine El-Chaar **Organization:** Ottawa Hospital Research Institute **Funder:** Canadian Institutes of Health Research	1. To determine the prevalence of symptomatic and asymptomatic SARS-CoV-2 infection through universal testing of all pregnant women admitted for delivery at The Ottawa Hospital (Civic and General campuses). 2. To assess the mother-to-infant transmission potential of SARS-CoV-2 through viral and antibody analysis of maternal and newborn samples collected from 12 hospitals across Ontario. 3. To evaluate the clinical characteristics, case management,	1. Maternal biosamples will be prospectively collected over a 3 month period from all women delivering at The Ottawa Hospital (TOH) to determine the rates of recent, symptomatic, and asymptomatic COVID-19 infection in this population. Samples will be tested for SARS-CoV-2 and anti-SARS-CoV-2 antibodies. 2. We will evaluate infection and antibody status among infants born to mothers delivering at a COPE Network hospital with confirmed or suspected COVID-19 to provide insight into the nature and risk of viral transmission.	1. With approximately 6000 births/year, we anticipate screening close to 1500 women over a 3-month period. 2&3. We anticipate that >50 mother-infant dyads will be identified from the participating sites	1. Protocol is being finalized. 2&3. Participant enrollment and sample collection are ongoing.	Jun-21
46	Title: Rapid research in the CHILD Cohort to inform Canada's response to the COVID-19 pandemic: investigating the prevalence and predictors of SARS-CoV-2 infection, and the health and psychosocial impact of the COVID-19 crisis on Canadian families PI: Meghan Azad, University of Manitoba, Canada Funders: Canadian Institutes of Health Research and Research Manitoba	To investigate SARS-CoV-2 infection prevalence (both symptomatic and asymptomatic), transmission and immunity among Canadian children and parents in the CHILD cohort, identify predictors and risk factors for infection susceptibility and severity, and understand the health and psychosocial impacts of the COVID-19 pandemic on CHILD families.	Embedded in the ongoing CHILD Cohort Study (www.childstuy.ca), a general population Canadian cohort with children born in 2009-12. Families will complete weekly text message-based symptom surveys, repeated serology testing through home sampling kits, and quarterly surveys on health and wellbeing. Immune/biomarker profiles will be measured in some pre-pandemic samples to identify factors linked to infection susceptibility and severity.	Anticipated: 3500 Canadian families (12,000 individuals)	Funded (May 1/2020 – April 30/2021)	04/2021 (with interim results available sooner; some real-time data to be shared with Knowledge Users from public health authorieis)

47	Title-Review of clinical characteristics and laboratory findings of COVID-19 in children. Site United States. Organisation-University of Minnesota. No Funding available.	OBJECTIVE: To conduct systematic review and meta-analysis to assess the prevalence of various clinical symptoms and laboratory findings of COVID-19 in children.	DATA SOURCES: PubMed, MEDLINE, and SCOPUS databases were searched. STUDY SELECTION: Studies were included if they reported symptoms or laboratory findings in children(age<18 years) with a laboratory-confirmed diagnosis of COVID-19 DATA EXTRACTION AND SYNTHESIS: Two authors independently extracted data which was evaluated by a third reviewer. Random effect metanalysis was used to determine pooled prevalence by DerSimonian and Laird method (DL).	700	ongoing.	July,30,2020
48	"Systematic review of susceptibility, transmissibility and severity of SARS-CoV-2 in children and adolescents" *Katy Gaythorpe, Natsuko Imai, Tara Mangal, Gina Cuomo-Dannenburg, Caroline Walters, Sangeeta Bhatia* . Imperial College London	A systematic review to assess the evidence on the role of children in COVID-19 transmission will be conducted focussing on three key questions: 1) Are children susceptible to infection? 2) Are children capable of transmitting infection? 3) What is the disease severity in children	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=184605	NA	Data extraction stage	Aug-20

49	Title: COVID-19 among children and adolescents and impact of school closure on outbreaks control: an overview of systematic review. Principal Investigator: Silvia Minozzi.Organization: Department of Epidemliology, Lazio Regional Health Service , Italy. Funder: no funding received	To provide a summary of the available knowledge of the characteristics of COVID-19 amongst children and adolescents, the role of children and adolescents in the spread of the disease and the impact of school closure on outbreaks control, by summarising the results of the systematic reviews. In details, five questions were addressed: 1. Which is the prevalence of the infection and of the disease among children and adolescents? 2. Which is the disease severity among children and adolescents? 3. Which is the risk of children and	Overview of systematic reviews. We searched (from 2019 up to May 18, 2020) MEDLINE, Embase, Scopus, Web of Science, Cochrane COVID-19 Register, WHO Global Research Database on COVID-19, preprint servers (bioRxiv and medRxiv) and coronavirus resource centre of The Lancet, JAMA, and N Engl J. We did not limit our search by language. Two review authors independently screenid articles and extracted data. Methodological quality of SR was assessed by the AMSTAR 2 checklist. We reported the data abstracted from the reviews in summary tables, one for each of the five overview's	18 SRs included	Data extraction and quality assessment completed. Draft of the paper under development	Submission of the paper expected in one month (end of July)

AGENDA

OBJECTIVES OF THE MEETING

1. TO GAIN A BETTER UNDERSTANDING OF LONG COVID: THE SCIENCE BEHIND AND THE PERSONAL IMPACT
2. TO DEFINE RESEARCH GAPS FOR FUNDERS AND RESEARCHERS TO TAKE FORWARD

BACKGROUND AND JUSTIFICATION

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection, can lead to a diverse range of clinical manifestations, ranging from an asymptomatic infection to an acute respiratory distress syndrome, and multi-organ failure with high risk of mortality. It is established that SARS-CoV-2 not only infects the respiratory tract but that ensuing viral replication and immune response also affects other organs, which can lead to a risk of heart, renal and liver injury, in addition to an acute systemic inflammatory response and accompanying circulatory shock.

While most people have uncomplicated recoveries, some have prolonged illness even after recovery from the acute illness. Identifying longer-term potential consequences and relationship with the acute illness is important for the care of patients. Understanding, in particular, how these interact and affect those already living with other conditions, such as cardiovascular disease and cancer, will be paramount. However, very little is known about possible clinical or psychosocial sequelae that may persist after the resolution of acute infection. A cohort of 143 patients followed after hospitalisation from COVID-19 in Italy, reported that 87% had at least one ongoing symptom, 55% with three or more symptoms at 60 day follow up; fatigue (53%), dyspnoea (43%), joint pain (27%) and chest pain (22%) being the most common. COVID-19 was associated with worsened quality of life among 44% of patients. Prolonged course of illness has also been reported among people with mild COVID-19 who did not require hospitalisation. Increasing evidence also suggests that infection with SARS-CoV-2 can cause neurological consequences, including altered mental status, comprising encephalopathy or encephalitis and primary psychiatric diagnoses. While these symptoms arise acutely during the course of infection, less is known about the possible long-term consequences. People with severe COVID-19 experience high levels of proinflammatory cytokines and acute respiratory dysfunction, which often require assisted ventilation. These are known factors suggested to cause cognitive decline.

Post-traumatic stress disorder (PTSD) and other consequences after intensive care unit (ICU) stay has been well documented previously. A systematic review of consequences after hospitalisation or ICU stay for severe acute respiratory infection (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERSCoV) found consequences up to 6 months after discharge. Common consequences, besides impaired diffusing capacity for carbon monoxide and reduced exercise capacity, were PTSD (39%), depression (33%) and anxiety (30%). There is an urgent need to assess the prevalence of and risk factors for longer-term COVID-19 physical and psychosocial consequences, to identify populations at risk, inform clinical care, prevention, rehabilitation, and interventional study design to improve recovery and patient outcomes.

During this two day forum, patient groups, researchers, research funders, public health and policy makers will join together to discuss the long-term effects of COVID-19, aiming to identify research gaps so that these questions can be answered in due course.

Date & Time (GMT)	Topic	Speakers	Chair
9 December 2020			
11:00 GMT	Start		
SESSION 1 11:00 – 11:20 (5 mins each)	**Welcome and Objectives of the Meeting** Introduction to GloPID-R & ISARIC Long COVID support group – typical questions asked by people living with Long COVID	**Prof Peter Horby,** Executive Director, ISARIC **Prof Charu Kaushic,** GloPID-R, Chair **Dr Margaret O'Hara**, Long COVID support group	
11:20 – 11:40 (5 mins each and reflections/ questions led by CK)	**Global patients' voices** We will hear from 3 people who are living with Long COVID in different parts of the world. We will learn what impact it has on their lives, what their main symptoms are, what questions they would like to have answered and to share any research they have led on.	**Dr Nisreen Alwan,** University of Southampton, UK **Mr Lwazi Mlaba,** Long COVID support group, South Africa **Ms Bhasha Mewar,** Long COVID support group**,** India	**Prof Charu Kaushic**
11:40 – 11:55	**Overarching summary of the knowledge/science of Long COVID** We will be brought up to date by a presentation on a review of the literature and on what projects are currently funded, as recorded in the UKCDR	**Dr Louise Sigfrid,** University of Oxford **& Dr Charitini Stavropoulou**, City University (joint presentation) **Dr Alice Norton** Head of COVID CIRCLE, UKCDR & GloPID-R	**Prof Charles Wiysonge** Co-Chair, GloPID-R

	COVID-19 project-tracking tool. At the end of Global Voices and the evidence presentation, we hope to have a baseline understanding of the definition of Long COVID. This may be refined as the meeting progresses.		
11:55 – 12:00	**Break**		
SESSION 2 12:00 – 12:45 (7 mins each, 10 mins questions at the end) **Dr Nisreen Alwan to join Q&A**	**What do we know about Long COVID from country experiences?** We will learn from 5 different experts on what Long COVID looks like in their country and what is being done to study and understand it. We welcome any research gaps identified.	**Prof Ivan Hung,** The University of Hong Kong **Dr Priscilla Rupali,** Christian Medical College Vellore, India **Dr Shinichiro Morioka/Dr Norio Ohmagari,** National Center for Global Health and Medicine, Japan (joint presentation) **Prof Christopher Brightling,** University of Leicester, UK **Dr Seong-Ho Choi,** Chung-Ang University Hospital, South Korea	**Prof Roberto Bruzzone,** Institut Pasteur and The University of Hong Kong **Dr Janet Diaz,** WHO
12:45 – 12:55 (7 mins & 3 mins for Q&A)	**Reflecting on Chikungunya** We will learn from another infection that has a chronicity about it by hearing about the methodology for research, public engagement	**Dr Andre Siqueira,** FIOCRUZ, Brazil	**Prof Piero Olliaro,** Director of Science, ISARIC

	strategies, and some of the likely challenges for COVID-19.		
12:55 – 13:00	**Break**		
SESSION 3 13:00 – 13:55 (7 mins each, 15 mins questions at the end) **Ms Claire Hastie,** Long COVID support group **Dr Andre Siqueira** **to join Q&A**	On-going Long COVID Studies	**Prof Fernando Bozza,** BRICNET, Brazil **Prof Simone Piva,** University of Brescia, Italy **Dr Joseph Fokam**, EDCTP, Cameroon **Mr Moses Badio,** Partnership for Research on Ebola Virus in Liberia (PREVAIL), Liberia **Prof Danny Altmann,** Imperial College, UK	**Mr Jean Marie Habarugira,** EDCTP **Prof Annelies Wilder-Smith,** London School of Hygiene and Tropical Medicine and Lee Kong Chian School of Medicine, Singapore
SESSION 4 13:55 – 14:00	Summary of the day set against the objectives and plan for next day	**Dr Gail Carson** Director of Network Development, ISARIC & Member of the GloPID-R Scientific Secretariat	

10 December 2020			
11:00 GMT	Start		
SESSION 5 11:00 – 11:10	Welcome and Summary of Day 1	**Dr Jake Suett** Long COVID Support Group	**Prof Yazdan Yazdanpanah,** INSERM
SESSION 6 11:10 – 11:55 (7 mins each, 10 mins questions at the end) **Dr Alex van Blydenstein,** Long COVID support group**,** South Africa, **to join Q&A**	On-going Long COVID studies	**Dr Alpha Keita,** CERFIG, Guinea **Dr Angela Cheung/Dr Margaret Herridge**, CANCOV, Canadian COVID19 Prospective Cohort Study, Canada (joint presentation) **Dr Joseph Breen**, NIH, USA **Dr Frances Simpson**, Coventry University, UK	**Dr Anna Kinsey,** MRC **Dr Daniel Munblit** Sechenov First Moscow State Medical University, Russia and Imperial College, UK
11:55 – 12:00	**Break**		
SESSION 7 12:00 – 13:00 (7 mins each, 10 mins questions for each sub-session) **Ms Bhasha Mewar to join Q&A**	Mental Health and Long COVID (first sub-session)	**Dr Fahmy Hanna,** WHO **Prof Simon Hatcher,** University of Ottawa, Canada **Dr M Netravathi**, National Institute of Mental Health and Neurosciences (NIMHANS), India	**Dr Fahmy Hanna,** WHO

	---------- On-going Long COVID studies (second sub-session)	---------- **Dr Ramzi Khamis,** Imperial College, UK **Dr Ryan Zarychanski,** University of Manitoba, Canada	---------- **Prof Luis Felipe Reyes,** Universidad de La Sabana, Colombia
13:00 – 13:05	**Break**		
SESSION 8 13:05 – 13:45	**Panel Discussion on Knowledge Gaps**	**2 patients' contributors:** **Dr Gina Assaf,** The Body Politic COVID-19 Support Group, US **Dr Margaret O'Hara** **2 researchers:** **Dr Janet Scott,** University of Glasgow, UK **Prof Fernando Bozza** **2 funders:** **Prof Yazdan Yazdanpanah** **Mr Jean Marie Habarugira**	**Dr Janet Diaz** **Prof Piero Olliaro**
SESSION 9 **Finish by 14:00**	Meeting wrap up and next steps		**Prof Charu Kaushic** **Prof Peter Horby**

Workshop on Post-Acute Sequelae of COVID-19

The goal of this meeting is to summarize existing knowledge on post-acute manifestations of COVID-19 and to identify key knowledge gaps.

Day 1: December 3, 2020		
https://videocast.nih.gov/watch=38878		
10:00- 10:05 **(all times in EST)**	Welcome	Dr. Anthony S. Fauci *(NIAID)*
10:06-10:08	Meeting Announcements and Logistics	Dr. Andrea Lerner *(NIAID)*
10:08-10:13	Current Challenges and Goals of the Meeting	**Workshop Co-Chairs:** Dr. Emily Erbelding *(NIAID)* Dr. Adaora Adimora *(UNC)*
Session I: Post-Acute COVID-19: Clinical Observations **Session Chairs:** Dr. John Brooks (*CDC)*, Dr. Michael Saag *(UAB)*		
10:15-10:30	Epidemiological and Clinical Landscape	Dr. John Brooks *(CDC)*
10:30-10:45 10:45-11:00	Experience from U.S. Clinics I Experience from U.S. Clinics II	Dr. Ann Parker *(Johns Hopkins)* Dr. Joshua Vasquez *(UCSF)*
11:00-11:15 11:15-11:30	Global Perspective Experience from South Africa	Dr. Janet Diaz *(WHO)* Dr. Sipho Dlamini *(University of Cape Town)*
11:30-11:45	The Post-Acute COVID-19 Experience	Dr. Peter Piot (*London School of Hygiene and Tropical Medicine)*
11:45-11:55	Speaker Question and Answer	
11:55-12:15	Discussion Panel: Dr. Saag and People Experiencing 'Long COVID'	
12:15-12:25	Break	
Session II: Viral Pathogenic Features and Host Immune Response **Session Chairs:** Dr. Charles Hackett *(NIAID)*, Dr. Kanta Subbarao *(WHO Collaborating Centre, University of Melbourne)*		
   12:25-12:35 12:35-12:45 12:45-12:55	Immunological Responses to SARS-CoV-2 Infection and Potential Role in Post-Acute Sequelae (B cells/Antibodies) (T cells) (Multisystem Inflammatory Syndrome in Children)	 Dr. Ignacio Sanz (*Emory)* Dr. Shane Crotty *(LJI)* Dr. John Wherry *(UPenn)*
12:55-1:10	Pathogenic Features of Coronaviruses and Manifestations of Extrapulmonary Infection	Dr. Stanley Perlman *(UIowa)*
1:10-1:25	Approaches to Researching Post-Acute Sequelae of SARS-CoV-2 Infection	Dr. Kanta Subbarao *(WHO Collaborating Centre, University of Melbourne)*
1:25-1:55	Discussion	
1:55-2:10	Break	
Session III: Post-Acute COVID-19- Perspectives		
2:10-2:25	Neurological/Psychiatric/Neuromuscular	Dr. Avi Nath *(NINDS)*
2:25-2:40	Cardiovascular	Dr. Wendy Post *(Johns Hopkins)*
2:40-2:55	Pulmonary	Dr. Terri Hough *(OHSU)*
2:55-3:10	Renal/GI/Metabolic	Dr. Hashem El-Serag *(Baylor)*
3:10-3:25	Immunologic/Rheumatologic	Dr. Judith James *(OMRF)*
3:25-3:40	Pediatric	Dr. Peter Rowe *(Johns Hopkins)*

3:40-4:00	Discussion and Question and Answer	
4:00-4:10	Day 1 Wrap Up	Workshop Co-Chairs

Day 2: December 4, 2020		
https://videocast.nih.gov/watch=38879		
10:00 – 10:20 **(all times in EST)**	Impact of Social Determinants of Health, Race and Ethnicity on Post-Acute COVID-19 Sequelae	Dr. Carlos del Rio *(Emory)*
10:20 – 10:30	Charge to the Breakout Session Breakout Session Logistics	Workshop Co-Chairs Dr. Andrea Lerner *(NIAID)*
10:30-10:40	**Break**	
Breakout Session 1 **(Neurological/Psychiatric/Neuromuscular)** https://videocast.nih.gov/watch=38882 Breakout Session 2 **(Cardiovascular)** https://videocast.nih.gov/watch=38880 Breakout Session 3 **(Pulmonary)** https://videocast.nih.gov/watch=38884 Breakout Session 4 **(Renal/GI/Metabolic)** https://videocast.nih.gov/watch=38883 Breakout Session 5 **(Immunologic/Rheumatologic)** https://videocast.nih.gov/watch=38885 Breakout Session 6 **(Pediatric)** https://videocast.nih.gov/watch=38881		

10:40 – 12:10 Breakout Sessions					
Neurological/Psychiatric/ Neuromuscular	Cardiovascular	Pulmonary	Renal/GI/Metabolic	Immunologic/ Rheumatologic	Pediatric
Chair: Dr. Anthony Komaroff *(Harvard)*	Chair: Dr. Wendy Post *(Johns Hopkins)*	Chair: Dr. Terri Hough *(OHSU)*	Chair: Dr. Jonathan Himmelfarb *(UW)*	Chair: Dr. Rafi Ahmed *(Emory)* and Dr. Julie McElrath *(Fred Hutch)*	Chair: Dr. Andrew Atz *(MUSC)*

12:10-12:25	**Break**	
https://videocast.nih.gov/watch=38879		
Report out from Breakout Sessions		
12:25 - 12:37	Neurological /Psychiatric/Neuromuscular	Dr. Anthony Komaroff *(Harvard)*
12:37 -12:49	Cardiovascular	Dr. Wendy Post *(Johns Hopkins)*
12:49 -1:01	Pulmonary	Dr. Terri Hough *(OHSU)*
1:01 - 1:13	Renal/GI/Metabolic	Dr. Jonathan Himmelfarb *(UW)*
1:13 - 1:25	Immunologic/Rheumatologic	Dr. Rafi Ahmed *(Emory)*/ Dr. Julie McElrath *(Fred Hutch)*
1:25 -1:37	Pediatric	Dr. Andrew Atz *(MUSC)*
1:37-1:55	DISCUSSION	
1:55-2:05	**Break**	
Summary Conclusions and Meeting Close		
2:05 – 2:15	Conclusions/Wrap-up	Workshop Co-Chairs: Dr. Emily Erbelding *(NIAID)* Dr. Adaora Adimora *(UNC)*

Attachment: Rapid Response Question Request

RAPID RESPONSE: LONG COVID

FOR IMMEDIATE RESPONSE - PLEASE CONTRIBUTE

'Long-COVID' – what we know, what it means for clinical practice and for targeted research. What is underway on establishing cohorts and other means of systematically understanding it and supplying care?

Date: Monday, November 30th, 2020
Deadline: Friday, December 4th, 2020, 7PM EST
To: CanCOVID Rapid Response Network

Our **ask** of CanCOVID members and their networks is to please share and populate this Rapid Response Form (table below) which requests the following information:

1. **Grey literature** (e.g. unpublished guidance and reports based on rigorous science); to add documents click here: **Long Covid: Grey Literature**
2. **Names of experts** that could be consulted; and
3. **Current research initiatives** that may yield relevant evidence in the near future on Long-COVID. To add documents click here**: Long Covid: Current Research Initiatives**

Our team at CanCOVID/REAL will gather existing evidence in the form of published syntheses and systematic reviews.

Your responses will be collated and summarized to inform a response for decision makers.

With sincere thanks in advance from the CanCOVID Secretariat!

For further questions please contact: info@cancovid.ca