Dealing with the Fallout:

Post-COVID-19 Condition and Its Continued Impact on Individuals and Society

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INTRODUCTION

In early 2023, the Office of the Chief Science Advisor published a report titled "*Post-COVID-19 Condition in Canada: What we know, what we don't know, and a framework for action*"[1]. The *PCC Report* took into account the existing scientific literature and published evidence through to October 2022, as well as the perspectives of people with lived experience and input from several expert roundtables held in 2022. During the following months, research into the frequency, manifestations, causes, and treatment of PCC intensified.

On February 27, 2024, a meeting of the Chief Science Advisor's Task Force on Post-COVID-19 Condition[2] was convened to take stock of the latest science and policy actions related to PCC and formulate priority recommendations based on the current state of science. The scientific updates and deliberations from this meeting, as well as recent literature up to June 2024, inform this report *"Dealing with the Fallout: Post-COVID-19 Condition and Its Continued Impact on Individuals and Society"*. In addition to providing recommendations, this report sets important goals to continue to raise awareness of PCC, to help prevent its development and to minimize its health and societal impact.

RECAP OF THE *PCC REPORT*

PCC Report Knowns and Unknowns: SARS-CoV-2 is a novel virus that began infecting people around the globe in 2020 at a scale unprecedented in our lifetime. The *PCC Report* noted that, as of August 2022, over 1 million Canadian adults had experienced or were experiencing long-term symptoms after acute COVID-19 illness, based on Statistics Canada data[1]. Other key findings included the vast range of symptoms with variable severity and duration, also referred to as "long COVID or post-acute sequelae of COVID-19 (PASC)". People suffering from PCC were working-age adults, often women with young families. PCC symptoms varied by type, severity and duration and, in most cases, PCC affected the ability to work and care for children. Risk factors cited included female sex, acute COVID-19 severity, and repeated SARS-CoV-2 infection. Individuals affected by PCC reported facing dismissiveness, stigma, lack of knowledge, and inadequate support when navigating health and social systems, including for disability insurance.

As expected with a new virus, there were significant gaps in knowledge raised in the *PCC Report*. Given the lack of common definitions amid evolving scientific knowledge, coupled with no formal clinical diagnostic criteria or diagnostic tests, managing PCC presented challenges to clinicians and caregivers. Other notable gaps included a lack of certainty about how the SARS-CoV-2 virus caused PCC and why symptoms, severity and illness duration varied among individuals. It was evident, but not understood, that women were (and continue to be) at increased risk of PCC. It was also not clear why SARS-CoV-2 infection accelerates the risk of other chronic conditions, like diabetes and heart disease. The *PCC Report* identified a number of important areas for further study. They include the effects on human development in children and on aging in adults as well as the labour, social and economic impacts of PCC.

Three-Point Framework: The *PCC Report* included a three-point framework which proposed 18 actions to help manage the health and socioeconomic impact of PCC in Canada and enhance pandemic preparedness and recovery (see Appendix Table 1). Many of these recommendations could also be applied more broadly to benefit other post-infection chronic conditions. This framework for action called for research on causal mechanisms and treatments; interconnected research with PCC clinical care delivery as part of a continuous learning framework; services to be developed and tailored to people and their families living with PCC, recognizing that females disproportionately suffer from PCC; and sustainable human and physical infrastructure to support PCC management, prevention, and research.

PCC SCIENTIFIC UPDATES

Epidemiological Data: Just over a year since the *PCC Report* was released, current data demonstrates that PCC continues to affect a significant number of individuals. The SARS-CoV-2 virus is still circulating, posing a continued risk, especially for the unvaccinated and reinfected. Based on the *Statistics Canada Canadian COVID-19 Antibody and Health Survey and Follow-up Questionnaire (CCAHS)*, as of December 2023, about 1 out of every 5 Canadian adults reported long-term symptoms following a SARS-CoV-2 infection[3]. Global PCC estimates vary between and within countries with differences in study methodologies. For example, a recent US population-based cross-sectional survey reported a range of ~2% to ~11% across different parts of the US[4]. The UK Office for National Statistics recently reported that an estimated 3.3% of people living in private households in England and Scotland were experiencing self-reported long COVID, affecting the day-to-day activities of 1.5 million people[5]. The Statistics Canada survey cited above revealed that 100,000 adults in Canada were unable to return to work due to PCC, with an additional 600,000 people having reported missing school or work for an average length of 24 days[3]. Strikingly, only 1 out of every 8 Canadian adults who sought healthcare services for long-term COVID-19 symptoms reported receiving adequate care[3]. Living with a long-term illness that affects day-to-day activities has spillover effects on the family, workforce, and labour market.

Burden: Consistently, studies continue to indicate that PCC symptoms and severity vary. Some individuals' symptoms resolve within a year, while some have lingering symptoms that may not interfere with daily life, and others still experience debilitating effects after three years. The severity of the acute COVID-19 phase is a key risk factor for developing PCC and the risk persists longer among hospitalized patients[6]. However, given the sheer numbers of people infected with SARS-CoV-2[7], the majority of cases of PCC stem from mild infection not requiring hospitalization.

Interestingly, recent research has found that the risk of PCC and many of its lingering symptoms have declined over the course of the pandemic. One study showed that the risk of PCC declined from about 10% in unvaccinated individuals who were infected with SARS-CoV-2 in the first year of the pandemic to about 3.5% among vaccinated people who were infected in the Omicron phase[8]. The two key drivers of reduction in risk of PCC over time are vaccination and, less so, changes in the SARS-CoV-2 strain from

pre-Delta to Delta to Omicron[8]. Even with this substantial reduction, PCC remains a concern as studies have demonstrated a long risk horizon lasting two to three years among infected individuals[8]. Further, reinfections may be linked to higher PCC frequency and severity, compared to single infections[21].

Representative cross-sectional surveys recently estimated the prevalence of disabling long COVID (defined as symptoms persisting more than three months post-COVID that significantly compromise daily activities) to be 1.5% of US adults[9], which would equal just under 4 million people. Study participants who reported having disabling long COVID disproportionately identified as female and as having a disability, anxiety and depression. An additional 4.5% of study respondents reported having long COVID with little or no activity limitations. Altogether, it is estimated that about 15 million US adults are living with long COVID[9].

Risk: The ongoing risk of infection and subsequent acute and chronic illness is not negligible. The SARS-CoV-2 virus continues to circulate with evolving variants of concern. To illustrate, COVID-19 wastewater monitoring in the US demonstrated high SARS-COV-2 viral activity levels in wastewater at the beginning of 2024, the second highest peak since the massive Omicron wave in early 2022[10]. With each SARS-CoV-2 reinfection, the risk of developing PCC is cumulative. That means two infections carry a greater risk than one infection and the risk after three infections is larger than after two infections[3]. As of June 2023, two out of three Canadians reported having had at least one COVID-19 infection and one in five Canadians had been infected multiple times[3].

PCC continues to have a broader socioeconomic impact on affected individuals and their families, as well as on the workforce and the economy. The overall chronic health effects of SARS-CoV-2 infection and the long-term labour, economic and societal impact of the pandemic, are all still unravelling.

Care and Treatment: PCC is a complex, multisystemic disease affecting many organ systems, often requiring a multidisciplinary healthcare approach, depending on an individual's unique symptoms. Over the last year, the care landscape has changed significantly in Canada. While there are few published reports, the number of new referrals in most PCC clinics (both community-based and speciality models) has gone down and stabilized or plateaued[11]. However, there appears to be a concentration of moderate to severe cases in PCC clinics as individuals with a higher level of disability are more likely to seek care and clinicians are unable to close cases requiring long-term follow-up. Therefore, the influx of new cases, although diminished, coupled with a reduced output, contributes to reduced access and growing waiting lists[11]. In addition, most PCC clinics still lack medical coverage for diagnostic tests and medication, potentially leading to incomplete disability insurance coverage or hazardous return to work.

Factors that could contribute to declining clinical referrals include insufficient outreach to primary care providers to raise awareness of PCC, and a continued lack of biomarker and standard testing approaches for PCC. It is also possible that fewer people require care over time. To illustrate, recent data following people infected very early in the pandemic with the ancestral strain, before vaccines were available, show that most of the PCC burden comes from the first year[6,8]. Unfortunately, a significant proportion of burden is still evident in years two and three[6,8]. These findings are consistent with earlier findings demonstrating that PCC can resolve for some (not all) people within a year for non-hospitalized cases of acute COVID-19[12].

More potential therapies are being tested since the *PCC Report*'s publication. As of June 2024, approximately 59 PCC-related clinical trials were identified on the US National Institutes of Health ClinicalTrials.gov website[13]. Of the total, about two thirds relate to PCC treatment while others aim to characterize the condition and PCC-associated risk factors[13]. Examples of treatment trials include the use of vitamins such as such as Vitamin K2 and Vitamin D3, or amino acid supplementation such as glutathione, to see how they impact symptoms. Others include the use of the SARS-CoV-2 antiviral Paxlovid and the antiviral Valacyclovir to treat symptoms; the non-steroidal anti-inflammatory drug (NSAID) Celecoxib for fatigue; and Rovunaptabin, a synthetic DNA compound drug BC-007, for fatigue and quality of life[13]. Trials with completion dates after June 2024 are summarized in Table 2 found in the appendix section at the end of this report.

PCC and Chronic Diseases: Studies continue to show that COVID-19 increases the risk for chronic diseases. PCC has a wide range of different symptoms and symptom clusters with corresponding risk factors and biological mechanisms that may respond differently to treatments. Symptoms can affect any of the body's systems, including cardiovascular (circulation and heart), musculoskeletal (bones, muscles and joints), pulmonary (lungs), metabolic (chemical processes in the body), gastrointestinal (digestive) and neurologic (mental, brain and nerves)[1, 14].

Unlike seasonal influenza, which is predominantly a respiratory virus, SARS-CoV-2 is pleiotropic — meaning it affects most systems of the body. SARS-CoV-2 infection increases the burden of cardiovascular disease, diabetes, neurologic impairment, and rheumatic, autoimmune conditions, as well as polygenic rare diseases overall[16-19]. While not exhaustive, select studies to illustrate examples of evidence of impacts on chronic diseases are described below.

NEUROLOGIC DISORDERS

Considerable scientific studies on COVID-19 neurological effects have been carried out. An increased rate of cognitive decline after SARS-CoV-2 infection has been reported for patients with dementia, Parkinson (PD), and Alzheimer's (AD) diseases, and COVID-19 (coupled with pandemic-related socioeconomic changes) could possibly trigger PD and AD[20]. Early autopsy studies in the United States initiative, *RECOVER: Researching COVID to Enhance Recovery*, also demonstrated an observable impact of COVID-19 on the brain[21, 22]. The mechanism through which COVID-19 increases the rate of cognitive decline is not yet known; its effect on the brain and nervous system is only now starting to be understood. Studies have shown that PCC can lead to significant decline in the IQ of patients[23, 24], although it seems unlikely that SARS-CoV-2 is the single driver of these complex diseases. One hypothesis is that for individuals already in the early stages of decline, SARS-CoV-2 infection may "tip them over" and act as a catalyst accelerating the development of other chronic conditions. Headaches and neurological symptoms appear to be one of the biggest differentiators amongst people with PCC[25]. Even among patients who recovered at home, there have been examples of long-term changes in the structure and the function and connectivity in the brain[26]. However, care must be taken in predicting long-term neurological sequelae.

IMMUNOLOGIC AND OTHER CHRONIC ILLNESS

The magnitude of the immune response to SARS-CoV-2 infection is likely precipitating effects in the acute and chronic phases of COVID-19. SARS-CoV-2 infection can lead to dysregulation of and long-term damage to the immune system, and an uncoordinated as well as a weakened immune-cell response to vaccination[27, 28, 29]. Studies have demonstrated highly activated immune cells, T cell alterations including less functionality, elevated cytokine levels (cells that recruit other immune cells) as well as higher levels of autoantibodies in individuals with long COVID[27, 28, 29]. As a novel virus, SARS-CoV-2 is interacting in an immunologically naïve way with the human immune system. There are nonetheless transferable lessons to be learned from other, less novel infectious diseases. For example, a recent study comparing COVID-19 with seasonal influenza showed the risk of developing another health outcome was greater for COVID-19[26]. Another recent Canadian population-based cohort study found that adults who survived hospitalization for COVID-19 had similar risks to adults hospitalized for influenza or sepsis for developing new rheumatoid arthritic, cardiovascular, neurologic, and mental health conditions. Their long-term risks were substantially higher compared to the general population[31].

Recent studies[32, 33] are also consistent with earlier reports[34] of approximately 1.5 to 2 times higher risk of various cardiovascular complications post-SARS-CoV-2 infection among US veterans, including dysrhythmias and other cardiac disorders. COVID-19 illness can result in new diagnoses of diabetes[35], which is listed among the possible long-term adverse consequences of COVID-19[29].

Mechanistic Pathways: The *PCC Report's* section on SARS-CoV-2 pathogenesis included details of possible causal pathways and how the range of acute COVID-19 symptoms relate to the presence of angiotensin converting enzyme-2 (ACE2) that serves as the SARS-CoV-2 virus cell surface receptor found in many cells and organs[1]. Since the *PCC Report* was published, possible biological pathways that lead to PCC are becoming better understood, such as immune exhaustion (as noted in the previous section) affecting both blood coagulation and the part of the immune system that cleans up damaged cells and promotes healing[36]. The pathogenesis and mechanistic pathways of how SARS-CoV-2 infection leads to PCC remain the subject of intense scientific research; more than 40 pathobiology studies are underway as part of the US RECOVER initiative, among others. While prevention remains essential, clarifying the "how" is the key to developing effective tests, treatment approaches, and therapies. Given the wide variety of symptoms, PCC could result from a dysfunctional response to SARS-CoV-2 infection with multiple potential pathogenic pathways[37, 38].

Possible mechanisms that lead to PCC can cause problems in any system of the body and include SARS-CoV-2 viral persistence, immune dysregulation, microbiome dysbiosis (effects in the gut), inflammation, vascular effects and micro clots, and mitochondrial dysfunction (diminished cellular "energy factories")[29]. These and other hypotheses are being explored scientifically. Evidence for a persistent virus, or piece of virus such as the spike protein, is limited, but the hypothesis remains a compelling scientific one that warrants further exploration[39]. Studies have also observed that *reactivation of a latent virus* after SARS-CoV-2 infection, such as Epstein-Barr virus (EBV), may contribute to the PCC symptoms observed[40]. Higher antibody responses directed against non-SARS-CoV-2 viral pathogens were observed among people with PCC, particularly for Epstein-Barr virus[41].

Vaccination: Notably, evidence demonstrates that vaccination reduces the risk of developing PCC by approximately 40% on average[14, 15]. The specific mechanisms of how vaccines reduce long-term symptoms are not yet clear and understanding them could also contribute to understanding how SARS-CoV-2 leads to PCC in some individuals. Vaccines could have a positive effect in a number of ways — by reducing the severity of acute COVID-19, a known risk factor for developing PCC, it could reduce viral load and temper the magnitude of the host immune response in some people.

PERSISTENT GAPS

Definitions and Clinical Guidance: Different definitions and terms, with related inclusion and exclusion criteria for adults and children, continue to inhibit consistent data capture, comparisons, and the ability to adopt interoperable data approaches, domestically and internationally. Definitional issues affect all aspects related to PCC management — care, research, and policy. Interim guidelines are urgently needed as people require treatment now for this emergent illness. The rigorous process for clinical practice guidelines takes time as published evidence accumulates and evolves.

Sub-populations: Data on First Nations, Inuit and Métis Peoples continues to be a persistent gap. Work needs to continue on priorities identified by communities for data collection and analysis. Data is also lacking on the impacts of PCC in older adults and how it might affect their functioning, mobility and cognition. It is also insufficient on children and youth, and on the full spectrum of PCC's effects. This is in part due to limited surveillance action within these populations and inconsistent definitions of PCC (as noted above). For example, multisystem inflammatory syndrome in children (MIS-C) is not consistently recognized as part of PCC. There are also jurisdictional and regional differences in which subspecialty leads the care for PCC in children (for example, dermatology and rheumatology), depending on symptoms.

Care and Treatment: There are no clinical practice guidelines yet in place to help healthcare providers consistently treat adults, children, or youth. There is no common blood test or biomarker for PCC, which presents a continued challenge for physicians to rapidly diagnose and refer patients who require specialized support. There is no standard pharmacological therapy for PCC. Available evidence about antivirals during acute COVID-19 shows a potential protective effect for long-COVID, but more studies and clinical trials are needed[42]. The care model for children tends to rely on a consultative model and engagement with primary care rather than the specialty clinic, multidisciplinary model seen for adults.

Pathogenesis: As noted earlier, gaps in our understanding of pathogenesis persist. Research is underway to address gaps and determine PCC mechanistic pathways while simultaneously treating patients who are in urgent need of care. Studying and understanding what mechanistically causes the symptoms is essential to developing and evaluating potential targets for therapy.

Socioeconomic Impact: The socioeconomic impact of PCC is substantial, but there is little recent data. A study published in the fall of 2023 estimated the total burden of PCC to the Canadian healthcare system at about 8 to 51 billion dollars CAD per year[43]. The report highlights the importance of adequate vaccination in reducing PCC impact and that estimates should be adjusted as more information becomes available[43]. In addition, individuals with self-reported long COVID symptoms were more likely to be unemployed[44]. Furthermore, about 20% of individuals with PCC are absent from work for a prolonged period of time[45]. PCC patient groups and healthcare organizations may offer social support to affected individuals and their families. There is little evidence of targeted social measures, but general and varied measures for disability can be pursued.

Prevention: There are gaps in public messaging about the importance of PCC prevention. PCC preventive actions include avoiding SARS-CoV-2 infection and reinfection through protective behavior, such as isolating when sick to avoid spreading disease and effective masking in crowded spaces, and making it easy to adopt protective measures through steps that government, institutions and employers can take. Equally important is indoor air quality and ventilation to reduce transmission of infectious diseases that transmit through the air, including SARS-CoV-2, influenza and other common respiratory viruses[46, 47]. Adequate ventilation and air filtration is often a key gap in buildings where people gather, including schools.

Another key action along with other measures to prevent PCC is vaccination. There are gaps in messaging about reducing the risk for PCC through vaccination across all ages. COVID-19 vaccination and messaging targeted to priority populations to protect against acute COVID-19 illness may have an unintended consequence of conveying that keeping COVID-19 vaccination up to date for acute and chronic effects is not really necessary for all age groups.

RECOMMENDED PRIORITY ACTIONS

Progress to Date: Some of the *PCC Report* recommendations have been initiated, while others are yet to be implemented. A key new initiative that was recommended is the establishment of the federally funded Long COVID Web, a Canada-wide health research network that aims to elucidate the causes of PCC and optimize care for patients[48]. As part of Long COVID Web, research priorities across four pillars have been established with short-term funding, including for investigating pathogenesis, biomarkers and treatment. Other progress includes the publication of 11 PCC good practice statements as part of an evidence-based PCC guideline development process[49]. There is also improved availability of PCC epidemiological and survey data in Canada[50] compared to when the PCC Task Force began its work. Importantly, more is being done to improve overall timely exchange, access to, and standardization of health information in Canada through the *Pan-Canadian Interoperability Roadmap*[51].

Ongoing and Future Action: It is clear that more efforts are needed in Canada to prevent and manage PCC, working domestically and through international collaboration. Existing management options to treat symptoms or prevent PCC are largely insufficient. At the same time, no curative options are available, and the limited understanding of the disease is a major hurdle to development of effective treatment. Broad collaborative research efforts are needed to further understand the underlying biological mechanisms that cause PCC. Particular attention is needed to understand PCC's impact on children, youth and older adults and for effective treatment. Definitional issues remain and effective clinical practice guideline development will require consideration of evolving definitions, including the recently published 2024 *US National Academies of Science, Engineering and Medicine Long COVID Definition*[52].

Priorities: Given the above, direct, broad and foundational priority actions related to care, research, policy, communication and systems are reiterated below. The priorities are not new and while some are refined, the majority are reflected in the more comprehensive recommendations proposed in the 2023 *PCC Report*. New priorities are highlighted. Priority actions are aimed at public, not-for-profit and private organizations, as relevant, including levels of government, employers, institutions and insurers.

I. DIRECT ACTIONS RELATED TO PCC CLINICAL PRACTICE AND RESEARCH

1. **Clinical Practices and Services**

   1.1. Urgently develop interim clinical practice guidance and diagnostic criteria by bringing together experts involved in providing care for people with PCC, along with individuals with lived experience taking into account the latest evidence and scientific knowledge.

   1.2. Enhance rehabilitation options for individuals with PCC in a learning health system context.

   1.3. Implement virtual and remote tools and approaches to monitor PCC treatment and recovery.

   1.4. Improve PCC outreach and training to healthcare providers, building on current efforts.

   1.5. Support a cross-Canada consolidated network of infection-associated chronic disease clinics with multidisciplinary care pathways to deliver clinical care and research protocols simultaneously, learning from existing models and evidence-based evaluations[54].

   1.6. ***New:*** *Use data analytics and artificial intelligence tools to help guide care and research (e.g. biomarkers and stratification of individuals for clinical trials).*

   1.7. ***New:*** *Encourage pediatric societies to develop a roadmap to improve research, care, and policy related to pediatric PCC.*

   1.8. ***New:*** *Make COVID-19 vaccines available to everyone over six months of age given the evidence that vaccination significantly reduces the development of PCC*[14].

2. **Research to Guide Practice and Policy**

PCC Pathogenesis

2.1. Accelerate foundational work on PCC pathogenesis for effective care interventions.

2.2. Determine the mechanisms by which SARS-CoV-2 infection increases the burden of chronic diseases.

2.3. Study PCC within the broader context of infection-associated chronic conditions.

PCC Therapies and Treatment

2.4. Expand and support clinical trials to test novel and repurposed drugs that treat and prevent PCC.

2.5. Coordinate and align Canadian study cohorts with other international initiatives to increase impact, for example with US RECOVER.

2.6. ***New:*** *Conduct secondary data analyses to further understand which PCC symptoms are predominantly reduced by COVID-19 vaccination, disaggregated by age and gender.*

Health and Socio-Economic Impact of PCC

2.7. Implement ongoing surveillance strategies to monitor the prevalence of PCC, such as through the use of population-level administrative data.

2.8. Continue investing in research to understand the progression of PCC via survey initiatives such as the Canadian COVID-19 Antibody and Health Survey[3].

2.9. Measure the impact of PCC on daily activities, taking an approach similar to the Canadian Survey on Disability[3].

2.10. Coordinate efforts to evaluate the direct and indirect costs of PCC, including from healthcare, labour and productivity, over an agreed-upon timeframe.

2.11. Increase research on the impact of PCC on vulnerable and diverse populations over time, such as children, older adults and people with cognitive frailty, establishing well-designed longitudinal observational studies, such as the pediatric POPCORN cohort study[53].

2.12. ***New:*** *Determine where health system support is most likely to be needed for individuals living with PCC* [2].

II. BROAD ACTIONS RELATED TO PCC SOCIOECONOMIC POLICIES AND COMMUNICATION

3. **Socioeconomic Policies and Programs**

   3.1. Accelerate the development and implementation of harmonized terms and definitions for PCC domestically and internationally for adults and children, building on existing efforts including the recently released US National Science, Engineering and Medicine long COVID definition[52].

   3.2. Modernize and adapt relevant policies and eligibility criteria so they are consistent with the disabling nature of PCC to maximize the participation of people living with PCC in society.

   3.3. ***New:*** *Incentivize investment in improving indoor air quality in buildings where large numbers of people gather.*

   3.4. ***New:*** *Anticipate post-acute sequelae of infectious disease outbreaks and incorporate their potential burden and management into pandemic preparedness and resilience strategies.*

4. **Communication and Outreach**

   4.1. Create a portal of PCC information and weblinks, including the Canadian COVID-19 Antibody and Health Survey (CCAHS), provincial and territorial actions and clinical trials information.

   4.2. Openly acknowledge that PCC continues to be a risk to Canadians while the SARS-CoV-2 virus circulates.

      4.2.1. Emphasize PCC prevention through evidence-based approaches to preventing and controlling infection, highlighting the protective effects of both indoor air quality and vaccination.

      4.2.2. Develop targeted messaging with culturally sensitive language for a variety of audiences, including, among others, the general public, healthcare providers and the insurance sector.

III. FOUNDATIONAL ACTIONS RELATED TO INFRASTRUCTURE, SYSTEMS AND COORDINATION

5. **Infrastructure, Systems and Coordination**

   5.1. Scale-up and monitor effective prevention interventions, such as improving ventilation in schools, long-term care homes, workplaces and public spaces as part of a first line of prevention of SARS-CoV2 infection and other known and emerging respiratory/airborne pathogens.

   5.2. Encourage innovation in PCC care models and evaluate them to inform future resilience in the healthcare system including the recruitment and retention of a thriving healthcare workforce.

CONCLUSION

When the *PCC Report* was first published in early 2023, it was recognized that it would take time, focussed efforts, and collaboration to understand the impact, pathophysiology, and best treatment approaches for PCC. The recommendations of the first *PCC Report* remain as relevant as ever. PCC continues to disrupt the lives of Canadians and the national economy[3, 43].

Several factors create a compelling argument to ramp up efforts to address PCC, such as the continued circulation of the SARS-CoV-2 virus and its variants, the enormity of the numbers of people who have been and will be infected with SARS-COV-2 worldwide, the related health and socioeconomic impact, and the growing understanding of the significant contribution of infectious disease to chronic illness burden. Evidence shows us that for both seasonal influenza and COVID-19, the burden of the long phase of illness eclipses the challenges raised by the acute phase[26]. While scientific studies are undertaken and the evidence-base grows to fill knowledge gaps and inform practice, individuals living with PCC require care, support, and treatment now. Importantly, once there is an agreed-to definition for PCC, it is essential to ensure its wide adoption. This will help secondary analyses on existing or ongoing studies that may shed new light on mechanistic pathways and help understand how vaccination reduces the risk of PCC. Going forward, we should further leverage current research efforts in Canada to participate in large-scale international networks and to partner in the development of a long-horizon global strategy for PCC and other post-infection chronic conditions.

Prevention of PCC is essential and the physical environment that contributes to the spread of SARS-CoV-2 and other respiratory illness should receive more attention. People spend the majority of their time inside of buildings. Therefore, improving indoor air quality, especially in schools, would provide a significant contribution to the prevention of PCC as well as other infectious diseases, and have far-reaching benefits[55], strengthening preparedness for climate change effects and pandemics. To illustrate, in 2008, the cost attributable to communicable diseases (a portion of which transmit through the air) in Canada was estimated to be over 8 billion dollars[56].

Future pandemics are likely to leave in their wake a significant number of people with long-term illness. This is a reminder that long-term health and socioeconomic impacts of infectious disease epidemics and pandemics must be part of emergency planning, management, and recovery. The next pandemic threat may not be far away — indeed, we can apply the recommended principles and approach to the ongoing global outbreak of highly pathogenic avian influenza-A (HPAI-A). HPAI-A is currently circulating in wild and domestic birds, with an increasing number of land and sea mammals also infected, including dairy cattle in the US[57]. While the risk to the general public in Canada is currently low[55], as more animals are infected around the globe, there are more opportunities for the HPAI-A virus to evolve and adapt into a pandemic strain with potentially high mortality, morbidity and disease burden. Around the world, health systems are still recovering from the COVID-19 pandemic. It is therefore essential to use the learnings from PCC and other infection-associated chronic conditions to improve our readiness for future health risks.

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APPENDIX

TABLE 1: PCC REPORT RECOMMENDATIONS AT A GLANCE[1]

PCC FRAMEWORK FOR ACTION RECOMMENDATIONS AT A GLANCE		
Direct Actions	**Broad Actions**	**Foundational Actions**
1. Establish common definitions and clinical practice guidelines	7.Update socio-economic policies	13. Set up science advisory council
2. Apply PCC diagnostic codes	8. Develop socio-economic resources that address needs	14. Whole of government PCC coordination structure
3. Promote equitable access to care pathways	9. Raise awareness	15. Address data collection and management
4. Develop strategic research plan	10. Provide integrated information platform of services	16. Infrastructure connecting research, care and prevention
5. Establish national research and care network	11. Develop educational approaches for health care providers	17. Scale-up prevention interventions, including ventilation
6. Advance five priority research areas: pathophysiology, therapeutics, prevention, clinical, socio-economic	12. Make prevention easy	18. Encourage innovation in PCC care models

TABLE 2: PCC-RELATED CLINICAL TRIALS WITH COMPLETION DATES AFTER JUNE 2024[13]

TITLE	FOCUS
Interventional	
1. Post-Acute Sequelae of Coronavirus-19 (COVID-19) With Dyspnea on Exertion and Associated TaChycardia TrEatment Study	Single Group Treatment — DRUG Metoprolol Succinate and walk test
2. Glutamatergic Modulation as a Treatment for Depressive Symptoms Among Patients With PASC: A Pilot Trial	Randomized Treatment — DRUG CI-581a | CI-581b
3. Home-based Brain Stimulation Treatment for PASC, Randomized Treatment	DEVICE: Active or sham Transcranial Direct-Current Stimulation (tDCS)
4. Treatment of Long CoronaVirus Disease (COVID) (TLC) Feasibility Trial	Randomized Treatment — DRUG Cetirizine |Famotidine| Placebo

TITLE	FOCUS
5. A Decentralized, Randomized Phase 2 Efficacy and Safety Study of Nirmatrelvir/Ritonavir in Adults with Long COVID	Randomized Treatment — DRUG Nirmatrelvir | Ritonavir | Placebo
6. TDCS-potentiated Generalization of Cognitive Training in the Rehabilitation of Long COVID Symptoms Randomized Supportive Care	DEVICE: Active Transcranial Direct-Current Stimulation (tDCS)|Placebo
7. Valacyclovir Plus Celecoxib for PASC, Randomized Treatment	DRUG: Valacyclovir celecoxib dosages| DRUG: Placebo
8. Exercise Interventions in PASC Randomized Supportive Care	BEHAVIORAL: Exercise
9. Does a Technology Enabled Multi-disciplinary Team-based Care Model for the Management of Long COVID and Other Fatiguing Illnesses Improve Clinical Care of Patients and Represent a Sustainable Approach Within a Federally Qualified Health Center?	Randomized model with patient reported outcomes
10. The Role of Glutathione Deficiency and MSIDS Variables in Long COVID-19 Randomized Treatment	DIETARY SUPPLEMENT: NAC (N-acetyl cysteine) | Alpha lipoic acid (ALA) |liposomal glutathione (GSH)
11. RECOVER-NEURO: Platform Protocol and Appendix (2) to Measure the Effects of Cognitive Dysfunction Interventions on Long COVID Symptoms	Randomized Treatment
12. Mental Intervention and Nicotinamide Riboside Supplementation in Long Covid	Randomized Treatment
13. To Investigate Efficacy, Pharmacodynamics, and Safety of BC 007 in Participants with Long COVID	Randomized Treatment — DRUG: BC 007 (Rovunaptabin) | Placebo
14. Diet and Fasting for Long COVID	Randomized Treatment
15. Supervised Computerized Active Program for People with Post-COVID Syndrome (SuperCAP Study)	Randomized Treatment — DEVICE: SuperCAP Program
16. RECOVER-VITAL: Platform Protocol and Appendix (2), to Measure the Effects of Antiviral Therapies on Long COVID Symptoms	Randomized Treatment — DRUG: Paxlovid doses | Placebo

TITLE	FOCUS
17. A Study of Amantadine for Cognitive Dysfunction in Patients with Long Covid Randomized Treatment	DRUG: Amantadine | OTHER: Physical, Occupational, Speech Therapy | Provider Counseling | Medications for symptoms management
18. Sauna for Long Covid	Randomized Treatment — DEVICE: Whole body hyperthermia
19. Obesity, Insulin Resistance, and PASC: Persistent SARS-CoV-2	Non-Randomized — PROCEDURE: Adipose Tissue Biopsy | DIAGNOSTIC TEST: Steady State Plasma Glucose (SSPG) Test
20. RECOVER-AUTONOMIC Platform Protocol and Appendix (2)	Randomized Treatment — DRUG: Intravenous immunoglobulin (IVIG) Ivabradine | BEHAVIORAL: Coordinated Care vs Usual Care
21. Evaluating a Comprehensive Multimodal Outpatient Rehabilitation Program for PASC Program to Improve Functioning of Persons Suffering from Post-COVID-19 Syndrome: A Randomized Controlled Trial	Randomized model
22. Nivolumab/Ipilimumab and Chemotherapy Combination in Advanced NSCLC Patients With HIV, HBV, HCV and Long Covid Syndrome	Non-Randomized Treatment — DRUG: Nivolumab and Ipilimumab
23. Neurocognitive Study in Long COVID and Postural Orthostatic Tachycardia Syndrome (POTS)	Randomized/Crossover Treatment: Reaction Time after 1500mL IV saline compared 50mL IV saline
24. Long COVID Ultrasound Trial — Single Group Device Feasibility (Splenic Ultrasound)	Single Group Device Feasibility — DEVICE: Splenic Ultrasound
25. Diaphragmatic Breathing (DB) Exercises for Post-COVID-19 Diaphragmatic Dysfunction	Randomized Interventional Model Treatment — DB Program
Observational	
26. The Canadian Respiratory Research Network Long COVID-19 Study	Prevalence of sequelae five-12 months post positive PCR test

TITLE	FOCUS
27. Neuropsychiatric Post-Acute Sequelae of SARS-CoV-2 (PASC) Using TSPO Positron Emission Tomography (PET) and magnetic resonance imaging (MRI)	Evaluate disruptions in blood-brain barrier
28. "Long COVID-19" on the Human Brain — Presence and Severity of central nervous system (CNS) and PASC Symptoms	Presence and severity of symptoms
29. Effect of Apollo Wearable (a portable device that provides vibrations) on Long COVID-19 Symptoms	"Post-Covid-19 Functional Status Scale" to assess functional recovery
30. Collection of SARS CoV-2 (COVID-19) Virus Secretions and Serum for Countermeasure Development	Determine risk factors which lead to severe vs non-severe COVID-19 clinical course in ambulatory patients
31. Yale COVID-19 Recovery Study	Effect of Vaccination
32. Understanding the Long-term Impact of COVID-19 in Adults (RECOVER)	Incidence and prevalence of symptoms
33. RECOVER Tissue Pathology: Understanding the Long-Term Impact of COVID-19	Decedent pathology
34. Skeletal Muscle in PASC and ME/CFS Patients	Bike exertion test
35. Predictors of Post-COVID Clinical and Cognitive Consequences	Measure neurocognitive function
36. Post-Acute Sequelae of COVID-19	Cohort study, various measures up to 5 years

This table includes trials with a completion date after June 2024 regardless of status, based on search results of the ClinicalTrials.gov website using PCC, PASC, and long COVID search terms. PASC refers to "post-acute sequelae of SARS-CoV-2 infection".