

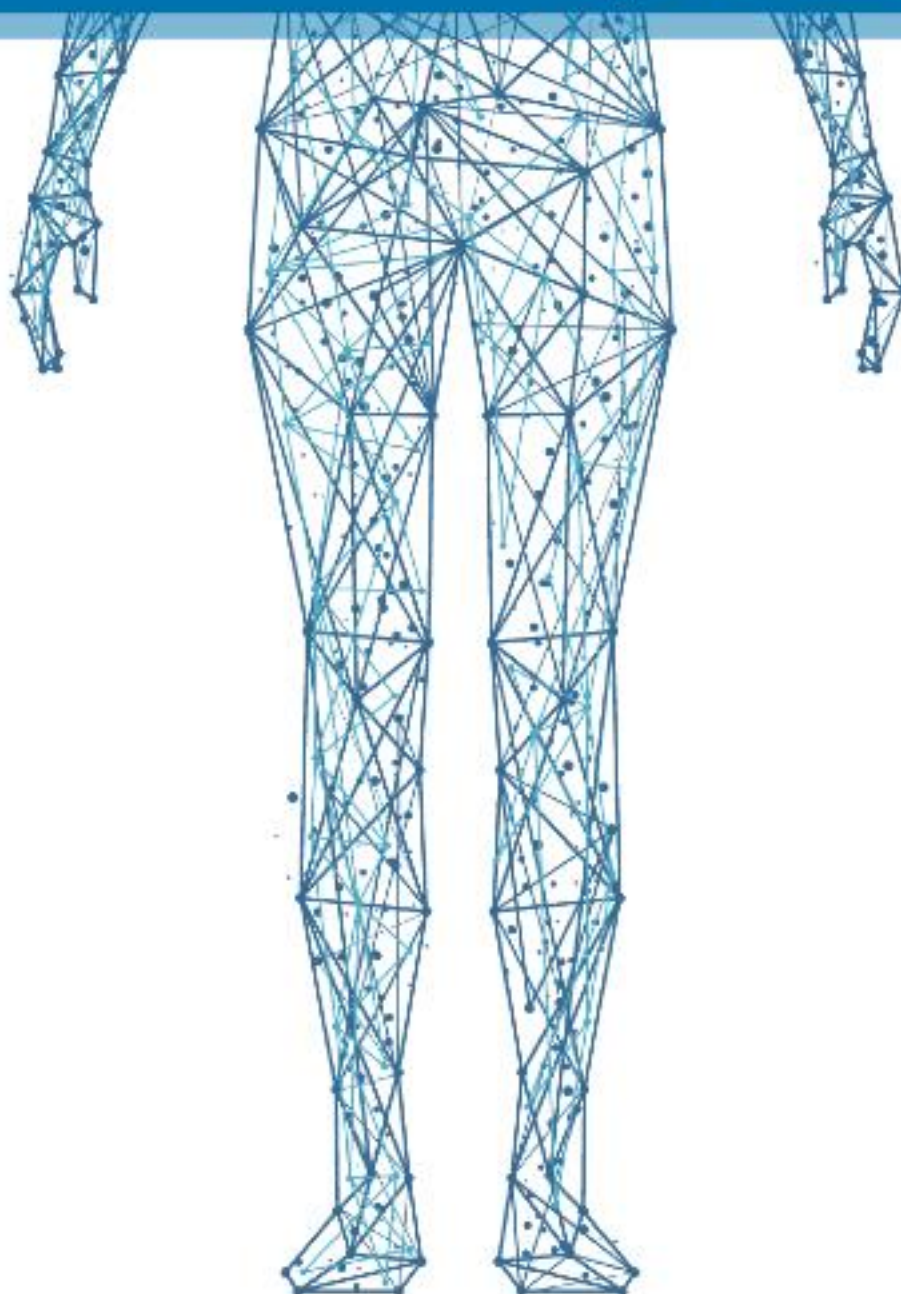


Expanding our understanding of Post COVID-19 condition

Report of a WHO webinar, 9 February 2021



World Health
Organization



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Thanks are also due to all the chairs, speakers and, most importantly, the panel members for their outstanding contributions during the meeting. See Annexes 1 and 2 for complete lists of speakers and panel participants.

Abbreviations

| | |
|-------------------|---|
| ACE-2 | angiotensin-converting enzyme 2 |
| AI | artificial intelligence |
| ARDS | acute respiratory distress syndrome |
| CAP | community-acquired pneumonia |
| CFS | chronic fatigue syndrome |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| DLCO | diffusing capacity for carbon monoxide |
| EHR | electronic health records |
| GI | gastrointestinal |
| GloPID-R | Global Research Collaboration for Infectious Disease Preparedness |
| GP | general physician |
| IASC | Inter-Agency Standing Committee |
| ICU | intensive care unit |
| ISARIC | International Severe Acute Respiratory and Emerging Infection Consortium |
| LMICs | low- and middle-income countries |
| ME | myalgic encephalomyelitis |
| NIH/NIAID | National Institutes of Health/National Institute of Allergy and Infectious Diseases |
| PICS | post-intensive care syndrome |
| PTSD | post-traumatic stress disorder |
| RCT | randomized clinical trial |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus-2 |
| SEID | systemic exertion intolerance disease |
| WHO | World Health Organization |
| 6-MWT | six-minute walk test |

Introduction

During the first wave of the COVID-19 pandemic, investigators already began to assemble longitudinal cohort studies to assess COVID-19 sequelae. By August 2020, WHO met with patients from the LongCovidSOS group and affirmed the need for recognition, research and rehabilitation. By September 2020, WHO had established the ICD-10 code for the Post COVID-19 condition. By January 2021, WHO had published its initial guidance on clinical management of patients after acute illness.

Subsequently, there has been an increase in the number and scope of Post COVID-19 condition research activities by public health agencies, academics, patient-led research groups and other stakeholders. However, a lack of consensus on the clinical case definition and limited understanding of the clinical characterization during the recovery period and associated pathophysiology have limited progress in diagnosis, treatment and management.

With the goal of advancing this field by bringing together stakeholders from around the world, WHO has organized a series of webinars with the following specific objectives:

- action priorities on recognition, research and rehabilitation;
- present up-to-date scientific knowledge on Post COVID-19 condition;
- enrich the discussion through working groups with expert panels.

On 9 February 2021, a first webinar entitled “Expanding our understanding of Post COVID-19 condition” was held under the auspices of WHO and in consultation with the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), Global Research Collaboration for Infectious Disease Preparedness (GloPID-R), National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID), LongCovidSOS and patient representatives. The meeting took place over a 5-hour period divided into the following three sessions:

- Session 1: Post COVID-19 condition: scene setting and lessons learned
- Session 2: Observations on Post COVID-19 condition: what we know
- Session 3: Working groups to develop clinical case definition and research gaps/methods.

For this initial webinar, participants were invited through various clinical networks, research networks and collaborating centres. Over 700 participants attended. Speakers were selected to present findings from large, published cohort studies that were found in systematic literature searches and through other relevant sources. Declarations of conflicts of interest were collected, assessed and managed by the responsible technical unit according to standard WHO procedures for all the speakers. All speakers were assessed as having no financial conflicts of interest.

The working groups were constituted with multidisciplinary panels to delve into pre-specified questions. The WHO steering committee was responsible for setting the agenda, the selection of speakers and formulating the working group questions. The outcomes from each working group are now being used to inform a Delphi process that will be used to draft a clinical case description for Post COVID-19 condition.

Session 1. Post COVID-19 condition: scene setting and lessons learned

This session had six speakers who were chosen to present information to set the scene. High-level summaries will follow, but for complete presentations please refer to our [website](#) (1).

An historical perspective

The first two presentations focused on learnings from other diseases: “Learning from previous viral infections, influenza, SARS, MERS, Zika” and “Learning from previous critical illness: post-intensive care syndrome”.

Dr Carlos A Pardo described the various infectious disease outbreaks of the past two centuries, such as the influenza pandemics of 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), 2009 (H1N1), as well as other viral outbreaks of emerging viruses such as Ebola Virus Disease (2014), Chikungunya (2013–2015), Zika virus (2015–2016), SARS (2002–2004) and MERS (2012); all in the run-up to this current pandemic of SARS-CoV-2 (2019). Neurologic complications have been well described. Dr Pardo cited an article in the *Lancet* published in 1891 reporting on the influenza pandemic describing various neurologic manifestations (i.e. neuralgia, nerve exhaustion, inertia) and the exceptionally “low tone of human vitality”(2), this was then followed by reports of neurologic effects of the influenza pandemic of 1918, and then more recently the neurologic complications associated with Zika virus (i.e. Guillain–Barré syndrome, encephalitis and optic neuritis, etc.) and with Chikungunya virus (i.e. disability at discharge) (3). He concluded that COVID-19 clearly had systemic and neurologic manifestations during the acute phase and that it also may last into the convalescent and recovery phases, leading to Post COVID-19 condition.

Professor Dale Needham presented on the post-intensive care syndrome (PICS), a syndrome developed by the Society of Critical Care Medicine to raise awareness about long-lasting symptoms and functional impairments experienced by survivors of critical illness (4). PICS is described as new or worsening impairments in one or more of the three main domains: physical, cognitive (5) and mental (6) health, arising after intensive care unit (ICU) treatment and persisting beyond acute care hospitalization. Notably, this term can be applied to either a survivor or family member. Over time, other symptoms have also been observed, including fatigue (7) and impairments that affect quality of life (8, 9) and employment (10, 11). Professor Needham described the work on the PICS core outcome set, which is sponsored and funded by the United States National Institutes of Health (NIH) and aims to improve long-term outcomes research for [acute respiratory failure](#) for every study of ICU survivorship (12-14). This core outcome set is being created via an international modified Delphi consensus process with panel members from more than 16 countries across six continents, including approximately 25% patient or family representatives (15). This same methodology can be used to develop a core outcome set for Post COVID-19 condition.

Learnings from global forums on Post COVID-19 condition

The next two presentations focused on learnings from the two most recent global meetings on this topic convened by the NIH and ISARIC-GloPID-R-Long COVID Support group.

Dr Andrea Lerner presented learnings from the NIH workshop on post-acute sequelae of COVID-19 that was held 3–4 December 2020. The goal of this workshop was to summarize existing knowledge and identify key questions and knowledge gaps in this area. Key findings highlighted were common reports of cognitive impairment and mental health concerns, disproportionate representation in the United States among racial and ethnic minorities and those with a lack of health coverage. Phenotypes are numerous and immune response may play a role. The gaps were summarized: need for common vocabulary/terminology; define epidemiology; describe phenotypes and natural histories; identify risk factors; impact of vaccination and therapeutics. Report proceedings have not yet been published. The NIH has issued a Notice of Intent to Publish Research Opportunity Announcements for the study of post-acute COVID-19.

Dr Gail Carson presented on learnings from the ISARIC-GloPID-R-Long COVID Support group Long COVID Forum that was held 9–10 December 2020. This meeting – which brought together patients, researchers and funders – under the theme, “Nothing about us without us” – reflected on the patient-led approach to prioritization of the agenda. The following priorities were highlighted: cause of illness; how to recover; how many others are affected; what is the definition; what are the clinical features; what about manifestations in children and other subpopulations (i.e. people living with HIV); mental health impact and how to intervene. Dr Carson raised concerns about the lack of studies on Long COVID, the focus on hospitalized patients and lack of studies on children and from low- and middle-income countries (LMICs). Their findings were published in *Lancet Infectious Disease* on 4 February 2021, with a schematic proposal for a comprehensive, inclusive research roadmap, including clinical research, patient-centred and health systems angles (16).

Exploring mechanisms

There was a presentation to bring together current thinking: “Immunology and pathophysiology of Long COVID – what we don’t know and what we need to know”.

Professor Daniel Altmann presented on the new Long COVID clinics within the National Health Service in the United Kingdom of Great Britain and Northern Ireland and the need for a multidisciplinary, holistic, coordinated approach; as well as the need for harmonized criteria for a working diagnosis to facilitate access to appropriate care. Emphasizing that to offer rationale treatments, resolving mechanisms is necessary (17).

Some working hypotheses for current investigations were proposed: residual damage to angiotensin-converting enzyme 2 (ACE 2)-positive infected tissue; ongoing immune stimulation from reservoirs of persistent infection; chronic perturbation of immune subsets following acute infection; and activation of an autoimmune response following acute infection. In addition, other important observations included that even asymptomatic cases can have radiographic lung abnormalities. ACE-2 positive cells (lung, heart, kidney and elsewhere) can be sites for potential fibrosis. A recent COVERSCAN MRI study of more than 200 individuals with Long COVID revealed multi-organ involvement, especially affecting both heart and lungs (18). Possible similarities between immune response associated with COVID-19 and those observed in Epstein-Barr Virus, Ebola Virus Disease (19) and Chikungunya virus were raised (20).

Finally, Professor Altman concluded that this new group of patients may place a significant burden on the health system, just by the sheer numbers, and cautioned that we do not know how long this may last. A call to arms was made to engage policy-makers and research funders to take action to find answers.

WHO update

This first session ended with a presentation by **Dr Janet Diaz** updating the audience on activities related to Post COVID-19 condition. Beginning in August 2020, WHO met with representatives of the LongCovidSOS group and affirmed the priorities of recognition, research and rehabilitation. In September 2020, the Classification and Terminologies unit, which had been progressively activating emergency codes for COVID-19 in ICD-10 and ICD-11, after consultation with relevant committees and reference groups, published the [Post COVID-19 codes](#).

An emphasis on the comprehensive and multidisciplinary approach for care of COVID-19 patients – which has already been the hallmark of the COVID-19 care pathway – was now extended to individuals after acute illness and incorporated into the [WHO COVID-19 clinical management: living guidance](#), new chapter entitled, “Care of patients after acute illness”. Input from various disciplines, such as rehabilitation services, brain health and mental health, were essential in this update.

Furthermore, it was acknowledged that mental health is a cross-cutting and integral component of all public health emergency responses and that WHO, in collaboration with partners in the Inter-Agency Standing Committee (IASC), has engaged in the development of operational tools and guidance for mental health and psychological support.

Finally, WHO announced the launch the [Post COVID-19 case record form \(CRF-4\)](#), a tool for standardized data collection after acute illness, that has three comprehensive modules to support standardized data collection globally, to be used either as part of clinical registries or clinical trials, to facilitate data aggregation and meta-analysis.

Session 2. Observations on Post COVID-19 condition: what we know

This second session gave the forum to various researchers to present their findings on [Post COVID-19 condition](#). All presentations can be found on the website (1).

Long COVID research findings and recommendations: patient-led research

Ms Hannah Davis from the Patient-Led Research Collaborative, which was established in partnership with University College London, presented the results of their second survey, which included 3762 respondents from 56 countries and examined 205 symptoms, their impact on work and life, antibody testing and diagnostics over a 7-month period (21). Most respondents were never hospitalized – 92% (3445 out of 3762) – and 18% (668 out of 3762) were health care workers.

Results found that systemic and neurological symptoms were most likely to persist at 6 months, and the most common symptoms were: fatigue; cognitive dysfunction; post-exertional malaise (worsening of symptoms after even minor exertion); sensorimotor symptoms (dizziness, tremors, paraesthesia); headache; memory troubles; insomnia; palpitations; shortness of breath; dizziness; speech problems; joint pains and chest tightness. Notably, respiratory symptoms were not commonly reported, but 93% (3505 out of 3762) of respondents still had symptoms at an average of 144 days of follow-up, and only 7% (257 out of 3762) recovered, with an average days to recovery of 91 days. Respondents who hadn't recovered by month 7 were experiencing an average of 14 symptoms.

Furthermore, of the persons experiencing “brain fog”, 67.5% (2169 out of 3214) required reduced work hours or were unable to work due to their illness; 86.2% (2853 of 3310) reported it mildly to severely impacted their work. Notably, there was no association between cognitive dysfunction or memory loss and age.

In conclusion, Ms Davis described multiple priority research questions to better understand Long COVID: timing of seroconversion; role of viral persistence; variations in immune response; etiology of post-exertional malaise and relapse; and role of appropriate investigations to include imaging, underlying immune responses, metabolic profiling, brain hypometabolism and hypoperfusion and altered T and B cell functioning. Additionally, a call out was made to remember to “ask the right questions” and need to include comprehensive selection of patients in research studies.

The remaining presentations focused on country experiences in Post COVID-19 cohort studies.

Six-month consequences of COVID-19 in patients discharged from hospital: a cohort study (China)

Dr Bin Cao presented a cohort study (n=1733) on the consequences of COVID-19 over 6 months in patients discharged from a hospital in Wuhan, China. Follow-up evaluation included: symptom survey, physical examination, standardized testing of functional limitations and health-related (i.e. MRC dyspnoea scale, EQ-5D-5L, EQ-VAS), and other diagnostic tests (i.e. blood tests, chest high resolution CT, 6-minute walking test [6-MWT], pulmonary function test, and ultrasound of lower limbs and abdomen). Notable results presented included: median age of 57 years, median follow up of 186 days from symptom onset and 1.3% mortality.

The most commonly reported symptoms reported were fatigue/muscle weakness 63% (2370 out of 3762), sleep difficulties 26% (978 out of 3762) and anxiety/depression 23% (865 out of 3762). But less than 10% (376 out of 3762) reported problems with mobility, usual activity or personal care. Multivariable regression analysis found association between severity of hospitalization and abnormal pulmonary diffusion testing, chest imaging and anxiety/depression. Females were at higher risk for pulmonary abnormalities and anxiety and fatigue/muscle weakness. In conclusion, the investigators suggested that this may be the main target population for long-term recovery interventions (22).

Expanding our understanding of Post COVID-19 condition (Italy)

Dr Marco Rizzi presented results of the Bergamo Project Italy (23), a large cohort follow-up study (n=1536) that started just after the first wave of the pandemic and included follow-up of high-risk patients at discharge to dedicated COVID-19 clinics. These clinics provided a multidisciplinary care model and standardized data collection including laboratory tests, chest imaging, pulmonary function tests and standard psychosocial and rehabilitation needs assessments. Preliminary analysis revealed mean age of 59 years, and at the first post-discharge visit the following symptoms were commonly reported: dyspnoea (509/1524, 33%), reduced diffusing capacity for carbon monoxide (DLCO) (346/1289, 28%) and post-traumatic stress disorder (PTSD) (477/1467, 32%). The speaker concluded that patients with Post COVID-19 condition require more selective and better resourced models of care to ensure feasibility and sustainability. A more detailed analysis is ongoing, and global collaboration welcome. Subsequently, **Dr Simone Piva**, presented follow-up of a small cohort of ICU survivors at 3 and 6 months (n=93) and reported on this cohort, which had a mean age of 62 years, in the following domains: pulmonary, physical and cognitive functions; and mental health and quality of life, using standardized scales. Notable findings included: moderately reduced diffusion capacity (47%); mildly reduced dominant hand dynamometry (40%); abnormal fatigue score (FSS > 36) (36%); mild cognitive impairment (18–26%); whereas mental health scores on depression, anxiety and PTSD were mostly normal.

Quality of life and long-term outcomes after hospitalization (Brazil)

Dr Regis Goulart Rosa presented outcomes of a prospective cohort study of adult hospitalized patients (n=931) followed up over a 1-year period. Patients were recruited from 55 centres in Brazil that participated in five randomized clinical trials (RCTs) that enrolled patients with varying disease severity (mild to critical). The primary outcome is health-related quality of life (EQ5D3L), and secondary outcomes included all-cause mortality, rehospitalizations, return to work or study, physical functional status, need for long-term ventilatory support, symptoms of anxiety and depression and symptoms of PTSD.

Preliminary results found that among survivors of hospitalization due to COVID-19, mortality was high during the months following discharge; rehospitalizations were common; the burden of physical and mental health disabilities was high; and the need for mechanical ventilation during hospitalization appeared to be a predictor of poor long-term outcomes.

Department of Biotechnology COVID-19 Research Consortium (India)

Professor Shinjini Bhatnagar presented the preliminary findings of a prospective observational cohort study that followed hospitalized COVID-19 patients (n=3832) after discharge and collected data on demographics, contact history, symptomatology, comorbidities, drug, exposure, travel history and hospitalization and treatment history. At the 6–10 weeks' visit, 5% (165 out of 3320) patients experienced one or more symptoms. Of the 85 patients with a median age of 65 years who had been evaluated at 6 months, fatigue was reported in 6% (5 out of 85) of patients. Noted, was the ongoing preparation to conduct observational studies in other fragile populations, including pregnant women, young children and adolescents and neonates. The speaker concluded that there is a need to define the common features, duration of illness associated with symptom clusters, clinical case description and now harmonized data.

Session 3. Working groups to develop a clinical case definition and research gaps/methods

Report of Working Group 1. Develop a clinical case definition and research gaps/methods

Co-Chairs: Dr Margaret Herridge, Dr Tarun Dua. See Annex 2 for all members of the panel.

Summary

It has become apparent that not all patients experiencing COVID-19 have full symptom resolution, and some patients report the emergence of new symptoms over time. Variations may represent heterogenous expressions of disease determined by host biology/genetics and/or distinct disease processes. However, differences might be also explained by the use of different methods for diagnostic approach and accuracy of symptom detection.

Challenges and opportunities

Participants highlighted the poor quality of some reports and their differences in study design and methods, which will complicate pooling estimates. There has been a lack of harmonized research to determine distinct phenotypes of Post-COVID-19 and variability in the spectrum of symptom complexes across end-organs and their severity. Delineating and validating distinct phenotypes is further complicated by variable access to diagnostics. Consequently, it may not always be possible to have laboratory evidence of preceding SARS-CoV-2 infection. The pathophysiology of post COVID-19 sequelae is poorly understood, and there is no robust association between severity of the acute illness and subsequent symptoms.

Proposed way forward

The framework must simultaneously capture clustering of symptoms by organ system; identify the severity of manifestations and differential expression across disparate patient populations (including adults, children, neonates, pregnant and breastfeeding women, and socially disadvantaged groups); determine potential risk or protective factors associated with Post-Covid-19 condition development; determine the association between severity of initial COVID-19 infection and treatment across different countries/health systems; and understand dynamic and variable host responses and their link to outcomes including functional and cognitive disability, mood disorders and health-related quality of life.

Identified clinical phenotypic patterns must be validated through a detailed evaluation and understanding of underlying pathophysiology. Research findings must be assessed for quality including the source of cases, the quality and intensity of the diagnostic assessment, and the accuracy of the investigation of newly diagnosed findings during follow-up. Finally, the case definition must serve an epidemiologic role to facilitate case surveillance and also to foster case management (see further information on surveillance at <https://blogs.bmj.com/bmj/2021/02/03/nisreen-alwan-we-must-pay-more-attention-to-covid-19-morbidity-in-the-second-year-of-the-pandemic/>). Patient-centredness must be amongst the highest priorities.

There is an emerging consensus that a stepwise approach should be adopted to align description, naming, understanding, prevention, management and research of this condition (which may be a group of conditions) and include an initial granular description of symptoms and outcomes, including the domains outlined above, with the subsequent identification of variable phenotypes.

An initial case definition could be fine-tuned later – before all the required data are available. If the initial infection is defined/diagnosed clinically – retrospectively or by lab confirmation – it may be considered that if a patient does not recover to baseline health, an assumption of Post COVID-19 condition is reasonable. A roadmap should identify research gaps, align research methodology, promote collaboration and prioritize patient-centredness when addressing each theme.

See Annex 3 for additional deliberations of Working Group 1.

Report of Working Group 2. Develop a clinical case definition; role of diagnostic testing

Co-Chairs: Professor John Marshall, Dr Maria del Rosario Pérez. See Annex 2 for all members of the panel.

Summary

Emerging literature suggests that Post Covid-19 condition is a multisystem illness with dominant manifestations that differ between patients and within patients over time. Therefore, understanding how to standardize diagnostic testing to inform clinical care and prognosis is important for patients, health care providers and health care systems. The range of symptoms include fatigue, post-exertional malaise, sensorimotor symptoms and brain fog as commonly overlapping symptoms, but up to 150 different symptoms have been associated with the condition to date. Diagnostic testing can provide information to clinicians and patients regarding both acute and chronic conditions within the context of a clearly identified phenotype, syndrome or disease entity.

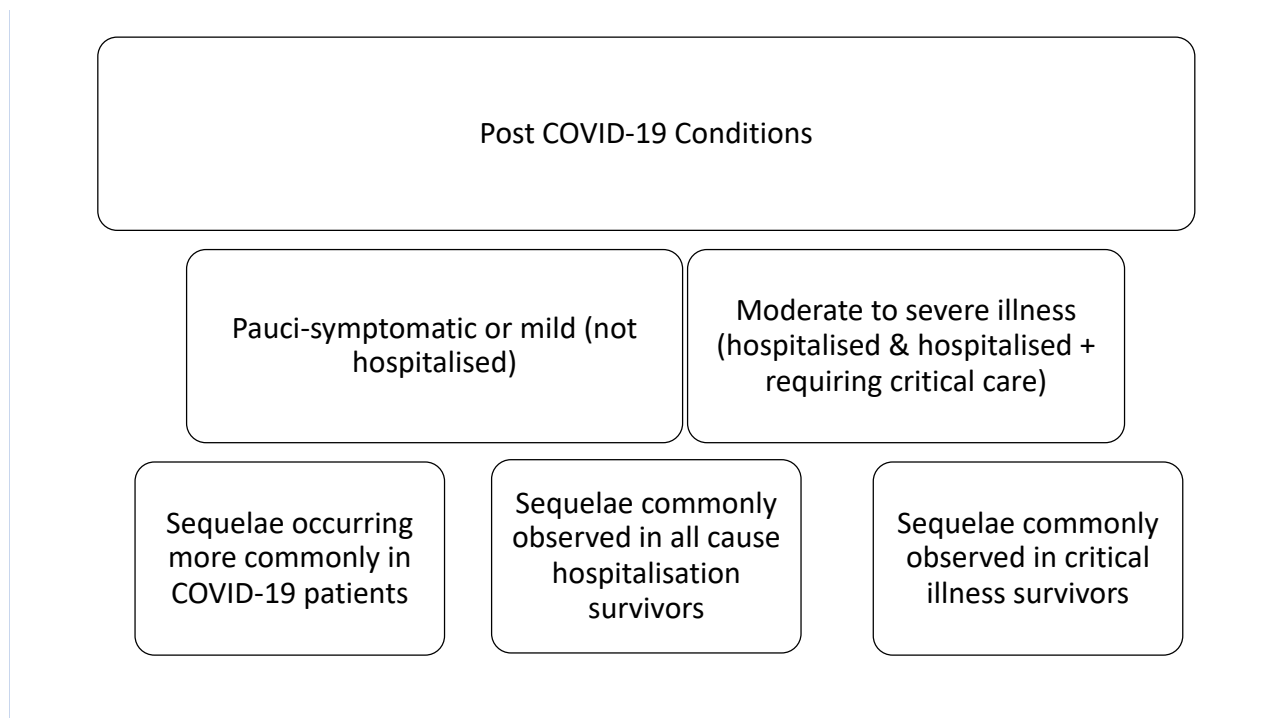
Challenges and opportunities

There is an urgent need to characterize and define Post COVID-19 condition before understanding the role of diagnostics. Potential aspects to be quantified and monitored include sustained alterations in innate and adaptive immunity, effects on the nervous system, abnormalities of thrombosis and endothelial function and other processes underlying prolonged organ-specific manifestations. Care must be taken to avoid bias against women, patients younger than 40 and patients older than 70, in whom antibody tests might not be as sensitive as in other groups.

Proposed way forward

Post-COVID-19 condition occurs in many different sets of patients, such as those hospitalized with COVID-19 illness of varying severity, those who have not been hospitalized or those having recovered from a pauci- or asymptomatic acute illness. A framework is proposed in **Fig. 1**.

Fig. 1. Umbrella description of Post COVID-19 condition



There appear to be at least two overlapping disease constructs subsumed under Post COVID-19 condition. The first is prolonged sequelae in patients with severe disease – for example, PICS (related to ICU support and related interventions) and the underlying organ injury that made the illness so severe. Second is a prolonged post-COVID-19 illness that disproportionately arises in patients whose initial illness was asymptomatic, mild or not even diagnosed/tested and involves multiple manifestations, the most common of which are fatigue, post-exertional malaise and cognitive dysfunction. It was noted that this presentation often has persistent or relapsing symptoms. Patients also generally have most of their clinical tests reported as normal. Many patients within this second group also have significant ongoing autonomic dysfunction and post-viral fatigue. There are other potential phenotypes, including individuals with respiratory symptoms (cough, breathlessness), cognitive, sensorimotor, gastrointestinal, renal, dermatological, reproductive, or cardiac symptoms. Most patients will have involvement in several of these categories.

The natural history of COVID-19, and its associated long-term consequences and sequelae, are just being unravelled, although precedence for post-viral malaise syndromes were reported as early as 1891 after the so-called Russian influenza. As highlighted in *Nature* as early as 11 August 2020, a negative COVID-19 test does not mean there has been a recovery. Likely, a “recovery” definition must include duration (e.g. does 1-year free of symptoms equal recovery?), severity and fluctuation of symptoms, as well as functionality and quality of life. Everyone who is symptomatic would remain a “case” until they fulfilled the recovery criteria or died. Accordingly, a major limitation for research and for clinical guidelines development is the absence of a case definition and homogenous terminology. Moreover, failure of resolution of the acute/index infection may underlie some of the late sequelae. A definition might differentiate between persistent sequelae after the acute phase of COVID-19 and Post-COVID-19 condition, corresponding to new onset of symptoms weeks to months following an apparent recovery from the initial acute COVID-19.

See Annex 4 for more details of Working Group 2 discussions.

Report of Working Group 3. Prevention, management and research

Co-Chairs: Professor Charu Kaushic, Dr Silvia Bertagnolio. See Annex 2 for all members of the panel.

Summary

It was acknowledged that much of the available evidence is only in hospitalized COVID-19 patients, which is a relevant group, but not completely representative of the full population affected by of [Post COVID-19 condition](#). Those COVID-19 patients who were managed in primary care, and even people who did not get diagnosed, are often dealing with an outpatient service that remains unaware that the symptoms of Post COVID-19 condition do not necessarily correlate with the severity of the initial infection. The heterogeneity of Post COVID-19 condition was a repeated theme for discussion. The group also acknowledged that Post COVID-19 condition shares symptoms with myalgic encephalomyelitis (ME) (also known as chronic fatigue syndrome [CFS]). The prevalence of Post COVID-19 condition ranges from 10–65% of individuals with primary SARS-CoV-2 infections in diverse clinical settings, but there is an absence of universal definitions and descriptions. Questions about whether a definition of Post COVID-19 condition is symptom-based should include a timeline for development of symptoms or include exemptions to the definition in need of further discussion.

Challenges and opportunities

It was repeated that the UK-CDR/GloPID-R Tracker found that less than 1% (45 out of 5000 plus) ongoing COVID-19 research studies focus specifically on Post COVID-19 condition (or its associated terminologies); and the majority of these studies follow hospitalized patients exclusively, and not those originally diagnosed with mild symptoms or never diagnosed.

Patient organizations are requesting that we learn from experiences with ME/CFS and other previous viral outbreaks such as SARS and MERS and involve patients and patient groups. Their motto is “Nothing about us, without us”. A patient representative from South Africa emphasized the need to include outpatients with mild disease or even pauci-symptomatic patients in any new trials.

Proposed way forward

There are multiple opportunities for advancing our knowledge through research. A need for the development of a Post COVID-19 core outcome set for clinical trials was highlighted. New trials with more than one intervention/drug and across the whole range of severity of symptoms developed during COVID-19 acute infections could be an important route to developing preventive approaches. Additionally, the occurrence of Post COVID-19 could be surveyed through extended follow-up of existing trials. Finally, due to sample size issues, there might be a need to pool data from several trials to possibly detect a protective/risk effect of any agent.

Biomedical research is required to elucidate pathophysiology behind symptoms to develop appropriate and effective treatment regimens. Multiple hypotheses (including but not limited to endothelial dysfunction, neuro-inflammation and immune dysregulation) are currently being considered. Animal models of COVID-19 could be useful for assessing the natural history of Post COVID-19 and for suggesting new drug targets to prevent or minimize this chronic condition. Many of the mechanisms and underlying pathogenesis could be studied more easily in animal models.

More research on primary care and in the primary care setting should be a focus, as many of these patients will be unable to access care in secondary/tertiary levels, especially in LMICs. Most patients with Post COVID-19 condition have been managed for their acute infection by family doctors. Moving forward, family doctors will likely manage Post COVID-19 conditions in most countries. There is a need to bridge the gap between research/academic and clinical medicine so that family doctors are in the best possible position to provide appropriate care. Research should place an emphasis on marginalized and socially or economically disadvantaged

populations, such as prisoners, migrants and refugees. Research on prevention of COVID-19 acute infections and Post COVID-19 condition should be explored to avoid COVID-19 compounding existing disadvantages.

Non-pharmacological interventions, such as physical rehabilitation, should also be explored at all health system levels. Overall, integration and coordination of care should be established to avoid a dichotomy between primary care versus specialist care. A continuum of care will be important. A strong call from this group was on making sure that there is comprehensive and universal health coverage for all those affected by COVID-19, with the theme “no one should be left behind”.

Further research on predictors for post COVID-19 condition will provide new evidence on protective/risk factors, and on the influence of chronic conditions and baseline health, not only on physical diagnosis and care, but also on psychological and social aspects of care. All assessments should be recorded, so that trajectories and times can be quantified. Studying the determinants of long-term effects and examining predictors for who will heal and who will develop Post COVID-19 should help determine when to start early therapy, early management and who should enter into extended care pathways. Health care workers would be a valuable group of subjects for studies for measuring the incidence of COVID-19 and determinants of Post COVID-19 condition.

Researchers should grasp the variety or heterogeneity of symptoms with physical assessments, imaging, biomarkers and a large number of diagnostic tests. In particular, cognitive assessment and other quantitative tests should be performed at the initial phase, when patients are discharged from hospital or attended primary care. Standardized protocols should be used in research.

A new tool just launched at this webinar and freely available is the newly developed [WHO CRF on Post COVID-19 condition](#). It should become an asset for data sharing and harmonization of data. Prospective cohorts with patient-level data and prospective meta-analyses of therapeutic effects of early treatment in preventing Post COVID-19 condition should be facilitated. Digital data sharing by health professionals, patients and the public is already available through apps and servers with standardized data collection and analysis. [For example](#) is a web-based patient-led registry and a symptom tracking app. We must bear in mind that, to date, most published studies are too small, too short and local; and their focus tends to be on one organ/system only. Making sense of heterogenous data sources and interpreting them correctly is an essential goal.

Artificial intelligence (AI) applied in real-time assessments also should be explored. Efforts to bypass existing legal hurdles around data sharing obtained within different jurisdictions should be streamlined with the aim of more effective use of all available clinical sources. One promising approach would be to expand work on prediction models to cover outpatients treated in primary care.

Researchers in the United Kingdom have started human challenge trials in which they actively infect individuals with increasing dosages of SARS-CoV-2 to identify thresholds for inducing infection (24). Many gaps in the understanding of Post COVID-19 condition could be addressed through these studies (25).

See Annex 5 for more information about the deliberations of Working Group 3.

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Annex 1. Agenda

Expanding our understanding of Post COVID-19 condition, first webinar 9 February 2021, 13.00 CET

| Time | Topic | Speakers |
|--|--|--|
| Plenary session | | |
| 13:00–13:10 | Welcome remarks | Dr Tedros Adhanom Ghebreyesus Director-General, WHO |
| Session 1. Post COVID-19 condition: scene setting and lessons learned | | |
| 13:10–13:20 | Opening remarks | Dr Maria Van Kerkhove Emerging Diseases and Zoonoses, WHO |
| 13:20–13:30 | Learning from previous viral infections: SARS, MERS, influenza and Zika | Dr Carlos A Pardo-Villamizar Johns Hopkins Myelitis & Myelopathy Center, Division of Neuroimmunology and Neurological Infections; Advanced Clinical Neurology, Johns Hopkins University School of Medicine, USA |
| 13:30–13:40 | Learning from previous critical illness: post-intensive care syndrome | Professor Dale M Needham Professor, Schools of Medicine (SOM) and Nursing, Outcomes After Critical Illness and Surgery (OACIS) Group; Department of Physical Medicine and Rehabilitation, Division of Pulmonary and Critical Care Medicine, SOM; Medical Director, Critical Care Physical Medicine and Rehabilitation Program; Johns Hopkins University, USA |
| 13:40–13:50 | Learnings from the National Institutes of Health (NIH) Workshop on Post-Acute Sequelae of COVID-19 (3–4 December 2020) | Dr Andrea Lerner Medical Officer, Immediate Office of the Director, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, USA |
| 13:50–14:00 | Learnings from the ISARIC-GloPID-R-Long COVID Support group meeting: Long COVID Forum (9–10 December 2020) | Dr Gail Carson Director of Network Development ISARIC, GloPID-R Secretariat, United Kingdom |

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|---|--|---|
| 14:00–14:10 | Pathophysiology/immunology: potential mechanisms | Professor Daniel Altmann Department of Immunology and Inflammation, Imperial College London, United Kingdom |
| 14:10–14:20 | WHO: efforts to advance our understanding of Post COVID-19 condition | Dr Janet Diaz Health Care Readiness, WHO |
| 14:20–14:30 | Break | |
| Session 2. Observations on Post COVID-19 condition: what we know | | |
| 14:30–14:40 | Global experiences from survey: Patient Led-Research COVID-19 | Ms Hannah Davis Patient Led-Research Collaborative University of London, United Kingdom |
| 14:40–14:50 | Experiences from China | Dr Bin Cao Vice President of China-Japan Friendship Hospital, Director of Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, China |
| 14:50–15:00 | Experiences from Italy | Dr Marco Rizzi Head Infectious Diseases Unit, Papa Giovanni XXIII Hospital, Bergamo, Italy Dr Simone Piva Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia; Department of Anaesthesia, Critical Care and Emergency, Spedali Civili University Hospital, Brescia, Italy |
| 15:00–15:10 | Experiences from Brazil | Dr Regis Goulart Rosa Critical care physician and post-ICU outcomes researcher, Hospital Moinhos de Vento, Porto Alegre, Brazil |
| 15:10–15:20 | Experiences from India | Professor Shinjini Bhatnagar Head, Maternal and Child Health Translational Health Science and Technology Institute, NCR Biotech Science Cluster, Faridabad, India |
| 15:20–15:30 | Break | |

Session 3. Working groups to develop a clinical case definition and research gaps/methods

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|--------------------|--|--|
| <p>15:30–16:45</p> | <p>Working Group 1: Develop a clinical case definition</p> <p>The panel will describe the following:</p> <ul style="list-style-type: none"> • Clinical clusters of signs or symptoms (phenotypes) • Is there a timeframe to include in the definition? • Are complications, such as stroke, acute coronary syndrome, pulmonary embolism, Guillain–Barré syndrome, part of Post COVID-19 condition? • How to link to pathophysiological mechanisms • Priority research questions and methods | <p>Chair: Professor Margaret Herridge Professor of Medicine, Senior Scientist, Critical Care and Respiratory Medicine, Director of Critical Care Research, University of Toronto; Director, The RECOVER Program Clinical Director Grace RECOVER Program for Chronic Critical Illness; Co-Lead, Canadian COVID-19 Prospective Cohort Study (CANCOV) University Health Network, Toronto, Canada</p> |
| <p>15:30–16:45</p> | <p>Working Group 2: Develop a clinical case definition; role of diagnostics</p> <ul style="list-style-type: none"> • How to include viral diagnostics (serology, rAG, PCR) • How to include immunologic, inflammatory, metabolic and coagulation tests • How to include imaging • How to include standardized assessment tools/scales • How to link to pathophysiological mechanisms | <p>Chair: Professor John Marshall Professor of Surgery, University of Toronto, trauma surgeon and intensivist, St Michael’s Hospital, Canada</p> |
| <p>15:30–16:45</p> | <p>Working Group 3: Prevention, management and research</p> <ul style="list-style-type: none"> • What pharmacologic interventions could be considered? What are potential targets? • What non-pharmacologic interventions should be considered? Patient-level interventions? Health system level interventions? • Research priorities: How should trials assess on longer-term outcomes? • What approaches can be used to collect standardized data and analysis? | <p>Chair: Professor Charu Kaushic Scientific Director of the Institute of Infection and Immunity of the Canadian Institutes of Health Research (CIHR); Chair of GloPID-R (Global Research Collaboration for Infectious Disease Preparedness); Department of Pathology and Molecular Medicine, McMaster University, Canada</p> |

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|-------------|---|--|
| 16:45–17:00 | Preparation of report from working groups | Panel members and Chairs |
| 17:00–17:30 | Report from the three working groups | Chairs |
| 17:30–17:35 | Post COVID-19 condition: a health emergencies perspective and closing remarks | Dr Mike Ryan Health Emergency Preparedness and Response, WHO |

Annex 2. List of participants

Panel members: Working Group 1

Chair: Professor Margaret Herridge

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Professor Bin Cao

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Professor Christopher G Chute

Johns Hopkins University, physician-scientist and biomedical informatician known for biomedical terminologies and health information technology standards (ICD-11).

Professor Francesco Landi

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Ms Elizabeth Semper President of the Association: COVID persistente España.

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Panel members: Working Group 3

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Annex 3. Development of a clinical case definition for Post COVID-19 condition (additional deliberations of Working Group 1)

Developing a case definition: There is an immediate need to move beyond case counting to prioritize intervention and further research, and a need for patient clinical registers. Case definition(s) might incorporate both detailed characterization and actionable items management. To prevent variability in the accuracy and reliability of case ascertainment, clear pragmatic criteria should be devised and adopted.

There will likely be a need for different case definitions. For instance, for an advocacy use case, one may need to be more inclusive (more sensitive), to enable individuals to access support and benefits and ensure that everyone with symptoms is included, regardless of confirmation of COVID-19. By contrast, surveillance and research definitions could require stricter criteria, such as laboratory- verified SARS-CoV-2 infection.

Use cases to consider include:

- **advocacy:** broadest definition, including self-reports;
- **clinical:** broad definition, based on clinical data and self-reports;
- **surveillance:** broad definition, based on ICD and other coding;
- **research:** strictest definition, based on “definitive” diagnoses.

Understanding the phenotypes: Phenotypes could be identified through electronic records (EHR) and large administrative datasets that permit detailed clinical characterization, disposition and treatment, health care utilization and determination of outcome trajectories over time. The use of these data sources, however, relies on validation procedures. Pre-existing/historic datasets and more recent surveys (e.g. the United Kingdom survey of 2500 non-hospitalized patients) may be informative, but sources of bias should be considered. Phenotypic data need to be further informed through translational biology/genetics across diverse patient populations and geographic and health system settings.

Further studies are needed on symptom clustering. Some clustering of symptoms may be focused on discrete organ systems, whereas others may extend across organ systems or manifest solely as systemic symptoms. Severity of illness, pre-existing comorbidities and attendant treatments may risk, modify or confound reported outcomes using a symptom or system-based model. Critically ill COVID-19 patients with complicating acute respiratory distress syndrome (ARDS) may manifest many symptoms consistent with PICS. Given the frequent development of multiple organ dysfunction and necessary complex critical care management, it may be challenging to delineate which post COVID-19 symptoms/organ dysfunctions are specifically attributable to COVID-19. It is worth noting the relapsing nature of the illness in most of those experiencing it; and this could even be part of a definition. Although a single etiology giving rise to variable, multisystem disease, may be discovered; a holistic approach should be streamlined to care. Patients should not be siloed for care by specialists. See Table 3A.1 regarding considerations for phenotypic groupings.

Table 3A.1 Phenotypes by organ system and pathophysiology

| Phenotypes by organ system | Phenotype by pathophysiology |
|--|---|
| <ul style="list-style-type: none"> • systemic symptoms (fatigue, etc.) • neurological • cognitive dysfunction/memory loss • mood disorders/psychological • respiratory • cardiovascular • musculoskeletal • metabolic • gastrointestinal • dermatological • allergic and immunological • other | <ul style="list-style-type: none"> • inflammation • immune subset dysregulation • autoimmune • coagulation/vasculopathy • viral perseverance/long-term infection • endocrine/metabolic. |

Setting a timeframe of case definition: There was no consensus on timeframe. There was clear consensus that only new symptoms/organ dysfunction post-acute illness should be included in the definition timeframe.

Some suggested timeframes included:

- **short-term:** an early post-acute infection timepoint of 4 to 8 weeks;
- **mid-term:** a later post-acute infection timepoint of 2 to 6 months;
- **long-term:** symptoms lasting more than 6 months.

It is unclear whether there should be an outer bound timepoint for inclusion as a post COVID-19 condition or what a specific final timepoint would be.

A graded documentation of the initial viral infection and the initial disease is essential for using timeframe information (see also WHO CRF of 8/9 February 2021). This should include the following.

- **level of evidence for viral infection:** none, antigen, RNA, antibodies;
- **disease severity:** none, mild, moderate, severe, critical;
- **level of evidence for disease severity:** self-report, clinical data.

Research gaps and methodology: There is a unique opportunity, early in the investigation of this condition, to align and coordinate efforts. Multinational, multidisciplinary, patient-centred collaboration should be encouraged, as should the development and adoption of consensus core datasets to characterize the acute illness and structured/timed follow-up. There may be a need to develop a core outcome set in Post COVID-19 condition to allow for data harmonization and further data meta-analysis. A consensus should be reached on what should be measured and how the outcomes should be measured. Suggested research priorities include:

- **Phenotype:** Examine multinational big data/health systems/EHR/solicited surveys/ ambidirectional (prospective and retrospective) cohorts to elucidate robust clinical phenotypes by symptom/organ system or pathophysiologic mechanism; ensure inclusion of vulnerable/fragile populations; investigation of non-infected controls to exclude comorbidities due to chance. It will be important to include the following populations: children, pregnant and breastfeeding women/neonates, hospitalized and non-hospitalized patients, all geographies, socially disadvantaged groups, ethnic backgrounds.
- **Mechanism:** Basic science (multiomic/genetic)/translational/pathophysiologic evaluation of proposed symptom/organ system phenotypes; and nested translational work from ambidirectional cohorts.

- **Others:** Immune phenotyping and biomarkers, imaging, prevention/rehabilitation/chronic pain (multimodality including physical/neurocognitive/mental health), family caregiver health outcomes as risk modification.

Working Group 1 acknowledged the various names and definitions in use in the academic and lay arenas to describe Post-COVID-19 condition that the group should be aware of and the need for global coordination and harmonization. At this stage, the group was unable to come up with a consensus definition of Post COVID-19 condition to be used in all settings and in all patients. Given that new evidence is being produced, definitions will be periodically revised. It can be considered an output for the next webinars/meetings.

Table 3A.2 Suggested names in the literature related to Post-COVID-19 condition

| Name | Reference |
|----------------------------------|---|
| Chronic COVID Syndrome | Baig AM. Med Virol. 2020 Oct 23. doi: 10.1002/jmv.26624 |
| Late sequelae of COVID-19 | CDC website (accessed 12 April 2021) |
| Long covid | Mahase E. BMJ. 2020 Jul 14;370:m2815 |
| Long Covid | Perego E, et al. Wellcome Open Research (editorial). 2020;5:224; The Royal Society |
| LONG COVID | Nature (editorial) (Let patients help define long-lasting COVID symptoms) 8 October 2020; Long COVID Forum 9–10 December 2020 from ISARIC/GloPID-R/Long COVID Support; Lancet (editorial) (Facing up to Long COVID) 12 December 2020 |
| Long haul COVID | Nath A. Long-Haul COVID. Neurology. 2020 Sep 29;95(13):559-560. Scientific American (Carolyn Barber, 29 December 2020) |
| Long-term COVID-19 | A special issue of Journal of Clinical Medicine (ISSN 2077-0383) |
| Post-acute sequelae | NIH |
| Post COVID syndrome | NHS website (accessed 12 April 2021) |
| Post-acute COVID-19 | Several papers in: BMJ, Eur J Phys Rehabil Med, Eur J Intern Med |
| Post-COVID-19 condition | WHO suggests use of the term Post COVID-19 condition , as it is neutral and lacks attribution of causality, and already has a designated ICD-10 code as U09.9 Emergency use ICD codes for COVID-19 disease outbreak (accessed 12 April 2020) |

Table A3.3 Definitions proposed in the literature for Post COVID-19 condition

| |
|---|
| <ul style="list-style-type: none">• Post-viral fatigue or chronic fatigue syndrome, systemic exertion intolerance disease (SEID), also known as myalgic encephalomyelitis.¹ |
| <ul style="list-style-type: none">• Symptoms persisting beyond four weeks after symptom onset suggestive of COVID-19.² |
| <ul style="list-style-type: none">• Multi-organ symptoms after COVID-19 are being reported by increasing numbers of patients. They range from cough and shortness of breath to fatigue, headache, palpitations, chest pain, joint pain, physical limitations, depression, and insomnia, and affect people of varying ages. At the Lancet-Chinese Academy of Medical Sciences conference on 23 November 2020, Bin Cao presented data (in press, <i>Lancet</i>) on the long-term consequences of COVID-19 for patients in Wuhan and warned that dysfunctions and complications could persist in some discharged patients for at least 6 months. So-called Long COVID is a burgeoning health concern and action is needed now to address it.³ |
| <ul style="list-style-type: none">• Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.⁴ |
| <ul style="list-style-type: none">• Individuals whose symptoms persist or develop outside the initial viral infection, but the duration and pathogenesis are unknown.⁵ |
| <ul style="list-style-type: none">• The onset of persistent or recurrent episodes of one or more of the following symptoms, within x* weeks of infection with SARS-CoV-2 and continuing for y* weeks or more.⁶ |

There are already a number of suggested definitions of Post COVID-19 condition proposed by a number of societies and authors, listed in Table A3.3. At this stage, we are unable to come up with a consensus definition of Post COVID-19 condition to be used in all settings and in all patients. Given that new evidence is being produced, definitions will be periodically revised. It can be considered an output for the next webinars/meetings.

¹ Komaroff AL. Advances in understanding the pathophysiology of Chronic Fatigue Syndrome. *JAMA*. 2019 Jul 5. doi: 10.1001/jama.2019.8312. PMID: 31276153.

² Perego E, Callard F, Stras L, Melville-Jóhannesson B, Pope R, Alwan NA. Why the patient-made term 'Long Covid' is needed. *Wellcome Open Research*. 2020;5:224.

³ Facing up to long COVID (editorial). *Lancet*. 2020;396(10266):1861. doi: 10.1016/S0140-6736(20)32662-3.

⁴ NICE guideline [NG188] COVID-19 rapid guideline: managing the long-term effects of COVID-19. 18 December 2020.

⁵ Barber C. The problem of 'Long Haul COVID'. *Scientific American*. 29 December 2020 (<https://www.scientificamerican.com/article/the-problem-of-long-haul-covid/?print=true>, accessed 12 April 2021).

⁶ Long Covid: what is it, and what is needed? (editorial). *The Royal Society*. 23 October 2020.

Annex 4. Role of diagnostics in clinical management (additional deliberations of Working Group 2)

The potential diagnostic testing strategies that inform clinical care and prognosis are numerous. Such strategies are important for patients, health care providers and health systems. Diagnostic testing should consider: the persistence of viral infection; multi-organ/system involvement; chronic immune system alterations; the role of high-sensitivity screening tests to perform multisystem involvement; and likely others. Diagnostics aid in sorting out questions of pathogenesis, diagnosis and potential new treatments. In the context of COVID-19 it is advisable to view diagnostics from three different perspectives – tests that are important from a public health perspective; those that are needed for a patient’s individual care; and those for research; all of which may overlap.

Pathophysiology: To date, many questions remain about the pathophysiology and are not necessarily mutually exclusive. These include:

- How does the virus and host interplay (including genetics and immune response)?
- Is the disorder associated with persistence of the virus, potentially in an occult reservoir such as the gastrointestinal (GI) tract or sustained viral foci in, for example, the liver, the bone marrow, the brain or the heart? Does this lead to ongoing immune stimulation and merit studies on antivirals?
- Is the disorder a consequence of direct tissue injury, possibly related to SARS-CoV-2 interactions with ACE-2 and epithelial damage with subsequent tissue injury and fibrosis or scarring?
- How does the dysregulation of the renin-angiotensin-aldosterone system as a consequence of downregulation of ACE-2 related to viral entry play a role?
- Further define the role of endothelial cell damage and thrombo-inflammation?
- Is the disorder a dysregulated host response (immune or otherwise) to the virus (raising the question of a potential genetic or epigenetic basis for illness)? Can this lead to chronic inflammation? Further characterization is needed (i.e. role of interferons, T cell lymphodepletion, proinflammatory cytokines (IL-6, TNF alpha).
- Are some patients suffering from a consequence of therapy, e.g. the effects of mechanical ventilation or steroids?
- How do cultural and socioeconomic factors shape the illness?
- Is the disorder specific to COVID-19 or similar to post-sepsis or post-trauma syndromes?
- Is the immune response different during the acute phase of COVID-19, depending on disease severity? Such a response may have protected patients from severe disease or death; but this immune response persisted after the acute illness and produced Post COVID-19 condition.
- What mechanisms are underlying the cause of neurologic manifestations (i.e. neuroinflammation)?

SARS-COV-2 laboratory diagnosis: Confirmation of SARS-CoV-2 infection is relevant and includes the use of antibody tests. Options include different types of immunoglobulin in addition to IgG and IgM. There is value in confirming the infection through antibody testing (expanding to different immunoglobulins); emphasizing that antibody testing needs to be appropriate for the time window. For example, if there are reservoirs in the gut, would this be reflected in the serum IgA response? If this is a hypersensitivity response, would we expect to see a big response? Additionally, there may be some variability based on the viral variant involved. In general, standard protocols and guidelines for SARS-CoV-2 testing should guide testing approaches. Considerations for testing:

- PCR, potential role for antigen tests that are more specific and utility of sequential testing.
- Seropositivity, titre of neutralizing antibody (IgM, IgA, IgE) to look at acute, chronic or past infection. Note, however, the low sensitivity and specificity that can be seen in the general population as well as in certain subpopulations (i.e. women, and those under age 40 years and over 70 years).
- Genetic testing for variability/susceptibility.

Host response/organ injury: Regarding the host response, one would want to look at whether or not the host was primed to respond to a prior viral infection (i.e. interferon testing). Specific markers of organ injury include elevated liver enzymes, elevated creatinine or presence of haematuria, proteinuria; endocrine abnormalities (such as adrenal axis, thyroid function, glucose levels) and the perturbation of the coagulation cascade (such as fibrinogen, D-dimers, antiphospholipid antibodies and markers of thrombotic and fibrinolytic turnover). In general, testing should always be clinically driven.

Inflammatory markers: Does acute inflammation turn into chronic inflammation? Inflammation mainly refers to a dysregulated host response. Inflammation may suggest the importance of genetic and/or epigenetic changes in the host. It would be important to know if patients have persistent high circulating levels of cytokines (as shown in community-acquired pneumonia [CAP]) or catecholamines (as shown after sepsis or burn). Other options include testing the autonomic nervous system with non-invasive, routine tests. This is an area that merits further investigation with standard research protocols.

Imaging modalities: Several modalities are available to use imaging to help diagnosis of Post COVID-19 condition. Conventional imaging may not reveal severe functional abnormalities that might only be seen by MRI, PET scan or echocardiography. The use of imaging in patients with Post COVID-19 condition should always be clinically driven. See Table A4.1.

Table A4.1 Potential role of imaging for assessment of Post COVID-19 condition

| Post COVID-19 symptom/signs phenotype | Imaging modality |
|---|--|
| Neurologic/psychiatry | Brain MRI, spine MRI, functional imaging and advanced MRI techniques, hybrid imaging (PET-MRI, PET-CT) |
| Cardiovascular | Echocardiography, cardiac MRI, coronary CT angiography, CT pulmonary angiography, doppler vascular ultrasound (carotids, extremities, transcranial), CT or MRI angiography |
| Pulmonary | Chest CT, chest radiography, lung ultrasound |
| Hepatic/renal/gastrointestinal, metabolic | Abdominal ultrasound, abdominal CT, abdominal MRI, nuclear medicine |
| Immunologic/rheumatologic | Different imaging modalities according to clinical indication |
| Paediatric | Different imaging modalities; due to risk of radiation, ultrasound and MR are preferable options |
| General | Different imaging modalities according to clinical indications |

Standardized tests, scales and tools: There may be a need to evaluate mental outcomes measured with psychological and physical tests. These questions go beyond what could be included in a working group discussion. A shortlist of potential lists or tools/scales are provided: health related quality of life (EQ-5D, 3L or 5L version; SF-36V2); mental health (HADS, IES-R); pain (EQ-5D pain); cognitive (MoCA blind); physical function (6-MWT); muscle and nerve function (handgrip); pulmonary function; and exercise capacity.

Annex 5. Prevention, management and research (additional deliberations of Working Group 3)

The deliberations, by question posed to panel members, are presented below.

Question 1: What elements should be taken into consideration for research into pharmacological interventions and potential targets?

- More research is needed. According to the ISARIC tracking tool, only 45 out of 5000 (less than 1%) of ongoing research projects focus on Post COVID-19 condition.
- Well-designed clinical trials with structured follow-up can be done. The five Brazilian post-trial experiences (I, II, III, IV and VI) reported by Dr Regis Goulart Rosa provide an example for appropriate design of other studies, that can be replicated in other sites around the world.
- It is a challenge to conduct trial designs with more than one intervention/drug; however large- scale platform trials are underway for acute COVID-19 and thus can also be done for Post COVID-19 condition.
- Patient representatives in LMICs (South Africa) request to include outpatients with originally mild COVID-19 or even pauci-symptomatic COVID-19, who now have Post COVID-19 condition, in trials.
- Pragmatic drug trials in primary care are recommended, as the bulk of patients rely on family doctors/GPs.
- Patient organizations (Solve ME, Patient Led Research and others) request increasing knowledge on lessons from history on CFS/SEIS, and previous pandemics. Also remember, “Nothing about us without us”.
- Complex management of disease by health systems for marginalized populations (e.g. prisoners, migrants, refugees).

Question 2: What are the most important considerations concerning non-pharmacologic interventions at patient level and health system level?

- Rehabilitation should focus on both physical and psychological/social aspects. Also consider interventions like Tai-Chi and other alternative and traditional approaches for wellness.
- Identifying biomarkers of inflammation (baseline and longitudinally) associated with Post COVID-19 condition can be key to predicting who needs to be included in care. Studies should be designed to understand determinants (risk factors) for Post COVID-19 condition. Methodologic options include using comparison groups via EHR or population-based studies.
- Include cognitive assessment and management plans from the onset.
- Include psychological and mental health effects on health staff as well as patients and their families.
- Public education and information are key.
- Coordination of a comprehensive care model is fundamental.
- Universal health coverage – “no one left behind”.

Question 3: How can the Post COVID-19 condition be assessed in trial outcomes?

- Potential outcomes should include a combination of symptoms, physical assessments, imaging, biomarkers and omics.
- Prospective meta-analyses of therapeutic effects of early treatment in preventing Post COVID-19 condition can be done from already completed trials.
- Standardized data collection necessary. The new WHO CRF is an asset and also needed is the Post COVID-19 core outcome set.
- Coordination of global data sharing to more rapidly answer questions.

Question 4: What approach should be taken for standardized data collection and analysis?

- Analysis should identify the positive/negative risk factors associated with the development and severity of Post COVID-19 condition.
- Meta-analysis of various studies is key component to bring together various evidence sources.
- Develop predicting models for outpatients to develop Post COVID-19.
- Consider AI, apps and real-time assessment of EHR; some existing legal and ethical hurdles should be leveraged for public good. By using pooled information from EHR, models could be extended to capture primary care predictors for hospitalization, and ideally follow-up after discharge.
- Universal definitions and descriptions on infection, healing, curing and post COVID-19 condition.

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