WHO update: post COVID-19 condition
Clinical case definition and update on clinical activities

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6 October 2021, 13:35–13:45 CET Salle C, WHO HQ
Advance our understanding of post COVID-19 condition

A series of three seminars on the WHO’s three “Rs”:

1. Recognition and burden
2. Research
3. Rehabilitation

“Without established mechanisms, no COVID-19 new treatments”
Post COVID-19 condition: milestones and timelines

- **September 2020**: International Classification of Disease (ICD) Developed
- **April 2021**: Developing survey for post COVID-19 case definition
- **May 2021**: Post COVID-19 case definition Delphi Round 1
- **May 2021**: Post COVID-19 core outcome set (COS) Identify outcomes
- **June 2021**: Post COVID-19 case definition Delphi Round 2: consensus meeting
- **June 2021**: Post COVID-19 COS Long list of outcomes Forming stakeholders Ethics approval and survey development
- **July - August 2021**: Clinical case definition Delphi process, results interpretation, online consensus meeting
- **6 October 2021**: Webinar 3: Expanding our understanding of rehabilitation
- **6 October 2021**: Post COVID-19 case definition publication of definition
Webinar 1: Recognition and burden (9 February 2021)

- **Aim:** Recognition and burden
- **14 speakers and a peak of 623 attendees**
  - Presentations describing cohorts from around the globe
  - 3 working groups discussed clinical descriptors, laboratory diagnostics and research priorities
- **Launch of the post COVID-19 condition CRF**

**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.

https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/data-platform/

https://www.who.int/publications/i/item/9789240025035
• Uses anonymized, individual-level data from hospitalized patients with COVID-19

• Generates global, regional, country reports that can inform national responses and evidence-based guidelines on clinical management of COVID-19.

• CRF 4: Describe mid- and long-term sequelae of patients discharged from hospitals or managed at home

N=481,681
Patient-level data on hospitalized COVID-19 patients (As of September 1, 2021)
Post COVID-19 Condition CRF

- Designed to build upon the Core CRF

**MODULE 1**
**Acute COVID-19 episode**

**Retrospective information**
- Demographics
- Diagnostic/other tests
- Co-morbidities
- Medications
- Complications/Co-infections
- Clinical Management (therapeutics + supportive care)
- Pregnancy Status upon Admission

**MODULE 2**
**Follow-up**

**Physician Encounter**
- Reinfection
- Vaccination status
- Occupation
- Functional status
- Signs and symptoms since acute episode

**MODULE 3**
**Follow-up**

**Clinical examinations, laboratory tests and diagnosis**
- Neurological exam
- Radiographic exam
- Blood tests
- Other clinical tests and scales
- New diagnosis of illness/complication
- Received

The WHO Global Clinical Platform for COVID-19: electronic platform now available
Understanding mechanisms of post COVID-19 condition

Considered at least seven potential causes (likely multifactorial)

1. Inflammatory/hyperinflammatory state
2. Immune dysregulation/autoimmune
3. Coagulation/vasculopathy
4. Direct viral toxicity/viral persistence
5. Autonomic dysfunction
6. Endocrine/metabolic
7. Maladaptation of the ACE-2 pathway

Post COVID-19 condition case definition by Delphi consensus
Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months, that cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.

* A separate definition may be applicable for children
Post COVID-19 condition by a two-round Delphi consensus methodology

The full case definition report developed between May – June 2021 can be found on the WHO website:

Participants represented 44 countries in every WHO region.

Majority from Americas and Europe and from high-income countries.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: WHO, Delphi Manager
Map Production: WHO Health Emergencies Programme
No difference in the backgrounds of participants in Rounds 1 and 2

Approximately 40% female in Rounds 1 and 2
A final total of 12 domains were included in the definition

1. History of SARS-CoV-2 infection
2. SARS-CoV-2 laboratory confirmation
3. Minimum time period from onset of symptoms (or from date of positive test for asymptomatic): 3 months
4. Minimum duration of symptoms at least 2 months
5. Symptoms and/or impairments: cognitive dysfunction, fatigue, shortness of breath, others
6. Minimum number of symptoms
7. Clustering of symptoms
8. Time-course nature of symptoms: (fluctuating, increasing, new onset, persistent, relapsing)
9. Sequelae of well-described complications of COVID-19 (stroke, heart attack, etc.)
10. Symptoms cannot be explained by an alternative diagnosis
11. Application of definition to different populations: Include separate definition for children, others
12. Impact on everyday functioning

Blue: Achieved consensus in Round 1
Purple: Achieved consensus in Round 2
Orange: Achieved consensus in Delphi panel group discussion
Post COVID-19 condition
Core outcome set
**Aim:** To rapidly develop a standardized core outcome set (COS) for global use in post COVID-19 condition (PCC) trials, other research and clinical settings

**Methods:** Optimal (COMET) methods

**Input from international stakeholders:** Patients with PCC, researchers, clinicians, caregivers and COS methodologists

**Design:** Delphi studies +/- consensus meetings
- Stage 1: “What” to measure – complete in November 2021
- Stage 2: “How” to measure – complete ASAP in 2022
**Post COVID-19 COS: Stage 1 “What” to measure**

**Methodology:** working group selected 24 outcomes for rating in 1\textsuperscript{st} round of Delphi study available in English, Spanish, French, Russian and Chinese languages

<table>
<thead>
<tr>
<th>Survival</th>
<th>Cognitive functioning, symptoms and conditions</th>
<th>Fatigue or exhaustion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular functioning, symptoms, conditions</td>
<td>Mental functioning, symptoms and conditions</td>
<td>Social role functioning and relationship problems</td>
</tr>
<tr>
<td>Endocrine and metabolic functioning, symptoms, and conditions</td>
<td>Taste- and/or smell-related functioning symptoms and conditions</td>
<td>Work/occupational changes and study</td>
</tr>
<tr>
<td>Hearing-related functioning, symptoms and conditions</td>
<td>Kidney and urinary-related functioning, symptoms and conditions</td>
<td>Stigma</td>
</tr>
<tr>
<td>Gastrointestinal functioning, symptoms and conditions</td>
<td>Reproductive and sexual functioning, symptoms and conditions</td>
<td>Satisfaction with life or personal employment</td>
</tr>
<tr>
<td>Pain</td>
<td>Respiratory functioning symptoms and conditions</td>
<td>Health care resource utilization</td>
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<tr>
<td>Sleep-related functioning, symptoms, and conditions</td>
<td>Skin, hair, and/or nail-related functioning symptoms and conditions</td>
<td>Family/carer burden</td>
</tr>
<tr>
<td>Nervous system functioning, symptoms and conditions</td>
<td>Physical functioning symptoms and conditions</td>
<td>Post-exertion symptoms</td>
</tr>
</tbody>
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Post COVID-19 COS: Stage 1 “What” to measure

1530 participants from 70 countries
- 25 European (66% participants)
- 19 Asian (6%)
- 12 South American (5%)
- 10 African (2%)
- 3 North American (19%)
- 2 Australian (2%)

3 key stakeholder groups
1. Professionals (researchers and/or clinicians with PCC expertise)
2. Professionals with PCC
3. People with PCC (family and caregivers)

2 new outcomes (suggested by > 1% of participants) added for 2nd round, launched 1 October 2021
Webinar 3: Expanding our understanding on rehabilitation

Over 3000 participants registered for today’s webinar

Objectives:
1. Introduction to rehabilitation for post COVID-19 condition
2. Interventions for rehabilitation for post COVID-19 condition
3. Models of rehabilitation Care for post COVID-19 condition
Acknowledgements

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