

## LONG COVID: A NEW DISEASE?

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**Received:** 6-III-2024

**Accepted:** 11-VI-2024

### Abstract

The definition of quaternary prevention as the set of interventions that avoids or mitigates the consequences of unnecessary or excessive activity of medical interventionism and the health system. The definition of a new disease is a complex process that involves the identification, characterization and description of a medical condition that has not been previously recognized or documented. Since mid-2020, the term chronic COVID/long COVID has been used to describe the presence of signs and symptoms after an acute SARS-CoV-2 infection, with multiple terminologies and definitions in international literature. Post-infectious syndromes, myalgia encephalomyelitis and fibromyalgia, are some of the diseases that have similarities with chronic COVID. This article presents an analysis relating the concepts of new disease and quaternary prevention with chronic COVID and other diseases described in the literature.

**Key words:** quaternary prevention, long COVID, myalgic encephalomyelitis, post-infectious syndromes, fibromyalgia

### Resumen

**COVID crónico: ¿una nueva enfermedad?**

Se define prevención cuaternaria como el conjunto de intervenciones que evita o atenúa las consecuencias de

la actividad innecesaria o excesiva del intervencionismo médico y del sistema sanitario. La definición de una nueva enfermedad es un proceso complejo que involucra la identificación, caracterización y descripción de un cuadro clínico que no ha sido previamente reconocida o documentada. Desde mediados del año 2020 se utiliza el término COVID crónico/long COVID para describir la presencia de signos y síntomas luego de una infección aguda por SARS-CoV-2, con múltiples terminologías y definiciones en la literatura internacional. Los síndromes posinfecciosos, la encefalomielitis mialgia y la fibromialgia, son algunas de las enfermedades que tienen similitudes con el COVID crónico. En este artículo se presenta un análisis relacionando los conceptos de nueva enfermedad y prevención cuaternaria con el COVID crónico y otras enfermedades descritas en la literatura.

**Palabras clave:** prevención cuaternaria, COVID crónico, encefalomielitis miálgica, síndromes posinfecciosos, fibromialgia

### KEY POINTS

#### Current knowledge

- Chronic COVID/long COVID emerges as a new disease in some patients who had an acute case of SARS-CoV-2. There are numerous terminologies and definitions for this concept, which can be confusing when making decisions.

### Contribution of the article to current knowledge

- Chronic COVID/long COVID is a poorly characterized entity that shares signs and symptoms with other diseases such as acute post-infection syndrome, myalgia encephalomyelitis and fibromyalgia. It is necessary to continue research studies to provide greater clarity to this health problem.

To contextualize this question, it is convenient to recall the definition of quaternary prevention as “the set of interventions that prevents or mitigates the consequences of unnecessary or excessive medical interventionism and health system”<sup>1,2</sup>.

One of the most relevant aspects of quaternary prevention is the denunciation of “disease mongering”<sup>3</sup> a critical term that refers to the practice of promoting the perception of common, existing, and often mild problems as new diseases requiring medical treatment. This tactic, mainly driven by the commercial interests of the pharmaceutical industry, seeks to expand markets by increasing the base of potential consumers, thereby promoting medications and treatments<sup>4</sup>.

Within the expressions of disease mongering, the following are described:

1. Medicalization of daily life: common or previously described symptoms are labeled as serious medical disorders. This can lead people, as in the case of COVID, to believe they need medical treatment for issues that could be managed as existing health situations are.

2. Exaggeration of prevalence: the perception of the prevalence of certain conditions is amplified to create public alarm. The inclusion of new diseases can lead to greater demand for studies and medications.

3. Expansion of diagnostic criteria: diagnostic criteria are broadened so that more people fall into the “sick” category.

4. Creation of new diseases: new diseases are invented or promoted, often backed by questionable scientific studies, creating the need for new treatments<sup>5</sup>.

The consequences of disease mongering can be summarized as follows:

1) Overmedicalization: individuals are subjected to unnecessary treatments, with the consequent risk of side effects and complications. The pressure to consume medications can lead to overmedicalization, reducing quality of life and increasing healthcare expenditure without adequate clinical justification.

2) Resource diversion: health system resources can be diverted toward the treatment of medically dubious or overdiagnosed conditions, to the detriment of serious diseases that genuinely need attention.

3) Stigmatization: the medicalization of already known conditions can increase the stigmatization of individuals, making them feel sick or defective for situations that are part of the spectrum of already described health situations<sup>6,7</sup>.

Disease mongering is a significant problem that requires a multidimensional response, including public education, strict regulation, and the promotion of independent research, to protect public health and ensure that medical treatments are based on genuine needs and not commercial strategies.

Defining a new disease exposes us to the danger of false positives: if someone feels unwell but this situation does not signify a new disease, labeling them with a nonexistent condition can have serious consequences, especially in sensitive times like a pandemic, involving threats to emotional stability, among others. The definition of a new disease is a complex process that involves the identification, characterization, and description of a medical condition that has not been previously recognized or documented; before accepting the existence of a new disease, medicine is obliged to consider ten dimensions that ensure avoiding the harms<sup>8</sup>:

- Identification of unusual cases
- Clinical investigation
- Laboratory studies
- Collection of epidemiological data
- Comparison with previously described medical conditions
- Literature review
- Diagnostic criteria

- Communication and publication
- Recognition and classification

### Identification of unusual cases

The first step is usually the identification of patients presenting unusual or atypical symptoms, signs, or clinical findings that do not fit any existing disease. This can occur sporadically or in groups of patients. The question in analyzing this dimension is: Do the symptoms, signs, or clinical findings not fit any existing disease? The answer to this question requires reviewing 5156 codes on 1348 pages of the International Classification of Diseases (ICD-10 CM)<sup>9</sup>.

### Clinical investigation

Once unusual cases are identified, detailed clinical investigation must be carried out to characterize symptoms, disease severity, clinical course, and any associated risk factors. At this point, it is necessary to evaluate whether the clinical questions are appropriate and if the types of studies attempting to answer them have appropriate designs<sup>10</sup>.

### Laboratory studies

The systematic affiliation of a new disease requires conducting laboratory studies, such as blood analyses, medical imaging, biopsies, or other diagnostic procedures, to obtain additional information about the disease and rule out that other conditions are not similar and authorize us to define a new entity. At this point, it is essential to recall the validity criteria for diagnostic studies, which include designs that incorporate patients with diagnostic doubt, comparison with an independent gold standard, and the application of diagnostic procedures and the gold standard to all patients<sup>11</sup>.

### Collection of epidemiological data

It is essential to collect information on the incidence and prevalence of the disease, as well as the demographics of affected patients, to better understand who is at risk for the supposed disease. Prospective cohorts and case-control studies are of undeniable value in this step of analyzing a new disease<sup>12</sup>.

### Comparison with previously described medical conditions

Researchers defining a new disease have the challenge of comparing the findings of the new disease with existing diseases to determine if it is a completely new entity or a variant of a known disease.

### Literature review

Existing medical literature must be reviewed to ensure that the disease has not been previously described worldwide. At this point, the use of a systematic review, a research work that, as its name describes, adheres to a systematic methodology attempting to control biases that deviate from the sought objective, is desirable in defining a new disease<sup>13</sup>.

### Diagnostic criteria

Researchers must identify specific diagnostic criteria for the new disease, allowing physicians to identify and diagnose future cases. At this point, each criterion must have a high probability to confirm or rule out the suggested new disease<sup>14</sup>.

### Communication and publication

Once the new disease has been defined and characterized, it must be communicated to the medical and scientific community through publications in unbiased medical journals and scientific conferences not influenced by conflicts of interest<sup>8</sup>. At this point, those who seek transparency must take into account that almost 50% of the publications consumed by healthcare professionals have potential biases<sup>15</sup>.

### Recognition and classification

Health agencies and regulatory bodies must recognize and classify the new disease, leading to the assignment of an official name and the implementation of management and prevention strategies. As a reminder, more than 50% of strong recommendations from the WHO are based on evidence of low or very low certainty<sup>16</sup>.

### Rigorous process of identification and characterization

It is important to note that defining a new disease is a rigorous process that involves collabo-

ration among physicians, researchers, epidemiologists, and other healthcare professionals. The precise identification and characterization of a new disease are essential for its proper management and to protect public health from falsely substantiated evidence<sup>17</sup>.

### Does chronic COVID exist?

Since mid-2020, when Elisa Perego used the term long COVID on social media to describe the presence of signs and symptoms after an acute infection by SARS-CoV-2<sup>18</sup>, numerous names have been suggested for this condition: prolonged COVID, persistent COVID, chronic COVID, long COVID, post COVID, post COVID condition, post-acute sequelae of COVID, among many others. All these terms refer to the same situation: defining the presence of signs and symptoms after the acute phase of SARS-CoV-2.

This situation generates difficulties, confusion when making decisions, and behaviors related to the care of patients with signs and symptoms that bring to consideration the probability of chronic COVID. In Table 1, we can observe some of the characteristics that, in the numerous definitions from different countries, organizations, and entities, have been used to describe this entity. All of them share the common goal of defining until when they consider the acute period of the disease, how they name and characterize the periods beyond the acute illness, and what considerations they make in their definitions<sup>19-28</sup>.

The only internationally recognized initiative is that of the WHO<sup>29</sup>. Representatives from five continents were consulted using the Delphi methodology in two rounds to achieve a definition of what they define as post-COVID-19 condition. This definition considers diagnosis three months after the acute period of the disease with symptoms that must persist for more than two months, not explained by an alternative diagnosis, and impacting daily life activities. Relevant symptoms highlighted include fatigue, difficulty breathing, and cognitive dysfunction, among others, persisting in a recurring or new onset pattern.

### Who could develop chronic COVID?

Not all patients affected by COVID-19 developed similar clinical pictures during the acute period of the disease. On one end of the spec-

trum, young patients without risk factors or underlying conditions may have been asymptomatic or mildly symptomatic. On the other end, older adult patients with existing illnesses or comorbidities may have experienced severe cases, requiring prolonged intensive care unit stays, with significant repercussions after the acute illness, complications, and unfortunately, many deaths. Similarly, the symptoms after the acute period did not exhibit the same characteristics.

After almost three years of the pandemic, we know the risk factors predisposing individuals to develop chronic COVID<sup>30</sup>. In Table 2, the results of a meta-analysis identify the association between different variables and the probability of developing chronic COVID. Notably, only vaccination with more than two doses acts as a protective factor, while the presence of other risk factors increases the probability, ranging from 10% higher in the case of smoking to almost three times more with the presence of other comorbidities. Within them, anxiety-depression, asthma, diabetes, chronic obstructive pulmonary disease (COPD), coronary artery disease, and immunosuppression were analyzed in order of frequency. An important aspect to highlight is the high predisposition in those patients who were hospitalized. However, this concept turns out to be very broad, as we cannot identify which factor within the patients, hospitalization is predisposing. A hospitalized patient could have been in a general ward or in the intensive care unit, without or with the support of oxygen therapy, high-flow nasal cannula, non-invasive ventilation, or with endotracheal intubation, with or without support from inotropic drugs, vasopressors, or under sedation, presenting adverse effects to treatments or intrahospital complications, and all these factors can be a cause, adjuvant, or confounder of chronic COVID.

We now know the risk of a patient with acute SARS-CoV-2 infection developing signs and symptoms described in Chronic COVID, and we can assess it by answering four yes-or-no questions: Did they require hospitalization? Do they have risk factors? Did they develop complications during the acute period of the disease? Did they develop sequelae during the acute period of the disease? Once the answers are obtained, we will find ourselves in one of the three sce-

**Table 1** | Comparison of different definitions of chronic COVID/long COVID

Organization	Terminology	Definition	Observations
NICE - SIGN Managing the long-term effects of COVID-19 <sup>20,21</sup>	Continuous symptomatic COVID-19	Signs and symptoms of COVID-19 between 4-12 weeks	Key points: include signs and symptoms with a time frame
	Post-COVID-19 Syndrome	Signs and symptoms of COVID-19 that appear or persist after 12 weeks and are not explained by another diagnosis	
	Prolonged COVID	Include both previous terms	
Nalbandian A, et al Post acute COVID-19 syndrome <sup>25</sup>	Subacute or persistent symptomatic COVID-19	Symptoms and abnormalities of COVID-19 between 4-12 weeks	Key points: include signs and symptoms with a time frame
	Chronic or Post COVID-19 Syndrome	Symptoms and abnormalities of COVID-19 that appear or persist after 12 weeks and are not explained by another diagnosis	
CDC Post-COVID conditions <sup>27,28</sup>	Prolonged COVID	Symptoms persisting for weeks or months and worsening with physical activity	Key points: include signs, symptoms, organ consequences, and hospitalization consequences, without a time frame
	Organ consequences of COVID-19	Clinical manifestations of organ involvement with COVID-19	
	Consequences of treatment and hospitalization for COVID-19	Clinical manifestations of hospitalization consequences from COVID-19	
Spanish Intersocietary Document Clinical Guide for the Care of Long COVID / Persistent COVID Patients <sup>22</sup>	Sequelae of COVID-19 or Post COVID	Symptoms following the sequelae suffered due to the structural damage of the complications experienced	Key points: include signs and symptoms with a time frame
	Persistent COVID or Long COVID	Persistent symptoms beyond 4 and even 12 weeks after acute illness	
IDSA <sup>24</sup>	Post-acute COVID-19	Signs and symptoms of COVID-19 after 3 weeks	Key points: includes both symptoms and sequelae
	Subacute COVID-19	Signs and symptoms from 4 to 12 weeks,	
Catalan Society of Family and Community Physicians <sup>23</sup>	Chronic subacute COVID-19	Signs and symptoms after 12 weeks	Key points: include signs, symptoms, with a time frame
Sociedad Argentina de Medicina <sup>26</sup>	Persistent Covid / Long covid	Persistent or new symptoms beyond 4 weeks	Key points: include signs, symptoms, without a time frame

**Table 2** | Risk factors for developing chronic COVID / long COVID

Risk factor	OR (95% CI)
Female gender	1.56 - (1.41-1.73)
Age	1.21 - (1.11-1.33)
High BMI	1.15 - (1.08-1.23)
Smoking	1.10 - (1.07-1.13)
Comorbidities*	2.48 - (1.97-3.13)
Hospitalization or ICU admission	2.37 - (2.18-2.56)
Vaccination ( $\geq 2$ doses)	0.57 - (0.43-0.76)

Tsmpasian V, et al. Risk factors associated with post-COVID-19 condition: A systematic review and meta-analysis. *JAMA Intern Med* 2023; 183: 566-80

BMI: body mass index; ICU: intensive care unit

\*Anxiety - depression, asthma, diabetes, chronic obstructive pulmonary disease, coronary artery disease, and immunosuppression

narios. Patients without hospital admission and who have no risk factors, did not develop complications or sequelae would be considered low risk. Patients without hospital admission but who have at least one risk factor and/or one complication and/or one sequelae, as well as patients with hospital admission who have no risk factors and did not develop complications or sequelae, would be considered moderate risk. Finally, patients with hospital admission who have one risk factor and/or had one complication and/or one sequelae would be at high risk of developing chronic COVID<sup>31</sup>.

### Chronic COVID: a familiar entity

Is chronic COVID or long COVID, as described in English literature, a new entity, or are we facing a clinically known picture under circumstances?

If we analyze that this clinical picture occurs after an acute viral episode, there are numerous descriptions in the literature of post-acute infection syndromes. A narrative review published by Choutka J<sup>32</sup> describes “unexplained post-infectious syndromes” (PAISs, in English), not only of viral but also of bacterial and parasitic origin. Related to viral causes and specifically related to Ebola, Dengue, SARS, Polio, and Chikungunya, post-infectious syndromes with specific names are described. However, other post-infectious viral syndromes, such as influenza, Epstein Bar, varicella zoster, can develop after the acute epi-

sode but do not have specific names that identify them. In this publication, the symptoms present in these syndromes were analyzed and grouped into 5 categories:

1. Exercise intolerance and fatigue,
2. Flu-like symptoms or “sickness behavior”: fever, low-grade fever, myalgias, malaise, sweating, and irritability,
3. Rheumatological symptoms: chronic and recurrent joint pain,
4. Neuropsychiatric symptoms: mental fog, impaired concentration and memory, difficulty finding words, and
5. Specific symptoms: alterations in taste and smell, in the case of SARS-CoV-2.

On the other hand, there are publications that describe chronic fatigue syndrome or myalgic encephalomyelitis and chronic COVID/long COVID, sharing similarities<sup>33</sup>, suggesting that they could be the same entity. The list of shared signs and symptoms<sup>34</sup> is extensive: fatigue, exercise intolerance, cognitive impairments, respiratory difficulties such as dyspnea and cough, myalgias, arthralgias, headache, palpitations, orthostatism, anxiety, depression, and a highlighted impairment in performing activities of daily living. A physiological and pathophysiological analysis has also been conducted between both entities, finding similarities<sup>35</sup>.

Other articles describe the high prevalence and similarity symptoms between fibromyalgia and chronic COVID, as well as the diagnosis of

fibromyalgia in patients who have experienced acute episodes of COVID-19<sup>36</sup>.

## Conclusion

The COVID-19 pandemic has given rise to the alleged presence of a multisystemic post-infectious clinical condition called chronic COVID/long COVID. There are numerous definitions and terminologies in the literature to define and classify this condition, which does not aid in analyzing, studying, and providing treatment for this situation. A recent systematic review of post-COVID-19-conditions highlights the heterogeneity of definitions, time periods, signs and symptoms<sup>37</sup>.

On the other hand, clinical pictures described in the literature share similarities with the proposed descriptions for chronic COVID. Among the most frequent are chronic fatigue syndrome/myalgic encephalomyelitis, fibromyalgia<sup>38</sup>, and acute post-infectious syndrome. We must add to this list another group of syndromes that should be considered in patients who, during their acute clinical picture, required hospitalization or intensive care unit admission and may be experiencing clinical pictures related to the myopathy-neuropathy syndrome of the critically ill patient<sup>39</sup>.

However, there is a distinctive factor within chronic COVID that has not been developed or considered: isolation. During the SARS-CoV-2

pandemic, patients remained isolated in their homes, losing the opportunity to work, recreate, and maintain social relationships. Many even lost their jobs with the economic impact this represents. Moreover, many patients suffered the loss of family members, neighbors, friends, and acquaintances due to COVID-19 infection. The nine-month isolation implemented in Argentina was a period of losses in various aspects of people's lives and has not been evaluated as a factor for the development of chronic COVID. Feelings such as fear, uncertainty, hopelessness, and loneliness are described in the general population during the SARS-CoV-2 pandemic, as well as an increase in psychological and psychiatric conditions, which some authors describe as a "parallel pandemic"<sup>40</sup>. But its impact on chronic COVID/long COVID is little known.

We still have a long way to go to achieve a consensus regarding unified terminology and definition of this condition. We must continue with research to clarify the similarities and resemblances that chronic COVID/long COVID has with other health problems.

As mentioned in the introduction of this article: before accepting the existence of a new disease, medicine is obliged to consider the dimensions that ensure avoiding the harms.

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**Conflict of interest:** None to declare

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