health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Date:	27 May 2022		
To:	**Dr MJ Phaahla, MP** **Honourable Minister of Health**	From:	**Ministerial Advisory Committee (MAC) on COVID-19**

DIAGNOSIS, TREATMENT AND MANAGEMENT OF LONG COVID

Problem Statement and Task to Committee

Globally as at 25 May 2022, there have been over 520 million cases worldwide and 3.8 million cases in South Africa of confirmed SARS-CoV-2 infection, which causes COVID-19. The majority of people with COVID-19 experience asymptomatic or mild disease, while approximately 5-10% of people with COVID-19 experience severe disease or critical illness[1].

Some patients who have been infected by SARS-CoV-2 may develop persistent or new symptoms after the acute infection lasting weeks or months. This has been called Long COVID or Post-COVID Condition. This condition may affect people of all ages. There is no evidence-based definition or management of Long COVID.

Questions to be addressed:

1. How should those at high risk of developing Long COVID be identified?
2. When should Long COVID be diagnosed or what criteria should be used to diagnose Long COVID?
3. What should be the management strategies of individuals with Long COVID?
4. How should individuals diagnosed with Long COVID be managed within the health system?

Background/Current Information

- Survival following acute COVID-19 has been reported in over 95% of cases both locally and globally. However, a proportion of COVID-19 survivors experience ongoing health issues. Health issues following initial SARS-CoV-2 infection include persisting symptoms, relapsing symptoms, new symptoms, new medical diagnoses, worsening of pre-existing medical conditions, or temporary/permanent disability. It is estimated that ~30% of patients with COVID-19 may face these sequelae. Several important risk factors for the development of Long COVID have been identified, and include advancing age, female sex, pre-existing comorbidities (including obesity, hypertension, diabetes mellitus, and asthma), and immunodeficiency (including HIV and malignancy)[2,3,4]. In addition, there is a gradient of risk based on the severity of the acute COVID-19 episode, with an increasing risk of Long COVID with increasing severity of acute COVID-19[5,3]. While patients who experienced severe acute COVID-19 are at greatest risk for developing Long COVID, the large numbers of people who experienced asymptomatic, mild or moderate acute COVID-19 constitute the majority of the overall burden of Long COVID[6].

- While similar phenomena have been seen with previous viral respiratory epidemics, the scale of the COVID-19 pandemic has resulted in a large number of patients experiencing this form of incomplete recovery.
- The natural history of SARS-CoV-2 infection remains incompletely understood, and the long term sequelae of COVID-19 are presently the subject of global scientific, clinical, public health and community interest.

Evidence review

- The World Health Organization (WHO)[6] has proposed a consensus definition for the Post-COVID Condition:
  "*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 and which 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".*
- In the South African context, we recommend the term "Long COVID", given its established use in the scientific literature, broader use within local communities, and its simplicity for the purposes of medical communication.
- The diagnosis is catered for by the ICD-10-CM Diagnosis Code of U09.9 (Post-COVID Condition, Unspecified).
- A living systematic review published in British Medical Journal (BMJ) Global Health on the characteristics of Long COVID found no eligible studies conducted in low- and middle-income countries or Africa. The majority of studies were carried out in Europe, Asia and North America[7].
- The epidemiology of Long COVID is incompletely understood, with limited data on patients who experienced mild or moderate acute COVID-19. Most of the available data reflect the epidemiology of Long COVID in previously hospitalized patients with acute COVID-19 (i.e. severe disease).
- The majority of studies globally have been conducted in adults and in cohorts of hospitalized patients post-discharge. Most included patients who required an Intensive Care Unit (ICU) admission during the acute COVID-19 illness[8].
- In South Africa, a study of previously hospitalized adults with COVID-19 revealed that more than two-thirds of patients reported an incomplete recovery at three months after their acute illness[8].
- Common symptoms of Long COVID are fatigue, breathlessness, cognitive difficulties (impaired memory and brain fog), muscle and joint pain, headache, persistent cough, and chest pain[10,11]. In addition, anxiety, depression, and sleep disturbance may also present as part of Long COVID.
- Symptoms can be characterized by physiological clusters into neurological (headache, insomnia, and anosmia and ageusia), neurocognitive (memory, concentration and cognitive impairment), psychological (anxiety, depression), systemic (fatigue, weakness), upper respiratory (sore throat, nasal congestion), cardiopulmonary (dyspnea, cough, chest pain, palpitations), musculoskeletal (muscle and joint pain), gastrointestinal (nausea, vomiting, and diarrhea), and vascular (chilblains, Raynaud's, cutaneous vasculitis). These symptoms may vary in frequency and intensity, although they are more likely to occur in patients who were previously hospitalized[8]. There is substantial overlap between the various clusters, with

symptoms from various clusters/domains occurring within the same individual. This multisystem presentation will require a multi-disciplinary/generalist approach.

- Long COVID symptoms are experienced in 10-35% of patients after mild COVID-19 infections. These patients are likely to constitute a much larger proportion of Long COVID than those diagnosed with severe disease, due to the high prevalence of mild COVID-19 infections in South Africa.
- Patients with Long COVID may experience persistent, new, or relapsing symptoms following acute COVID-19. In addition, these symptoms are associated with significant reductions in functional status (personal, social, and occupational) and quality of life[5,12].
- While most symptoms appear to abate over time, the natural history of the condition is not yet known.
- Long COVID is associated with an increased risk of new respiratory illnesses, diabetes mellitus, chronic kidney disease, chronic liver disease, and cardiovascular disease[13].
- Patients who have recovered from acute COVID-19 may experience an increased risk for deep vein thrombosis, pulmonary embolism, bleeding, stroke, arrhythmias, myocarditis, ischaemic heart disease, and death[14,15,16].
- The impact of Long COVID on quality of life can be severe, with significant limitations to social and occupational functioning. These have been found to have a substantial negative impact on quality of life, ability to work, and carry out daily activities[17]. On average, individuals experiencing Long COVID function at 59% of their pre-COVID abilities, and over 20% of individuals are unable to return to work. Poor quality of life is associated with prior ICU admission and fatigue[18].
- Vaccination against SARS-CoV-2 may be an important public health measure for Long COVID, as
    - Vaccinated individuals have a lower risk of SARS-CoV-2 infection, and severe COVID-19, in particular.
    - Vaccinated individuals who experience breakthrough infection have a 49% lower risk of developing persistent symptoms[19,20].
    - Vaccination of individuals experiencing Long COVID may hasten the resolution of persisting symptoms[21].
- There are presently no registered or evidence-based therapeutic interventions available for the treatment of the Long COVID.

There is currently no widely accepted definition for the condition in children.

Recommendations

In the absence of evidence-based clinical guidelines, the following recommendations are made:

Diagnosis

- In the absence of an evidence-based set of criteria, the WHO endorsed consensus clinical case definition should be used to guide the allocation of this diagnosis in individual cases.
- An initial evaluation with full blood count, creatinine, thyroid function test, glycated haemoglobin, chest radiograph, electrocardiogram, and spirometry may be appropriate for patients presenting with dyspnea, cough, palpitations, or fatigue.
- These assessments should not supersede existing algorithms for the evaluation of potentially life-threatening clinical presentations (e.g. acute chest pain).
- Biomarker-based diagnostic signatures require further validation before implementation, but may be useful tools for distinguishing the clinical presentation of Long COVID from other clinical diagnoses. These may include interleukin-6, c-reactive protein, interferon β, SARS-CoV-2 antibody titres, and other inflammatory and immunological markers.

Treatment and management

- Currently, there are no evidence-based treatment options available for Long COVID. However, there are many potential treatment options under evaluation.
- Treatment strategies should be guided by the individual clinical presentation, and aimed at ameliorating symptoms until more directed therapies are available.
- Identification and optimisation of the management of existing comorbidities, new comorbidities, and complications of acute COVID-19, are important goals in the management of patients with Long COVID.
- Vaccination, including booster doses for eligible individuals, should be encouraged in patients with Long COVID.
- The judicious use of steroids in specific circumstances (such as post-COVID organizing pneumonia) should only be considered after multi-disciplinary specialist discussion.
- Linkage of individuals with Long COVID to clinical research programmes should be encouraged. This will permit the generation of local data, and provide access to emerging therapies.
- Establishing multi-disciplinary specialist clinics (or clinics with the potential for specialist inter-disciplinary collaboration/referral) will be needed for the assessment and management of complex cases on a referral basis. Regional clinical experts should be identified to lead such efforts.
- There is a need for health education on Long COVID directed at advising patients about the condition, when and where to seek professional advice, ways to self-manage their symptoms, and how to access sources of support.

Long COVID Management in the Health Services

<u>Public Sector</u>

- Separate services to manage Long COVID patients either in primary care or hospital services are not recommended, but patient management should be determined by the presenting symptoms and diagnosis (refer to MAC on COVID-19 advisory on *Integrating COVID-19 into Essential Health Services*[22]).
- Primary Healthcare referral to district or regional level Medical Outpatient Department with onward referral to tertiary level services depending on the predominant clinical presentation is recommended.

- Multidisciplinary teams should be established within tertiary level services (internal medicine, pulmonology, cardiology, immunology, neurology, psychiatry, occupational therapy, physiotherapy).

Private Sector

- General Practitioner or Family Physician entry level management with specialist referral depending on the predominant clinical presentation is recommended.

Clinical Guidelines

- Long COVID should be recognised by the National Department of Health (NDoH) as a medical condition.
- The NDoH should lead in the development of evidence-based clinical guidelines for Long COVID, similar to those provided by the National Institute for Health and Care Excellence[23].

Surveillance

- The National Institute for Communicable Diseases (NICD) should be requested to establish a surveillance system to establish the incidence and prevalence of Long COVID.

Training

- The NDoH Knowledge Hub should prepare courses on Long COVID for public and private sector clinicians.
- The College of Medicine should be approached to consider a diploma in the management of COVID and Long COVID in a similar way as it runs a diploma in HIV and TB.

Research

- The South African Medical Research Council should be requested to put out a call for proposals specifically looking at the epidemiology, pathophysiology, diagnosis and management of Long COVID.

Information and research gaps

The following information and research gaps should be addressed:

- Risk factors for the development of Long COVID.
- Biological mechanisms resulting in Long COVID/Pathobiology of Long COVID.
- Long COVID in people living with HIV.
- Biomarkers for the diagnosis and prognostication of Long COVID.
- Diagnostic criteria for Long COVID.
- Validated screening tools for the various clinical presentations of Long COVID.
- Treatment of Long COVID, particularly in a high TB/HIV burden setting.
- Presentation, case definition, and diagnostic criteria for Long COVID in children.

Rationale for recommendations

- Long COVID is an emerging public health challenge which requires a coordinated public health response. Establishing research activities and clinical services are an important part of this response, and will provide opportunities for developing a more granular understanding of the local burden of the condition, and greater access to care for affected individuals.

Thank you for consideration of this advisory.

Kind regards

PROF KOLEKA MLISANA **PROF MARIAN JACOBS**
CO-CHAIRPERSONS: MINISTERIAL ADVISORY COMMITTEE ON COVID-19
DATE: 27 May 2022
CC:

» **Dr SSS Buthelezi (Director-General: Health)**
» **Dr N Crisp (Deputy Director-General: National Health Insurance)**

Disclaimer: As stipulated in its Terms of Reference, the MAC on COVID-19 is an advisory Committee to the Minister of Health and does not have any delegated powers to act on behalf of, or to commit, the Minister or Government to any actions. Recommendations offered by the MAC on COVID-19 constitute evidence-informed advice only and do not represent final decisions of the Minister of Health or government.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*. 2020 Feb 15;395(10223):497-506.

2. Daugherty SE, Guo Y, Heath K, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ*. 2021;373:n1098. Published 2021 May 19. doi:10.1136/bmj.n1098.

3. Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study [published correction appears in Lancet. 2022 May 7;399(10337):1778]. *Lancet*. 2021;398(10302):747-758. doi:10.1016/S0140-6736(21)01755-4.

4. Writing Committee for the COMEBAC Study Group, Morin L, Savale L, et al. Four-Month Clinical Status of a Cohort of Patients After Hospitalization for COVID-19 [published correction appears in JAMA. 2021 Nov 9;326(18):1874]. *JAMA*. 2021;325(15):1525-1534. doi:10.1001/jama.2021.3331.

5. PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following 7ospitalization in the UK: a prospective observational study [published online ahead of print, 2022 Apr 22]. *Lancet Respir Med*. 2022;S2213-2600(22)00127-8. Doi:10.1016/S2213-2600(22)00127-8.

6. Malkova A, Kudryavtsev I, Starshinova A, et al. Post COVID-19 Syndrome in Patients with Asymptomatic/Mild Form. *Pathogens*. 2021;10(11):1408. Published 2021 Oct 30. doi:10.3390/pathogens10111408.

7. World Health Organization, 2021. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021.

8. Michelen M, Manoharan L, Elkheir N, et al. Characterising long COVID: a living systematic review. *BMJ Glob Health*. 2021;6(9):e005427. doi:10.1136/bmjgh-2021-005427.

9. Dryden M, Mudara C, Vika C, et al. Long COVID in South Africa: Findings from a longitudinal cohort of patients at one month after hospitalization with SARS-CoV-2, using an ISARIC multi-country protocol. *COVID-19 Special Public Health Bulletin*. 2021;19(S2).

10. Aiyegbusi OL, Hughes SE, Turner G, et al. Symptoms, complications and management of long COVID: a review. *J R Soc Med*. 2021;114(9):428-442. doi:10.1177/01410768211032850.

11. Akbarialiabad H, Taghrir MH, Abdollahi A, et al. Long COVID, a comprehensive systematic scoping review. *Infection*. 2021;49(6):1163-1186. doi:10.1007/s15010-021-01666-x.

12. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. 2021;38:101019. doi:10.1016/j.eclinm.2021.101019.

13. Ayoubkhani D, Khunti K, Nafilyan V, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ*. 2021;372:n693. Published 2021 Mar 31. doi:10.1136/bmj.n693.

14. Katsoularis I, Fonseca-RodrÃguez O, Farrington P, Jerndal H, Lundevaller E H, Sund M et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19: nationwide self-controlled cases series and matched cohort study *BMJ* 2022; 377 :e069590 doi:10.1136/bmj-2021-069590.

15. Xie, Y., Xu, E., Bowe, B. *et al.* Long-term cardiovascular outcomes of COVID-19. *Nat Med* 28, 583–590 (2022). https://doi.org/10.1038/s41591-022-01689-3.

16. Bhaskaran K, Rentsch CT, Hickman G, et al. Overall and cause-specific hospitalisation and death after COVID-19 hospitalisation in England: A cohort study using linked primary care, secondary care, and death registration data in the OpenSAFELY platform. *PLoS Med*. 2022;19(1):e1003871. Published 2022 Jan 25. doi:10.1371/journal.pmed.1003871.

17. van Kessel SAM, Olde Hartman TC, Lucassen PLBJ, van Jaarsveld CHM. Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review. *Fam Pract*. 2022;39(1):159-167. doi:10.1093/fampra/cmab076.

18. Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. *BMJ Evidence-Based Medicine* 2021;26:107-108.

19. Antonelli M, Penfold RS, Merino J, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis*. 2022;22(1):43-55. doi:10.1016/S1473-3099(21)00460-6.

20. Kuodi P, Gorelik, Zayyad H, et al. Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients infected between March 2020 and November 2021. 2022. Preprint at medRxiv https://doi.org/10.1101/2022.01.05.22268800 (2022).

21. Strain, WD, Sherwood, O, Banerjee, A, et al. The Impact of COVID Vaccination on Symptoms of Long COVID. An International Survey of People with Lived Experience of Long COVID. Preprint at SSRN http://dx.doi.org/10.2139/ssrn.3868856.

22. Ministerial Advisory Committee on COVID-19, 2022. Advisory on Integrating COVID-19 into Essential Health Services. Pretoria: National Department of Health.

23. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the longterm effects of COVID-19. 2022. Available from https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742.