COVID

Editorial

Long COVID: An Epidemic within the Pandemic

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Coronavirus disease 2019 (COVID-19), a life-threatening infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in the Chinese city of Wuhan in late 2019 and has subsequently spread worldwide, reaching pandemic proportions [1]. At the time of writing (i.e., May 2023), COVID-19 has already caused nearly 7 million official deaths, according to World Health Organization (WHO) statistics [2]. Although the WHO COVID-19 emergency committee recently decided to no longer classify COVID-19 as an international public health emergency, SARS-CoV-2 infections and/or reinfections still cause a large number of deaths worldwide, with an excess mortality still estimated at approximately 10,000 deaths per day [3]. In addition to the still significant organic injuries that can develop during an acute SARS-CoV-2 infection, particularly in frail, old and unvaccinated individuals, there is now established evidence that the so-called post-viral syndrome (i.e., a common consequence of many viral infections encompassing a kaleidoscope of organic and psychiatric disorders) [4] is a fairly common sequela of COVID-19 in officially recovered patients, variously termed "post-COVID", "long-haul COVID", "long COVID" and so forth.

The use of a uniform, validated and trustworthy definition of the term "long COVID" is certainly the most important issue when it comes to this condition, because the use of different terms can only lead to great confusion. A specific ICD-10-CM (International Classification of Diseases, Tenth Revision, Clinical Modification) code has been developed for recognizing the post-viral clinical syndrome that develops after SARS-CoV-2 infection. Such a diagnosis code U09.9 (post-COVID-19 condition, unspecified) refers specifically to patients presenting suggestive symptoms that are new or persist for at least three months after diagnosis of a SARS-CoV-2 infection and that persist for more than two months without other reasonable explanations [5]. While this definition is certainly reasonable from a clinical standpoint, the spectrum of abnormalities and/or functional impairments that develop after recovering from an acute SARS-CoV-2 infection is broad and not necessarily limited to the—always obvious—clinical signs and symptoms. For this very reason, we recently proposed to also include "radiological/laboratory abnormalities" among the possible changes observed in patients with long COVID [6]. For example, fatigue is a paradigmatic symptom in patients with long COVID (in fact, it is the most common prolonged physical consequence), encompassing a multifactorial pathogenesis [7]. On the other hand, lower than normal hemoglobin levels have been described in a large number of patients after recovering from SARS-CoV-2 infections [8], and this lower hemoglobin level can therefore be considered an important cause of fatigue that could be misrecognized or misdiagnosed, especially when patients have sedentary habits. Nevertheless, anemia should always be considered as a long COVID condition when it develops after an acute SARS-CoV-2 infection. Consequently, anemic patients, whether symptomatic or not, should be classified as having long COVID. Similarly, a variety of fibrotic abnormalities have been reported in patients with long COVID [9]. Although many biological or functional anomalies may remain asymptomatic over a long period of time, they are very likely to become symptomatic with advancing age and physiological decline. Therefore, it seems

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appropriate to include a set of objectives (i.e., biochemical, metabolic and structural) but still asymptomatic signs of parenchymal injury in the definition of long COVID to allow a more timely and accurate identification of patients at risk of becoming symptomatic in the future.

As a result of the high clinical, social and even economic burden, the epidemiology of long COVID deserves special focus. According to WHO data (although we certainly acknowledge that the numbers are greatly underestimated due to undertesting and/or underreporting) [2], the number of European subjects with an officially reported SARS-CoV-2 infection at the end of April 2023 was approximately 276 million out of 749 million inhabitants (i.e., 36.8%) [10]. The analogous situation in the United States is 103 million SARS-CoV-2 cases out of 331 million inhabitants (i.e., 31.1%), thus having a very similar prevalence. Applying these numbers on a broader scale, one might conclude that up to one-third of the entire world's population may have experienced a SARS-CoV-2 infection, and many more will do so in the future, as this virus will remain among us (and live with us) for a long time to come [11].

According to recent data published by the Global Burden of Disease Long COVID Collaborators, the official prevalence of long COVID may be as high as 0.9% of all infected individuals 12 months after symptom onset [12]. However, a recent meta-analysis published by O'Mahoney et al. including 194 studies with 735,006 subjects [13] estimated that approximately 45% of individuals who survived a SARS-CoV-2 infection had at least one unresolved COVID-19 symptom at 6 months, irrespective of the hospitalization status. Important information was also provided by a meta-analysis by Han and colleagues [14], who concluded that the pooled prevalence of fatigue and/or weakness and dyspnea and/or breathless at 1 year follow-up was 28% (95%CI: 18–39%) and 18% (95%CI: 13–24), respectively. During the same one-year period, Mugdal et al. found in their meta-analysis that 57% of individuals who had recovered from a SARS-CoV-2 infection still reported at least one unresolved symptom [15]. Taking for granted these latter figures (i.e., a prevalence of approximately 50% of persistent symptoms), a total number of 138 and 51 million people in Europe and in the United States, respectively, may have longstanding COVID-related complaints. According to the most recent Heart Disease and Stroke Statistics 2023 Update published by the American Heart Association (AHA) [16], 29.3 and 28.6 million U.S. citizens have been diagnosed with diabetes or have cardiovascular disease, respectively. The epidemiologic burden of either of these conditions is half of that potentially caused by long COVID, which must hence now be considered a primary public health problem which is expected to impose a dramatic public health burden on all those who will seek treatment for their post-COVID disturbances.

This is indeed an epidemic within the pandemic, paving the way for a series of important considerations, as summarized in Table 1.

Table 1. Preparing for the next pandemic.

✓	Continue the scientific research on coronaviruses and other pathogens
✓	Preserve wildlife reservoirs and stop environmental disruption;
✓	Increase healthcare preparedness (both diagnostic and clinical)

First, we must all clearly acknowledge that the pandemic is not over. Although the severity of acute infection has gradually declined over time due to virus attenuation, natural immunity, widespread vaccination and improved therapeutic management [17], it would be extremely dangerous to relegate SARS-CoV-2 to an endemic, benign disease. Therefore, scientific research on the biology, clinical epidemiology, prevention and treatment of COVID-19 must continue. We must not repeat the mistake of 20 years ago when the SARS epidemic may have been underestimated by policy makers and much of the scientific community [18].

Regardless of the future clinical impact of COVID-19, the incidences of zoonotic spillover (i.e., the relative ease with which coronaviruses and other pathogens can be

repeatedly transmitted from animals to humans) have increased exponentially in recent decades. This is certainly fostered by invasion of wildlife reservoirs and gradual disruption of the environment that has increased the proximity between wildlife (e.g., bats), domestic animals and humans [19]. Therefore, a new sustainable and adaptive relationship between humanity and nature needs to be created.

Last but not least, one of the most important lessons learned from this pandemic is that most health systems worldwide were inadequately prepared. Response capacities in several areas of clinical (e.g., emergency departments, intensive and subintensive care units, pneumology and infectious disease departments) and diagnostic (e.g., virology, microbiology and general laboratory services) medicine were quickly overwhelmed, resulting in a sizable number of patients being underdiagnosed, undertreated or mistreated [20]. In the future, therefore, it will be important to develop reliable approaches to streamline diagnostics and medical care that can be rapidly activated to address not only pandemics, but also a kaleidoscope of other natural threats that are becoming increasingly common, such as earthquakes, volcanic eruptions, thunderstorms/hurricanes, severe snow/ice storms, floods, tidal waves, drought, firestorms/wildfires, war/civil disorder, terrorism and bioterrorism. As the ancient Latin saying goes, "errare humanum est, perseverare autem diabolicum" (i.e., "to err is human, but persisting [in error] is diabolical").

Further lines of research should then be pursued, including the study of the genetic and immunological determinants of COVID-19, particularly with regard to inborn errors of metabolism, viral persistence and/or reactivation, along with the possible role of superantigens in immune activation and autoimmunity [21]. For example, congenital defects in interferon (IFN)-γ and IFN-α/β immunity have a strong influence on the severity of many viral infections, including those caused by SARS-CoV-2. Recently, a specific genotype of *tyrosine kinase 2* (*TYK2*) was found to impair IFN-γ production and to be responsible for nearly 1% of tuberculosis cases, whilst neutralizing autoantibodies to IFN-α/β were found to be present in up to 15% of patients with critical COVID-19 illness [22]. Both inherited and acquired defects in type I INF immunity are also known to influence susceptibility to development of severe or even critical forms of SARS-CoV-2 infection in both children and adults [23]. Thus, a deeper understanding of these important immunologic perturbations will pave the way to better unravel the pathogenesis of COVID-19 and to develop an effective treatment that can be used in the acute phase of the infection and also as potential treatments for patients with long COVID.

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References

1. Cucinotta, D.; Vanelli, M. WHO Declares COVID-19 a Pandemic. *Acta Biomed.* **2020**, *91*, 157–160. [CrossRef] [PubMed]
2. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Available online: https://covid19.who.int/ (accessed on 8 May 2023).
3. Kupferschmidt, K.; Wadman, M. 'It's Still Killing and It's Still Changing'. Ending COVID-19 States of Emergency Sparks Debate. Science, 5 May 2023. Available online: https://www.science.org/content/article/who-ends-pandemic-emergency-covid-19-deaths-fall (accessed on 8 May 2023).
4. Behan, P.O.; Behan, W.M. Postviral fatigue syndrome. *Crit. Rev. Neurobiol.* **1988**, *4*, 157–178. [PubMed]
5. Pfaff, E.R.; Madlock-Brown, C.; Baratta, J.M.; Bhatia, A.; Davis, H.; Girvin, A.; Hill, E.; Kelly, E.; Kostka, K.; Loomba, J.; et al. N3C Consortium; RECOVER Consortium. Coding long COVID: Characterizing a new disease through an ICD-10 lens. *BMC Med.* **2023**, *21*, 58. [CrossRef] [PubMed]

6. Lippi, G.; Henry, B.M.; Favresse, J.; Plebani, M. Addressing standardized definitions of post-COVID and long-COVID. *Clin. Chem. Lab. Med.* 2023, *Epub ahead of print*. [CrossRef]
7. Poole-Wright, K.; Guennouni, I.; Sterry, O.; Evans, R.A.; Gaughran, F.; Chalder, T. Fatigue outcomes following COVID-19: A systematic review and meta-analysis. *BMJ Open* **2023**, *26*, e063969. [CrossRef] [PubMed]
8. Lai, Y.J.; Liu, S.H.; Manachevakul, S.; Lee, T.A.; Kuo, C.T.; Bello, D. Biomarkers in long COVID-19: A systematic review. *Front Med.* **2023**, *10*, 1085988. [CrossRef] [PubMed]
9. Bazdar, S.; Kwee, A.K.A.L.; Houweling, L.; Wijck, Y.d.W.-V.; Hoesein, F.A.A.M.; Downward, G.S.; Nossent, E.J.; der Zee, A.H.M.-V. A Systematic Review of Chest Imaging Findings in Long COVID Patients. *J. Pers. Med.* **2023**, *13*, 282. [CrossRef] [PubMed]
10. Worldometers. Available online: https://www.worldometers.info/world-population/europe-population/ (accessed on 8 May 2023).
11. Callaway, E. COVID's future: Mini-waves rather than seasonal surges. *Nature* **2023**, *617*, 229–230. [CrossRef] [PubMed]
12. Global Burden of Disease Long COVID Collaborators; Hanson, S.W.; Abbafati, C.; Aerts, J.G.; Al-Aly, Z.; Ashbaugh, C.; Ballouz, T.; Blyuss, O.; Bobkova, P.; Bonsel, G.; et al. Estimated Global Proportions of Individuals with Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. *JAMA* **2022**, *328*, 1604. [CrossRef] [PubMed]
13. O'Mahoney, L.L.; Routen, A.; Gillies, C.; Ekezie, W.; Welford, A.; Zhang, A.; Karamchandani, U.; Simms-Williams, N.; Cassambai, S.; Ardavani, A.; et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *eClinicalMedicine* **2022**, *55*, 101762. [CrossRef] [PubMed]
14. Han, Q.; Zheng, B.; Daines, L.; Sheikh, A. Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms. *Pathogens* **2022**, *11*, 269. [CrossRef] [PubMed]
15. Mudgal, S.K.; Gaur, R.; Rulaniya, S.T.L.; Agarwal, R.; Kumar, S.; Varshney, S.; Sharma, S.; Bhattacharya, S.; Kalyani, V. Pooled Prevalence of Long COVID-19 Symptoms at 12 Months and Above Follow-Up Period: A Systematic Review and Meta-Analysis. *Cureus* **2023**, *15*, e36325. [CrossRef] [PubMed]
16. Tsao, C.W.; Aday, A.W.; Almarzooq, Z.I.; Anderson, C.A.M.; Arora, P.; Avery, C.L.; Baker-Smith, C.M.; Beaton, A.Z.; Boehme, A.K.; Buxton, A.E.; et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation* **2023**, *147*, e93–e621. [CrossRef] [PubMed]
17. Mattiuzzi, C.; Henry, B.M.; Lippi, G. Correlation between relative age-standardized mortality rates and COVID-19 mortality over time in Italy. *Acta Biomed* **2023**, *94*, e2023056. [CrossRef]
18. Wong, T.W. "Will the SARS epidemic recur?" A retrospective analysis of the experts' opinions. *J. Epidemiol. Community Health* **2006**, *60*, 87. [PubMed]
19. McNeely, J.A. Nature and COVID-19: The pandemic, the environment, and the way ahead. *AMBIO* **2021**, *50*, 767–781. [CrossRef] [PubMed]
20. Filip, R.; Puscaselu, R.G.; Anchidin-Norocel, L.; Dimian, M.; Savage, W.K. Global Challenges to Public Health Care Systems during the COVID-19 Pandemic: A Review of Pandemic Measures and Problems. *J. Pers. Med.* **2022**, *12*, 1295. [CrossRef] [PubMed]
21. Brodin, P.; Casari, G.; Townsend, L.; O'Farrelly, C.; Tancevski, I.; Löffler-Ragg, J.; Mogensen, T.H.; Casanova, J.L.; Abel, L.; Aiuti, A.; et al. Studying severe long COVID to understand post-infectious disorders beyond COVID-19. *Nat. Med.* **2022**, *28*, 879–882. [CrossRef] [PubMed]
22. Casanova, J.-L.; Abel, L. From rare disorders of immunity to common determinants of infection: Following the mechanistic thread. *Cell* **2022**, *185*, 3086–3103. [CrossRef] [PubMed]
23. Bucciol, G.; COVID Human Genetic Effort; Meyts, I. Inherited and acquired errors of type I interferon immunity govern susceptibility to COVID-19 and multisystem inflammatory syndrome in children. *J. Allergy Clin. Immunol.* **2023**, *151*, 832–840. [CrossRef] [PubMed]

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