THE BEST OF THE WEEK (20 feb – 26 feb 2023)

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Why we need a deeper understanding of the pathophysiology of long COVID

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Abstract

The most recent estimate of people living with post-COVID-19 condition (also known as long COVID) globally has surpassed 65 million1 and, without clear diagnostic or treatment options available, this number is steadily increasing. There are more than 200 reported symptoms associated with long COVID,1 affecting virtually every organ system.

Although some long haulers recover, many people have had symptoms since early 2020. The condition is a blanket diagnosis that represents a heterogeneous set of pathophysiological processes. As such, several factors can affect the presentation of long COVID, such as the severity of acute infection, age, sex, pre-existing comorbidities, genetics, socioeconomic factors, and other environmental factors. Long haulers who survived severe acute SARS-CoV-2 infection are most likely to be men older than 50 years with lingering tissue damage and scarring. People with long COVID after a less-severe infection are most likely to be younger women (aged 36–50 years) whose acute infection has triggered adverse physiological responses.

The main disease hypotheses for the root causes of long COVID include viral persistence (infectious virus, viral RNA, or viral proteins), autoimmunity triggered by the infection, reactivation of latent viruses, and inflammation-triggered chronic changes leading to tissue dysfunction and damage

There is growing and compelling evidence that SARS-CoV-2 infects and produces its RNA and proteins in a wide range of cell types in tissues, including the gastrointestinal, respiratory, cardiovascular, lymphoid, endocrine, urogenital, ocular, skin, muscular, and peripheral nervous system and CNS tissues.2 Circulating spike proteins are observed in 60% of patients with long COVID between 2 and 12 months after infection.3 Although the presence of viral RNA and proteins do not necessarily indicate persistent infection, viral RNA can trigger innate immune responses and viral proteins might cause tissue damage and stimulate persistent activation of lymphocytes, which lead to chronic inflammation.

In people with long COVID, assessment of autoantibodies to human exoproteome using rapid extracellular antigen profiling revealed no significant differences from people without long COVID.4 However, autoantibodies to intracellular antigens5 or autoreactive T cells might have a role in long COVID.

There is also emerging evidence for latent herpesviruses reactivation in people with long COVID. Reactivation of latent Epstein-Barr virus, but not the acute mononucleosis infection, is found in people with long COVID,4, 6 and Epstein-Barr virus viraemia at the time of acute COVID is predictive for long COVID.5

Local inflammatory response to SARS-CoV-2 in one organ can cause lasting alterations in distant tissues and organs. In a mouse model, even mild lung-restricted COVID-19 (in which the infectious virus became undetectable within a week) was found to induce prolonged changes in the CNS, including microglial activation, oligodendrocyte loss, and reduced myelination, for up to 7 weeks after infection.7

Beyond these potential root causes, many secondary pathological changes have been observed in people with long COVID, including the formation of micro-clots and platelet activation,8 reduced cortisol,4, 5 and mitochondrial dysfunction.9

Despite the multifactorial pathogenesis, available data show that long COVID is an organic post-acute infection syndrome (PAIS) with clear physiological dysfunction that is often not consistently apparent using standard medical diagnostic tests. This discrepancy highlights the need for a new generation of more sensitive testing procedures for people with PAIS. Although it is not known whether pre-existing psychological diagnoses might influence the risk of long COVID (eg, by affecting the host endocrine and immune systems), it is neither productive nor clinically or scientifically valid to classify long COVID as a psychosomatic condition.

As avoiding COVID-19 becomes increasingly difficult, we argue that deep biological analyses will identify biomarkers for long COVID and possibly identify distinct endotypes driven by different root causes so that the risk of contracting long COVID is better defined. Biomarker identification will not only be crucial for identifying predisposing factors but also allow us to implement safer, evidence-based policies. Similarly, molecular, cellular, and physiological analyses will inform precision interventions that target the root causes of each long COVID endotype. For example, persistent viral infection could be targeted by antivirals; long COVID driven by autoimmune disease could be treated using monoclonal antibodies that target lymphocytes or drugs that block cytokines and cytokine signalling; and, if the reactivation of herpesviruses contributes to disease, targeting such viruses using antivirals or vaccines could be considered. Diagnostic criteria considering the root causes to prevent and treat long COVID will require large longitudinal studies. If therapeutic targeting of root causes is not feasible, the downstream pathological changes of long COVID could still be treated.

Ideally, potential therapies should be assessed in double-blinded, placebo-controlled, randomised clinical trials. However, such studies are quite costly, are labour intensive, and require substantial government, regulatory, and industry support.

Syndromes like Long COVID are not new. Other PAISs, such as myalgic encephalomyelitis and chronic fatigue syndrome and post-treatment Lyme disease syndrome, have overlapping symptoms with long COVID.10 Thus, the inclusion of individuals with other forms of PAIS as comparison groups in long COVID research is important for broadening overall understanding and widening the impact of this research. Finally, the current knowledge surrounding long COVID would not be possible without the hard work and dedication of patient-led communities striving for answers.

Kogan NE et al
Leveraging Serosurveillance and Postmortem Surveillance to Quantify the Impact of Coronavirus Disease 2019 in Africa
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Abstract

Background

The coronavirus disease 2019 (COVID-19) pandemic has had a devastating impact on global health, the magnitude of which appears to differ intercontinentally: For example, reports suggest that 271 900 per million people have been infected in Europe versus 8800 per million people in Africa. While Africa is the second-largest continent by population, its reported COVID-19 cases comprise <3% of global cases. Although social and environmental explanations have been proposed to clarify this discrepancy, systematic underascertainment of infections may be equally responsible.

Methods

We sought to quantify magnitudes of underascertainment in COVID-19's cumulative incidence in Africa. Using serosurveillance and postmortem surveillance, we constructed multiplicative factors estimating ratios of true infections to reported cases in Africa since March 2020.

Results

Multiplicative factors derived from serology data (subset of 12 nations) suggested a range of COVID-19 reporting rates, from 1 in 2 infections reported in Cape Verde (July 2020) to 1 in 3795 infections reported in Malawi (June 2020). A similar set of multiplicative factors for all nations derived from postmortem data points toward the same conclusion: Reported COVID-19 cases are unrepresentative of true infections, suggesting that a key reason for low case burden in many African nations is significant underdetection and underreporting.

Conclusions

While estimating the exact burden of COVID-19 is challenging, the multiplicative factors we present furnish incidence estimates reflecting likely-to-worst-case ranges of infection. Our results stress the need for expansive surveillance to allocate resources in areas experiencing discrepancies between reported cases, projected infections, and deaths.

Maintaining Health Care Innovations After the Pandemic

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Abstract

The COVID-19 pandemic exposed the worst failings of the health care system, but it also stimulated a flurry of innovations that could lead to a much-improved delivery system. These were innovations that were born out of necessity: telemedicine access and use skyrocketed, new hospital-at-home services emerged, ambulatory surgical centers expanded their menu of procedures, and a variety of novel therapeutics—such as widespread vaccine distribution, new medical diagnostics, and innovative monoclonal antibodies—were introduced.1 The collection of new services with flexible delivery mechanisms suggested a future that reduces the scope of the legacy and costly brick-and-mortar delivery system and instead forges ahead toward a new era of digital medicine.

With the crisis now behind us, we are witnessing an attempted retrenchment from this spate of innovation. Whereas industry leaders partnered with policy makers during the pandemic to meet the urgencies of the moment, some are now demanding a return to prepandemic delivery models. The period of creativity was made possible by emergency regulatory relaxations, targeted funding, Emergency Use Authorizations, flexible payment models, and a Federal Retail Pharmacy Program that partnered with more than 41 000 retail pharmacy locations nationwide.2 Now, dominant industry interests—as they are prone to do3—are attempting to ensure that temporary measures lapse, old funding mechanisms return to prominence, and regulatory relaxations end.

How can we retain the substantial, potentially transformational innovations that emerged during the pandemic? We argue that preserving useful innovations and combatting the pressure to discard them requires testing the innovations' clinical quality and value. While traditional interests are making arguments that challenge the economic and quality benefits of the innovations, their business models are not subject to the same robust evaluation. The public needs access to data to scrutinize and, when appropriate, challenge these industry-led assertions. Enabling and preserving value-enhancing innovations require rethinking the health care data infrastructure.

Consider virtual care, which is by far the largest transformation in the market. Medicare saw an increase from 840 000 telehealth visits in 2019 to 52.7 million in 2020.4 Virtual care seemingly provided substantial benefits to patients—providing access during COVID-19 waves for patients receiving routine care services,5 for patients in rural communities (saving hours of travel time for appointments), for working families, and for those with demanding diseases requiring quotidian assistance from clinicians.

A legitimate debate is raging over the benefits of this transition to telehealth. Did it improve access for all populations or exacerbate health disparities? Did it provide the quality of care that could sustain or improve health outcomes? Finally, does telehealth save money, or is it yet one more costly layer atop the traditional care model?6,7

We are in danger of permitting these questions to be answered by the hospitals that worry about losing revenue from lost office visits, physicians who are employed by the hospitals, and insurers who are beholden to the hospital for access to monopolized services. These important policy debates might become resolved not by the merits of the initiatives but instead by short-run financial pressures of these legacy business models. Without definitive public data sources and support for an independent assessment of the COVID-19 response, patients, policy makers, and innovation-seeking payers will be unable to assess the economic or consumer benefits of these innovations and thus unable to counter anti-innovation arguments made by vested interests.

Another danger is letting these policy debates turn on the early experiences and almost inevitable failures of early innovating firms. Often, successful business innovation requires generations of business model development, as first movers cede to followers that learn from the mistakes of early entrants (and do not bear the cost of establishing the market). Nevertheless, the failures of first-mover firms or models are

typically used to broadly attack the innovation model. Building innovative and profitable business models takes time and investment, investment that can be rapidly curtailed in an environment that favors the status quo.

One might wonder why insurance providers, which have terabytes of data, do not use them to drive efficiency-enhancing innovation on behalf of their insureds. Experience reveals, however, that insurers have not been the drivers of innovation that drives down costs. One likely reason is that when they are dependent on monopolist or oligopolist health care systems for service delivery, they are hesitant to challenge the hospitals' core business model. Another reason is that their financial incentives, in part driven by the medical loss ratio and other regulations, do not encourage them to drive down costs; in fact, the medical loss ratio can mean that insurers benefit when spending increases. A third reason is that rethinking health care financing is onerous. It requires a facility with business model innovation that entails risk and uncertainty. Finally, even if insurance providers did find ways to use data to drive efficiencies, they are unlikely to make those data public and instead would use them to acquire private gains over their competitors.

The absence of the clinical, equity, and financial data that could evaluate these differing points of view is the Achilles' heel of the US COVID-19 pandemic response.8 The massive struggles to integrate public and private data to track the pandemic did not fully succeed. For example, there is no common platform to integrate medical quality home pulse oximeter sensor data with those from electronic health records. The continued reliance on paper medical records, as illustrated by the individual Centers for Disease Control and Prevention COVID-19 vaccination status cards, caused a massive failure in vaccine safety assessment that could instead have provided large-scale postmarketing surveillance data.

Policy makers can and should play a leading role in building up a useful data infrastructure. The final rule implementing the 2016 21st Century Cures Act mandated that electronic health records have application programming interfaces to provide patients with electronic access to their data,9 and aggressive implementation of this rule can provide data access to commercial and academic evaluators. Such an open infrastructure can also invite new types of clinical services for patients, though policy makers should also develop appropriate payment models for these new digital services. Policy makers might even build a new data infrastructure to aid health care markets much as Franklin Delano Roosevelt solved a similar crisis for financial markets. During the Great Depression, Roosevelt created the US Securities and Exchange Commission to provide the uniform data repository that, for the first time, permitted evaluation of the comparative financial performance of publicly traded firms. He called it the Truth Agency to underscore its data role.10

Winston Churchill (and many others) famously said that we should never let a good crisis go to waste. We are in danger of doing exactly that: we may be wasting the benefits of a good crisis. Many heroes rose to the occasion during the COVID-19 pandemic, and the innovation model of relaxed and supportive government policy and a motivated private sector achieved several outstanding successes. But sustaining these innovations will be challenging absent data that can assess what actually happened.

The stakes are higher than many policy makers imagine. Carrying legacy health care business models into the digital age will likely cause health care costs to rise at a double-digit rate over the next few years. The pandemic unleashed decades-worth of pent-up innovation concepts that were largely blocked by competing status quo business models across the health care ecosystem. Evaluating and perhaps extending the record of successful innovation arising from the pandemic will require advocacy, courage, and data-driven leadership from across the health care ecosystem.