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Review Article

COVID-19 – a Five-Year Update

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Abstract

Background: This review aims to categorically describe novel advancements to our understanding and management of COVID-19 and associated short- and long-term sequelae such as Long COVID.

Methods: Indexing services (Scopus and PubMed) were used to identify pertinent studies, prioritizing original research, meta reviews and updated institutional guidelines from 2022 onwards. Papers not published in English (or where full-text translation was not available), those skewed in terms of gender distribution of participants, conducted on non-human populations and proposal and opinion papers were excluded. For the purposes of this paper, Long COVID was taken to mean the persistence of symptoms longer than 8 weeks after an acute COVID-19 infection. After deduplication, application of the exclusion criterion and checking for relevance, 52 sources were identified for this review. The keywords used for this literature search were COVID-19, Long COVID, Chronic COVID, SARS-CoV-2.

Results: New COVID-19 variants challenge vaccine efficacy, highlighting socioeconomic disparities in vaccination rates. Long COVID exhibits complex symptoms, including cognitive decline and physical health impacts. The virus's affinity for ACE-2 receptors suggests broader health implications, including reproductive and metabolic disorders. COVID-19 can cause a drop in IQ proportional to severity of disease experienced.

Conclusion: COVID-19's multifaceted health impacts necessitate ongoing research and targeted interventions. Addressing socioeconomic disparities, updating vaccine formulations, and understanding long-term effects are crucial. Equitable healthcare policies are essential to mitigate COVID-19's global health threat and inform future strategies.

Introduction

COVID-19 changed the world as we know it in 2019. It was the largest healthcare catastrophe of the digital era - causing a total of over 700 000 000 acute cases and over 7 000 000 deaths globally[1] - and raised some serious questions about our collective readiness to combat pandemics. Although 5 years have passed and the virus is not as intensely spoken about as the early days of 2019, we are not out of the woods yet. As we usher in the post-pandemic era, it is essential to understand that we haven't necessarily "beaten" COVID-19 yet. Rather, it seems that this is a problem we are learning to live with, coexist beside. For one, as of January 2024, there were a weekly 2577 deaths in the United States of America that were attributed to COVID-19.[2] Similarly, it was found that there were a total of some 147 000 new cases reported globally in the month of April 2024.[3]

There was also shown to be a 23% increase in COVID-19 related emergency department admissions[3] across the United States in the month of June 2024, but this follows predictable seasonal trend lines associated with the infection itself. Intriguingly, although these statistics paint a picture of the state of incidence of acute COVID-19 cases, it is pertinent to also think about the vast number of people still suffering with the debilitating effects of Long COVID.

Long COVID, a well known sequelae of an acute COVID-19 infection refers to the persistence of symptoms beyond the acute phase of COVID-19 infection, generally taken to mean the persistence of symptoms beyond 4-8 weeks. It was estimated that over 17 000 000 people currently have Long COVID in the United States of America as of 2024.[4] To put some context to this gargantuan figure, it is estimated that the incidence in 2024 for all types of cancer in the United States will be 2 001 140 cases.[5] Similarly, the global incidence of cancer in 2023 was estimated to be around 20 000 000 cases.[6]

It is therefore evident that this is a developing healthcare crisis that we have not put to bed yet.

Materials and Methods

A literature search was conducted on indexing services like PubMed and Scopus using relevant keywords in order to find studies that were relevant, factually important and recent. The keywords used for this search were "COVID-19", "Long COVID", "Chronic COVID", "SARS-

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CoV-2" and "Post-Acute COVID-19 syndrome"

Papers not published in English (or where a full-text English translation was not available), research on a non-human population, opinion pieces and proposals were excluded. Notably, research focusing on solely paediatric populations was avoided, in order to increase external validation of studies and easier generalization to the mass populous. This literature review includes original research, review papers, meta-analyses and institutional guidelines. The basis of this shortlisting was to provide the most detailed narrative with the newest information and aid clinicians in clinical decision making. As a rule no papers with significant biases were included. Once a study passed the inclusion/exclusion criteria phase, the contents of the study were then examined in detail by the author to determine relevance to this paper. In total 52 sources were reviewed in order to formulate this comprehensive review. This review was written in accordance with the PRISMA 2020 guidelines. The PRISMA flow diagram can be found in Figure 1.

Results

Vaccines and New Variants

Although the WHO estimates that over 56% of the global population has completed a primary series of the COVID-19 vaccine as of December 2023,[7] the emergence of new variants is putting the pressure on vaccine manufacturers to offer newer formulations and boosters with a wider breadth of immunity. Additionally, there are socioeconomic barriers as well as healthcare disparities to be addressed in the conversation of vaccine dispersal too. For instance, although over 56% of the global population is estimated to have completed a primary series, developing nations exhibit extremely poor primary series vaccination rates - Yemen boasts a 3% population vaccination rate whereas it is 4% in Papua New Guinea and 9% in Senegal.[7] Unfortunately, due to inconsistent tracking and reporting, incidence of COVID-19 statistics are not available for Yemen and Papua New Guinea, but was found to be 23 cases in the last 28 days in Senegal.[7] The COVID-19 vaccination statistics for various countries are available in Figure 2.

Adding to the already low vaccination rates in certain countries is the fear surrounding potential side-effects to the vaccine. For instance, a recent study found a statistically significant increase in the incidence of Guillain-Barré syndrome, pericarditis and myocarditis after the administration of various different COVID-19 vaccines.[8,9] However, it must also be stated that a recent analysis found that vaccine administration did indeed lead to a lower inflammatory response in individuals if they did eventually get infected with the disease.[10] That is to say, even though the vaccine may have certain side effects—a common theme in almost all medication—the benefits definitively seem to outweigh the risks.

Additionally, the rapidly mutating nature of the virus needs to be addressed. Although most, if not all, variations so far have been less severe and lethal than the original Alpha and subsequent Beta variants,[11] the same cannot be said for infectivity. For instance, it was found that the Omicron strain was more infectious than the Alpha, Beta and Delta strains.[12] Currently, it is estimated that somewhere between 16% and 37% of all active COVID-19 cases in the USA are attributable to the KP.3 variant – a subset of the FLiRT variants.[13] Interestingly, the FLiRT variants themselves arose from the JN.1 variants which subsequently arose from the Omicron variant of the virus.[14] It has also been shown that these FLiRT variants might be more resistant to traditional COVID-19 vaccinations as compared to other variants of the virus.[15]

It is therefore evident that there is a need to be attentive towards the rapidly emerging new strains, especially those with higher infectivity, and to focus research on the vaccine efficacy of currently available concoctions on

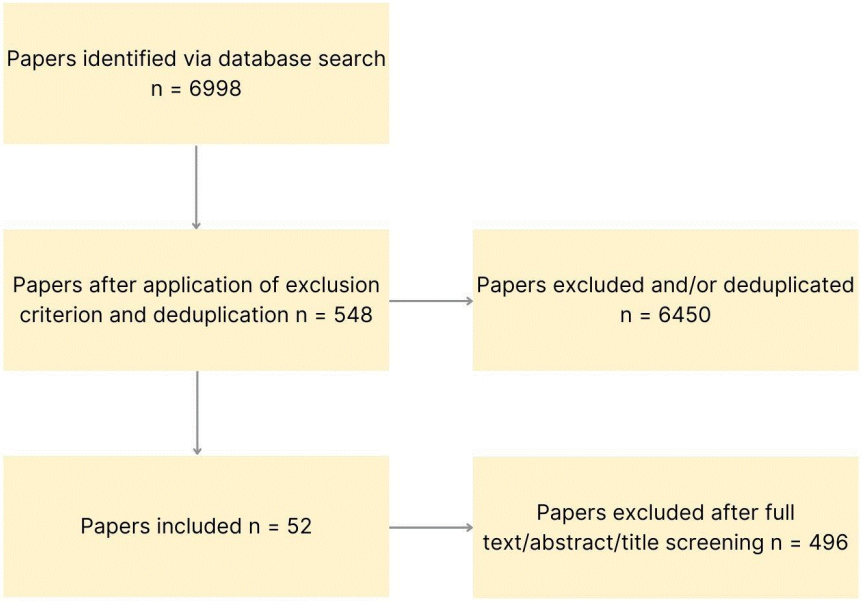

Figure 1. PRISMA Flow Diagram

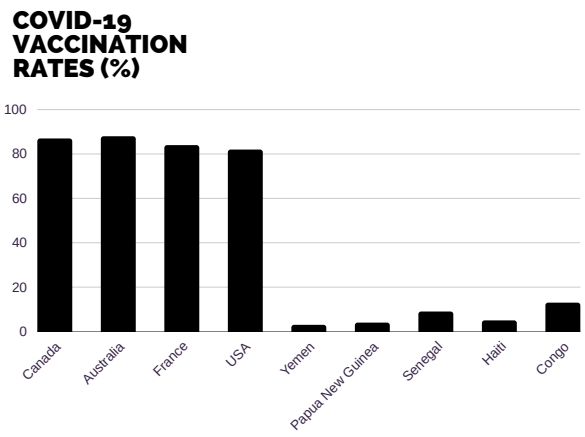

Figure 2. COVID-19 Vaccination Rates for High-Income vs Low-Income Countries

newly emerging strains. Pharmaceutical manufacturers also may well need to produce new boosters yearly in order to confer immunity to new strains.

Long COVID

Firstly, it is important to address the fact that five years on, there is still no official, universally ratified definition for Long COVID or post-acute-COVID-19 syndrome. In general, clinicians may take Long COVID to mean any persisting symptoms that last beyond 4-8 weeks, with the WHO considering it to be the continuation or development of new symptoms 3 months after a bout of acute COVID-19.[16]

Recently, a panel of experts published a report to finally construct an inclusive definition for Long COVID – "a chronic condition that occurs after SARS-CoV-2 infection and is present for at least three months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems".[17] This definition too, however, has not yet received universal ratification.

As of 2024, the CDC estimated that some 17.8% of all adults in the USA are currently affected by Long COVID.[18] Intriguingly, it was also found that Long COVID ran in households - meaning if a patient experienced persistent COVID-19 symptoms, there was a good chance that their housemates would experience persisting symptoms too.[19] While this is an interesting finding, there is no meaningful causality established, nor is it readily evident as to why this result was observed. Further research is definitely warranted to examine this link.

Another study expounded on the similarities shown between Long COVID and Chronic Fatigue syndrome. It is known that in both these syndromes, in addition to the similarities in presentation such as chronic fatigue, lowered quality of life and so on, there is also a dysfunction in the TRPM3 ion channel in Natural Killer cells of the patient.[20] Whether this is a disease causative dysfunction or somehow a consequence of the disease itself is not well understood, but this link is maintained nonetheless. To that end, the same study also showed that the drug Naltrexone could be used in patients of either syndrome to restore function to these impaired TRPM3 ion channels[20] – a potential treatment for the Long COVID syndrome. Future research could identify this drug as a disease modifying or curative agent for Long COVID and must be conducted urgently.

In terms of symptoms, a common symptom of Long COVID is brain fog – shown to be found in 89% of patients.[21] Although a standard MRI on patients with Long COVID that were experiencing brain fog showed no significant results, a Dynamic Contrast Enhanced MRI (DCE-MRI) found that a significant disruption to the blood brain barrier with increased whole-brain leakage in the cohort with the disease as compared to a control.[22] This finding furthers our understanding of the complex pathophysiology of this virus and can guide our clinical decision making in the future when thinking of potential treatment modalities in long term patients. Brain fog in general was a very difficult symptom to diagnose and manage clinically, but it should bring relief to patients and clinicians alike that there has been identified a pathophysiological reason behind it. Although it is highly unlikely that this imaging technique will ever be used to merely diagnose brain fog in Long COVID, the finding still furthers our understanding of the fundamental mechanism behind the development of brain fog and could even guide management regimens.

Another positive finding is that it was found that there was resolution of chronic immune activation in patients with Long COVID at the 24-month mark[23] – indicating that this could potentially be a self-limited phenomenon, but there is not enough data to make extrapolatory claims as of yet. Patients with Long COVID reported a higher quality of life, lower levels of inflammatory biomarkers like CRP and better platelet counts around the two-year mark. Intriguingly, whilst the previous study talks about the physical aspects of the disease, it was contradictorily found that patients were three to four times more likely to develop brain fog around the 24-month mark – a timeframe that was also associated with an increased risk for the development of depression and anxiety.[24] What's positive however is the fact that the odds of developing brain fog seem to significantly decrease when vaccination status is accounted for.[24]

It was also found that a healthy lifestyle prior to infection with COVID-19 was predictive of a decreased risk of developing Long COVID. Maintaining a healthy BMI, never smoking, adequate exercise and regular sleep were all shown to be inversely associated with the risk of developing Long COVID in a dose-dependent manner.[25] Interestingly, another study found that recovery from COVID within three months was less likely in women and those with prior cardiovascular disorders.[26] This is important as multiple studies have already shown that women are more likely than men to be affected with Long COVID.[27,28] The sex-specific link to developing COVID-19, Long COVID and also recovery might be

one that is worth exploring in the realm of research. This same study also found that being vaccinated provided a protective effect against developing Long COVID.[26]

It is evident that COVID-19 is an immensely complex virus and that we are still in the infancy of our understanding of it, especially with the myriad of long term consequences that seem to accompany it.

COVID-19 – The Broader Impact on Health

It is also known that COVID-19 has an affinity for ACE-2 receptors, a receptor that the virus uses to gain entry into cells.[29,30] Subsequently, COVID-19 has been shown to upregulate the production of ACE-2 proteins - a protein with a role in a myriad of chronic diseases including cardiovascular diseases and diabetes.[31] In fact, post mortem studies show that patients with severe COVID-19 have a higher expression of ACE-2 proteins in lung tissues as compared to the control cohort.[32] On the one hand, this is a positive finding in the sense that research can look to develop novel treatment modalities using the ACE-2 protein or ACE-2 receptor as a target.

Conversely, however, is the sombre realisation that if COVID-19 has an affinity to ACE-2 then we must start to wonder where else in the body this affinity can cause the accumulation of the virus. For one, the COVID-19 virus has been found to replicate in and infect pancreatic beta-cells via their ACE-2 receptors.[33] It is shown that the pro-inflammatory biomolecules and cytokines associated with an acute COVID-19 infection may impair homeostatic pancreatic islet cell function and cause diabetes.[33]

Similarly, a study hypothesised that since ACE-2 receptors have a high prevalence in testicular tissue, then the COVID-19 virus would be present too.[34] Although semen samples failed to show the presence of COVID-19, when the researchers looked at the sperm cells themselves, there were clear indications of the presence of COVID-19.[35] Another study directly found the presence of COVID-19 virus in the penile tissue of recovered patients. The study further hypothesised

that the widespread endothelial dysfunction seen in COVID-19[36] can contribute to erectile dysfunction.[37]

In that same vein, an inverse relationship was also found between spermatogenesis and increased ACE-2 receptor expression, suggesting a potential mechanism via which COVID-19 may lead to infertility in men.[34] Women too, were found to experience a decline in sexual health as a result of COVID-19, with over 60% affected females at risk for experiencing sexual dysfunction.[38] Women also apparently experienced a worse sexual dysfunction if they presented with Long COVID, as compared to acute COVID, which itself was worse than the case of a healthy woman who had never experienced a COVID-19 infection.[39]

In terms of the myriad of ways in which the virus may manifest in patients, we are still discovering new symptoms and sequale. It has been documented that COVID-19 causes dysphonia during the acute phase of the infection,[40] as well as up to 70% patients having been seen to experience long term dysphonia after the acute infectious period.[41] Additionally, newer research shows a case of an adolescent patient with bilateral vocal cord paralysis post-COVID-19, requiring long term Tracheostomy.[42] The discovery that COVID-19 can cause vocal cord pathology as well as chronic dysphonia is something clinicians can keep in their mind whilst considering long term management options and prognostic outlooks.

Treatment and Future Research

Studies have shown that the HLA-DQ2 protein (often associated with Celiac disease) is associated with a milder COVID-19 infection.[43] Similarly, it was found that high expression of the HLA-DQ2 protein in the blood and nose of healthy volunteers before being inoculated with COVID-19 was associated with preventing a sustained infection.[44] This is immensely important because it is one of the very few studies that have discovered a protective factor against COVID-19. Further research is urgently needed in not just how this can be put to use in a clinical setting but also how and if this protective effect extends to the development and/or management of Long COVID too.

In the vein of treatment modalities, the WHO also recently updated their guidelines with regards to COVID-19 drugs – firstly, they outlawed the usage of Remdesivir in the treatment of COVID-19, citing a lack of sufficient evidence of benefit.[45] They also recommend the usage of monoclonal antibodies to treat non-severe patients with the highest risk for hospitalisation.[45] This in fact brings up a very important area for future research – there is an evident need to not only study and propose a standardised treatment regimen and dosages for both acute COVID-19 and long COVID, but also the need to develop a universally accepted model to predict the risks for hospitalisation and development of Long COVID in patients.

Similarly, new research shows that Cannabis usage, even after accounting for tobacco usage, vaccination status and other comorbidities, appears to be an independent risk factor for COVID-19 associated complications. Cannabis users had a higher risk of hospitalisation and ICU admission than their non-cannabis-using counterparts.[46] Contradictorily, yet another study showed that cannabinoid usage may help reduce the severity of and mount a more robust immune response against a COVID-19 infection.[47] Some studies have also found that cannabinoids may be useful in mounting a response against not just COVID-19 but also its subsequent variants.[48]

It must be said however, that not enough research currently exists in this field and there are some obviously contradictions in the literature. Nonetheless, this is an interesting and potentially important area of research that is sparse and requires more resources and studies to examine.

Pediatric Considerations and Neurocognitive Decline

Various studies have shown that in utero COVID-19 exposure has been linked with infants born with lower birth weights than infants without exposure to COVID-19.[49,50] Interestingly, these low birth weight infants were found to exhibit a higher rate of weight gain during their first year of life as compared to the control cohort, exhibiting a so-called catch-up phenomenon.[50] This pattern of catch-up growth has been hypothesised to cause future co-morbidities in these infants such as cardiovascular disease and metabolic pathology.

These are important findings for physicians to keep in mind so as to not only adequately and appropriately treat their pregnant patients but also to account for when evaluating pediatric developmental milestones and trend lines.

Studies also show that COVID-19 is objectively associated with cognitive dysfunction and improper memory and task execution.[51] Concerningly, this cognitive decline was found to be the equivalent of a three to nine point drop in IQ, depending on the severity of initial symptoms as well as whether or not symptoms persisted. For instance, an ICU administration was associated with a nine point IQ decline whereas persistent symptoms were associated with a six point decline.[51] This is an immensely important finding, and the first study to objectively attempt to quantify the cognitive decline experienced post-COVID-19. Further research is urgently warranted in this field and clinicians need to keep this significant cognitive decline in mind when designing management plans.

Conclusion

This paper highlights the significant health impacts of COVID-19 and its evolving landscape. The emergence of new variants continues to challenge vaccine efficacy, necessitating ongoing updates to vaccine formulations and boosters. Socioeconomic barriers and healthcare disparities in vaccine distribution persist, particularly in developing nations.

Long COVID remains a complex and poorly understood condition, with a diverse set of symptoms and presenting significant neurocognitive and physical health challenges. Vaccination has shown some protective effects against severe outcomes, but the virus's affinity for ACE-2 receptors raises concerns about its broader health implications, including reproductive health and metabolic disorders. Further research is urgently needed and could potentially uncover a therapeutic target for Long COVID management in the form of ACE-2 receptors.

Current treatment guidelines emphasise the need for targeted therapies and a better understanding of the virus's long-term effects. Emerging research on symptoms like dysphonia and the role of lifestyle factors underscores the complexity of COVID-19's impact. Cognitive decline associated with the virus, quantified in recent studies, highlights the urgent need for further research and interventions. The protective role of HLA-DQ2 should also be comprehensively studied as this could not only predict future outcomes in patient cohorts but also potentially serve as a therapeutic target. It is also urgently necessary to examine the extent of sexual dysfunction caused by the virus and try to establish causality. The link between infertility and infection must be thoroughly studied.

In summary, COVID-19 presents a multifaceted threat to global health, emphasising the need for ongoing research, targeted interventions, and equitable healthcare policies to mitigate its impacts and inform future strategies.

Competing Interests

There are no conflicts of interest to declare.

Data Availability Statement

No datasets were produced during the creation of this paper.

Ethical Approval

No ethics approval was necessary for this paper.

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