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Review Article

Coronavirus Disease; Long COVID: Global War Against a Novel Virus

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Abstract

Current coronavirus pandemic is unprecedented and the global response to a great extent, has demonstrated how unprepared we were, despite the past experiences of earlier 'flu' pandemics. Now we are in the third year of the pandemic, with the fifth COVID surge rising in many countries. The pandemic started, with the emergence of Alpha variant from Wuhan, China and has continued to evolve into more and more transmissible variants, Beta, Delta and currently, Omicron. We warned you but you did not listen, says a report titled "A World at Risk" published in September 2019, by the Global Preparedness Monitoring Board (GPMB). When the new coronavirus was identified in Wuhan, China, the virus's entire genetic makeup, or 'genome' was published online within days. Advances in gene sequencing has allowed scientists, to trace and monitor the spread of the virus worldwide and the evolving nature of newer variants. The viral outbreak was followed by immediate surge of academic publications, in less than five months more than 15,000 publications appeared and exceeded 80,000 by the end of 2020. The media reported every milestone, in the spread of the virus worldwide, as well as about the vaccines and drug development activities. Unfortunately, the spread of false and misleading information by some sources, drowned credible information. The magnitude of development that has taken place and the speed with which mRNA vaccines and antiviral drugs were developed during this crisis, is historical and remarkable. Pharmaceutical companies achieved "things we never thought could be done", to combat the pandemic quickly. In just over a year, due to the biggest vaccination campaign in history, more than 12 billion doses of vaccines have been administered across 184 countries. On a global scale, 73 countries have given at least one dose, to 75% of the population. With 2.8 billion people worldwide, still not vaccinated against COVID-19, the health experts worry that we are prematurely moving away from the pandemic. We are at war with a killer virus, which has caused unprecedented economic crisis. Some people who have been infected with the coronavirus, have reported their experience of long-term effects and lingering COVID-19 symptoms, known as post COVID conditions (PCC), or long COVID, or as the experts refer, post-acute sequelae of SARS-CoV-2 (PASC). We have not seen the end of COVID-19 epidemic, as we still have new surges of this virus in various geographical regions of the world. In a large study of 47,780 patients discharged following COVID-19, almost a third were admitted again to the hospitals and a similar proportion were diagnosed with respiratory diseases, according to studies published in the Lancet and British Medical Journal (BMJ). The National Health Services of UK officially launched a long COVID service, to support recovery in October of 2020. Post COVID Care Centers (PCCC) are opening across the country, bringing together multidisciplinary teams, across a broad range of specialties. Long Covid Services in Europe is highlighted by the 6.6-billion pounds funding it has received. The World Health Organization (WHO) has urged member countries, to prioritize rehabilitation for the medium and long-term consequences of COVID-19 and to gather information on "long Covid: more systematically. The COVID-19 pandemic was caused by $16 trillion virus and the cost of long COVID is estimated at $2.6 trillion. These numbers are nothing but estimates. No one knows, the true economic burden of such diseases.

Keywords: *COVID-19; SARS-CoV-2; Novel Virus*

Introduction

Coronavirus disease 2019 (COVID-19, SARS-CoV-2) has caused unprecedented economic, social and healthcare crisis. It caught off guard, the public healthcare experts, exposed how poorly they were prepared, to face a global health emergency. Researchers from Armed Force Institute of Pathology, Maryland, USA write in their seminal article, '1918 Influenza: the mother of all pandemics', "the 'Spanish Flu' pandemic of 1918-1919, which caused approximately 50 million deaths worldwide, remains an ominous warning to public health [1]". Whereas Nobel Laureate Joshua Lederberg wrote two decades ago that, "the future of humanity and microbes likely will unfold as episodes of a suspense thriller, that could be titled "Our Wits Versus Their Genes [2,3]". I for one, never thought, that we would be facing such a situation, in less than two decades. Coronavirus is not an unknown virus. It was discovered in the 60s. The first description of human coronavirus, a family of viruses, that now include SARS-CoV-2, the cause of the current Covid-19 pandemic, was published in the BMJ in 1965 [4]. The evolution of this virus, over a period of time, to a more and more infectious and pathogenic novel strain, makes the substance of the thriller episode, that Lederberg refers to in his Nature article [3].

The year 2018, marked the 100th anniversary of the deadliest pandemic in the human history. One third of all the people in the world, were sick and had acute respiratory symptoms. An influenza virus called influenza type A subtype H1N1, is now known to have been the cause of the extreme mortality during this pandemic. How did influenza virus develop into such a deadly killer virus? What kind of genes were acquired and incorporated into the avian influenza genes, that code for the novel surface proteins in the 'Spanish Flu' virus? Even after a century of exploratory studies, we do not know the answers too many of these burning questions. Influenza viruses are classified by subtypes, based on the properties of their hemagglutinin (H) and neuraminidase (N) surface proteins. In 2009, H1N1 was spreading fast worldwide, the WHO reported it as a pandemic. Despite the fact, that the people still get sick with swine flu, the disease has not caused any global emergency. It is now known, that quite often, various strains of 'bird flu' or 'swine flu' viruses combine, to create novel, powerful new pandemic strains, which were responsible for 1957, 1968 and 2009 outbreaks. According to experts, these later outbreaks, all created in part by the 1918 virus, claimed millions of additional lives, earning the '1918 flu' the infamous title of "the mother of all pandemics".

A consortium of international researchers on Infectious diseases from China, Germany, Singapore and the US, reported a large number of SARS-related coronaviruses (SARS-CoV) from horseshoe bats, from different parts of China in 2005 [5]. This very important international collaborative study of five years (funded jointly by China and the US) demonstrated, that these viruses were highly diverse in their S gene, open reading frames (ORF), ORF3, ORF8, especially in hypervariable N-terminal domain (NTD) and receptor binding domain (RBD). Further cell entry studies revealed, that that three newly identified SARSr-CoVs with different protein sequences, were all capable of using human angiotensin 11(ACE2) as the receptor, suggesting for the first time, that SARS-CoVs were capable of direct transmission to humans and such variants were circulating in bats, in the caves in Yunnan, China. According to a report in the journal Science of June 2020, the National Institute of Health halted the massive analysis of bat coronaviruses in China. The US government has published the most comprehensive analysis ever done of such viruses, which included data on partial genetic sequences of 781 coronaviruses [6]. On May 21, 2020, the New York Times reported, that 77 Nobel laureates have asked for an investigation, into the cancellation of a federal grant to EcoHealth Alliance, a group that researches bat coronaviruses in China. On the other hand, Dr Anthony Fauci, the Director of the National Institutes of Allergy and Infectious Diseases of NIH, was harassed by the right-wing press, as well as right-wing legislators for facilitating the NIH funding of these studies.

The China Novel Coronavirus Investigating Research Team, reported the first human cases of pneumonia of unknown cause, linked to seafood wholesale market in Wuhan, China, in December of 2019 [7]. They isolated the coronavirus from human airway epithelial cells and named it, 2019-nCoV. Coronaviruses are enveloped positive-sense RNA viruses, with a large RNA genome and a unique replication capability. Six coronaviruses are known to cause human diseases. Four viruses, 229E, OC43, NL63 and HKU1 cause common cold

symptoms, in immunocompromised individuals. The two other strains, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), have been linked to fatal illness, since the time an outbreak was reported in Guangdong Province in China, in 2002 and 2003 [8]. On 30 January 2020, World Health Organization (WHO), officially declared the COVID-19 epidemic as a public health emergency of international concern. The Chinese scientists rapidly isolated SARS-CoV-2, from a patient on 7 January and revealed the genome sequencing of the SARS-CoV-2 [9,10]. Researchers in the United States, the United Kingdom and Australia, have expressed their disappointment, by the slow release of information from China about COVID-19's origins [11].

Since COVID-19 pandemic started from Wuhan, China, more than 524 million people globally, have been infected with the virus; of those, more than 6 million have died, including more than one million in the United States alone, the most advanced nation in the world. The coronavirus has spread more globally and rapidly, than other viruses responsible for the previous pandemics, suggesting that rising international connectivity and urbanization has played a key role in the transmission between and within territories [12]. In a large systematic study and meta-analysis of 4.3 million patients from 68 countries, African Americans, Hispanic and Asian American individuals, had a higher risk of COVID-19 positivity and ICU admission than White individuals. Socioeconomic disparity and clinical care quality were associated with COVID-19 mortality [13]. In the New York Times coronavirus briefing, dated May 16, 2022, Jonathan Wolf writes, "More Americans have died from COVID-19, than in all the country's wars combined. The shocking death toll is the result of many factors, elected officials who downplayed the threat of the virus and resisted safety measures', a decentralized, overburdened health system that struggled with testing, tracing and treatment; and lower vaccination rates achieved, than in other rich countries".

In a population-based UK cohort study, researchers found that older age, male sex, obesity, ethnicity, other neurological conditions, history of organ transplant and auto immune disease, were to varying degrees, stronger risk factors for COVID-19 deaths [14]. The first studies reporting characteristics of hospitalized patients with COVID-19 showed, that the most common comorbidities were hypertension, diabetes, obesity, cardiovascular diseases, chronic pulmonary disease, chronic kidney disease, cancer and chronic liver disease. Worldwide, there are over a billion individuals with hypertension, obesity and prediabetic conditions. These individuals are at 'high risk' for experiencing severity of COVID-19. We have discussed the role of metabolic diseases in enhancing the severity of COVID-19, in several of our earlier articles [15-30]. In this overview, we briefly discuss the future after the COVID-19, which would, be the effect of Long COVID-19 sequelae.

SARS-CoV-2 biochemistry, transmission

Coronavirus 2019 is a single stranded, positive sense RNA virus and has a genome size of 29.99 kb, containing open reading frames (ORFs). The first ORF covers two-thirds of the viral RNA, which encodes polypeptides, for the viral replicase gene-transcriptase complex. The remaining ORFs, translate four main structural proteins, spike (S) Protein, membrane (M) protein, envelope (E) protein and nucleocapsid (M) protein. Of these four surface proteins, S protein is a transmembrane glycoprotein, which facilitates the attachment and entry of the virus into target cells [31]. The viruses that belong to this group, use a variety of receptors, to enter host cells. MERS-CoV uses dipeptidyl protease 4 (DPP4) and angiotensin converting enzyme 2 (ACE2). SARS-CoV-2 seems to prefer ACE2 as the host receptor to enter the cells and primarily infects epithelial cells. The viral spike glycoprotein (S protein) binds to the host cellular receptor and seems to be the main determinant of infection and transmission. The spike protein is a large transmembrane protein and is highly glycosylated. Extracellular domain consists of two subunits (S1 and S2), which facilitate the host-cell receptor recognition and membrane fusion. The second determinant of infection is the activation of host proteases. Molecular mechanisms involved in cell entry of the viruses is a complex process. Transmembrane serine proteases (TMPRSS2) and lysosomal cathepsins, together with proteases such as cathepsin and furin, facilitate SARS-CoV-2 entry into host cells [32]. Both in MERS-CoV and SARS-CoV-2, presence of furin cleavage sites, seem to facilitate the entry into the host cells [33].

Like all viruses, coronavirus also takes control of host cells and produces copies of itself. Each new copy of the virus contains tiny

copying errors or variations in its genome, hence they are called 'variants'. According to the WHO, the Delta variant (B.167/2) is the 'fastest and fittest' variant, as much as 50 to 60 percent more transmissible, than the Alpha variant (B.1.1.7), which was 50 percent more transmissible, than the original strain of COVID-19. Once the Omicron variant surfaced in South Africa, it virtually took over the other dominant variant, Delta variant worldwide, faster than any other previous strains. Scientists believe that there is no transparent path of transmission, linking Omicron to its predecessors. If so, where did Omicron come from? And how it is much more highly transmissible, than the Delta variant? Researchers in this field are investigating three theories [34]. 1) First, although scientists have sequenced millions of SARS-CoV-2 genomes, they might have missed a series of mutations that eventually led to Omicron. This variant may have evolved the needed mutations in one or more immunocompromised individuals, as part of a long-term infection. 2) Second, it could have emerged unseen in other animal hosts and jumped to humans in South Africa. 3) Third, omicron's mutations seem to be extremely rare, indeed never seen before. Furthermore, it consists of three distinct sub lineages called BA.1, BA.2 and BA.3, all emerged at the same time. The omicron variant of COVID-19, has become the dominant strain of the virus, circulating in the U.S. and rest of the world. It is more easily

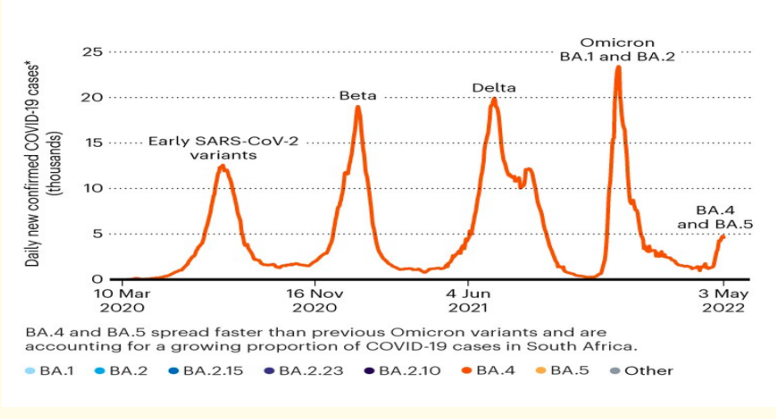

Figure 1: *Early SARS CoV-2 variants emerged in 2020 with successive beta and delta appearing in 2020-2021. Omicron variant appeared in November of 2021 in South Africa. (Source: Public Domain: Our World in Data).*

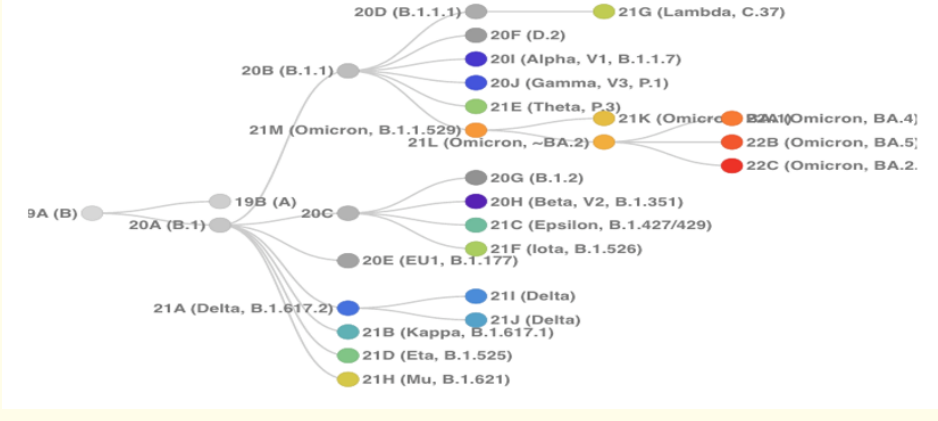

Figure 2: *Schematic representation of SARS-CoV-2 variants including omicron variants. Phylogenic Relationships of SARS-CoV-2 Variants. (Source: Nextstrain). https://covariants.org.*

spread, than previous strains because, it has more mutation in the spike proteins, than any other variant discovered so far.

During its short existence, Omicron strain has accumulated close to a dozen amino-acid changes in its spike protein. The receptor-binding domain is an easy target for antibodies, hence much of the research soon will concentrate on Omicron transmission mechanisms. Despite its increased rate of infection and transmission, it seems to be less lethal than the Delta variant. John Burn-Murdoch in a tweet, recently commented on the promising news from South Africa, where the BA.4/BA.5 variants have passed quietly, with high levels of immunity, with little impact on rates of severe illness or death. According to experts, though Omicron does trigger less severe disease in

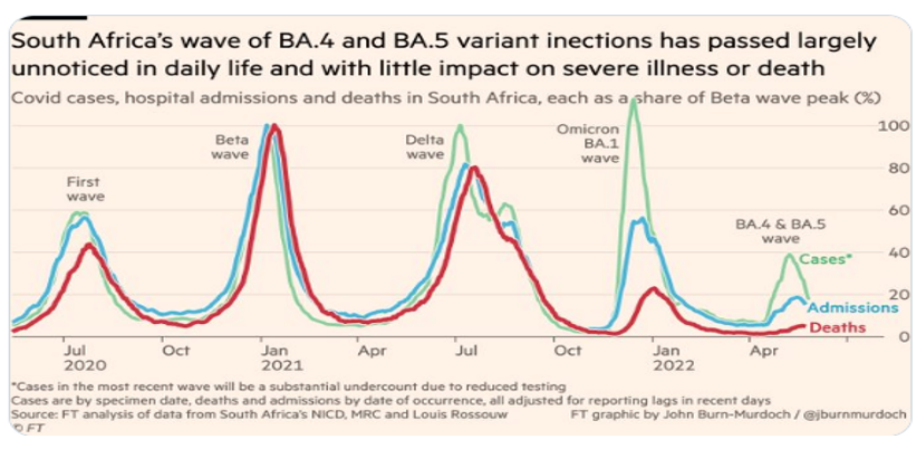

Figure 3: *Graphic representation of SARS-CoV-2 variants and their severity. (Source: John Burn-Murdoch, Twitter Tweet).*

those who catch it, this does not necessarily make it any less dangerous. Evidence consistently suggests that Omicron is more contagious than the already highly transmissible Delta variant, with rapid increases in cases seen in several countries.

SARS-CoV-2 clinical complications

In a study of over 370,000 confirmed COVID-19 positive cases, from January to May 2020 with known COVID symptoms, that were reported to the Center for Disease Control (CDC), United States, cough (50 percent), fever (43 percent), myalgias (36 percent) and headache (34 percent) were the most common symptoms [35]. Other features, including diarrhea, sore throat and smell or taste abnormalities also have been reported. The most common morbidities present in a total of 5700 hospitalized patients in the USA, were hypertension (56.6%), obesity (41.7%) and diabetes (33.8%) [36]. Coronaviruses are responsible for respiratory infections, causing the common cold like symptoms. Earlier pandemic of coronaviruses included, Severe Acute Respiratory Syndrome Virus (SARS-CoV) and the Middle East Respiratory Syndrome Virus (MERS-CoV). These viruses were known to have probability of higher infections, in immune compromised individuals. Comorbidities increasing the severity of the disease included hypertension, obesity, diabetes vascular diseases, heart, lung, kidney or liver disease, blood disorders, malnutrition and immune deficiencies [36]. Virus infection and spreading within the respiratory tract, is due to the capability of receptor binding proteins, to bind different isoforms of sialic acid present on host receptors.

Preferred receptor for entry into host cells by coronavirus, is the angiotensin enzyme 2 (ACE2), which is present in many tissues including endothelial cells. A healthy endothelium, one of the largest organ, covers the lining of all blood vessels, which supply oxygen and

nutrients to the cells, tissues and organs. Hence, the entry of coronaviruses into ACE2 receptors, provides safe passage to this pathogen, to all the host tissues and organs. New York University researchers also demonstrated that covid-19 exposed platelets, change cells lining of blood vessels (endothelial cells) largely, through a protein called P-selectin, which makes platelets stickier and more likely to form clots. Endothelial cell dysfunction and impaired microcirculatory function contribute markedly, to the life-threatening complications of COVID-19, such as venous thromboembolic diseases and multiple organ involvement [15-19,21,28-30,37,39]. We and others have described coronavirus disease, as a multisystem disease, since this virus uses a ubiquitous ACE 2 receptor, which is present abundantly on vascular endothelium. Therefore, there is considerable speculation, that lasting effects of the disease and long term sequelae of COVID-19 clinical symptoms, could persist even after the infection subsides.

Long COVID, causes and concerns

Long Covid is not fully understood by the public health experts, clinicians, scientists, or the lay individuals. There is no internationally agreed definition or guidelines, by the professional societies, or regulatory agencies at the time of this writing. Guidance for UK health professionals refers, to symptoms that continue for more than 12 weeks, which cannot be explained by another cause. The Office for National Statistics (ONS) of the UK, estimates about 1.5 million people in the UK have "long Covid". The U.S. Government Accountability Office, Science and Tech Spotlight reports, that it could be in the range of 7.7 - 23 million, according to some estimates. The full magnitude of health and economic effects is unknown and is expected to be significant. According to Center for Disease Control (CDC), USA, the long covid is the occurrence of new, returning, or ongoing health problems, four or more weeks after an initial infection with SARS-CoV-2, the virus that causes COVID-19. This new condition is also known as post-acute COVID, post-COVID conditions and chronic COVID. Symptoms of long COVID vary from person to person, depending on the severity and organ system damaged by the COVID. They may include fatigue, cognitive impairment (or brain fog), muscle or joint pain, shortness of breath and heart palpitations.

According to Fair Health Analysis, from October 2021 to January 31, 2022, 78,000 privately insured people (who were diagnosed with the code U09.9 post-COVID condition unspecified), were treated, for a post-COVID condition. More than half of the 236 million people, who have been diagnosed with COVID-19 worldwide since December 2019, will experience post-COVID symptoms, more commonly known as "long COVID" - up to six months after recovering, according to Penn State College of Medicine researchers. In an article published in JAMA, the researchers report a systematic review of 57 studies, comprising more than 250,000 survivors of COVID-19, most sequelae included mental health, impaired cognition, pulmonary and neurological disorders, which were prevalent longer than 6 months, after SARS-CoV-2 exposure [40]. Authors conclude that long-term PostAcute SARS-CoV-2 (PASC) must be factored into existing healthcare systems, especially in low-and middle-income countries. According to these researchers, globally, the pooled PASC prevalence estimate was 0.43, whereas the pooled PASC prevalence for patients who had to be hospitalized was 0.57 [41]. Even though a large proportion of the current evidence for PASC focuses on hospitalized patients, a German study found that 34.8% of COVID patients, with only a mild acute infection, had PASC at 7 months post infection [42]. This study adds to a growing body of evidence, that while patients who have been hospitalized are at greater risk for long COVID, people with mild or moderate COVID, who make up most COVID-patients, can still experience debilitating post-COVID symptoms.

Long COVID seems to pose risk, to even vaccinated people according to a study by researchers at Washington School of Medicine in St. Louis, MI and the Veterans Affairs Health Care System. The study of more than 13 million veterans (longest cohort study), found that vaccination against the virus that causes coronavirus disease, reduced the risk of death by 34% and the risk of getting long COVID by only15%, suggesting that vaccines offer little protection against lingering symptoms of COVID than expected. In an article published in Nature Medicine, the Chief investigator Al-Aly notes that, "Our current approach, will likely leave many people with chronic and potentially disabling conditions, that have no proven treatments. This will not only affect people's health, but their ability to work, life expectancy, economic productivity and societal well-being. We need to have a candid national conversation, about the consequences of our current

approach [43]". A large UK study (47,780) of COVID-19 patients discharged from hospitals, published in *Lancet* and *BMJ*, found that once discharged, patients experienced increased levels of distress and psychological symptoms [44,45]. Sixty four percent of the patients, experienced breathlessness and 55% reported fatigue. On MRI, abnormalities were seen in lungs (60%) heart (26%), liver (10%) and kidneys (29%). The US had 81 million cases of COVID-19. Even the lower- end estimate of 12% people, with 3 or more symptoms of long COVID, implies, that 9.6 million in the US, may develop long COVID symptoms [46].

Long COVID, persistent clinical symptoms

According to Charles Bangham, Professor of Immunology Imperial College, London, "It is now clear, that beating an initial infection of this virus, is not the end of the story. For a significant proportion of people, Covid-19 is turning out to be a long-term illness, a condition that has become known as "Long Covid". He further elaborates this problem, "A major part of the problem is, that we still do not have a widely accepted definition of, exactly what Long COVID is? To even begin to estimate, how much of a problem the condition is, we need to have a clear idea of how to identify it". We and others have discussed, as to how SARS-CoV2 variants have evolved, from a simple respiratory virus, to one that can infect the lining of the blood vessels (endothelium), and thereby gain access to all the organs. This could explain, why we see damage of multiple tissues and organ systems. How many subjects suffer Post-Acute SARS-CoV2 symptoms? "The WHO says its 10%, while a study from the UK found 30%. The proportion affected is likely to be different between the countries". Two years after infection with COVID-19, half of patients (650/1,190) who were admitted to hospitals, still had at least one symptom, according to the longest follow-up study to date, published in the journal, the *Lancet* [47]. Survivors with Long COVID symptoms at 2 years, had lower health-related quality of life, worse exercise capacity, more mental abnormality and increased health-care use after discharge, than survivors without long COVID symptoms. The authors of this longest follow-up study conclude, "The study findings indicate that there is an urgent need to explore the pathogenesis of long COVID and develop effective interventions to reduce the risk of long COVID".

Currently, most of the clinics, public health experts and regulatory agencies rely on the nasal, salivary, or blood tests (anal swabs and fecal analysis may become tests of choice soon) to detect the presence of viral particles and to determine the COVID positive or negative status. Is this sufficient to say, that the body has cleared the viral particles completely? Scientists are studying whether long COVID could be linked to viral fragments found in the body months after initial infection. The news that coronavirus might persist in the body, came from the work published by Saurabh Mehandru of Icahn School of Medicine at Mount Sinai, New York and his colleagues. Mehandru and his team found viral nucleic acids in the gastrointestinal tissue, collected from people who had been diagnosed with COVID-19, average four months earlier [48]. Whereas Bhatt and her colleagues, found that few people continued to shed viral RNA into their stool, seven months after the initial mild or moderate SARS-CoV-2 infection, well after the respiratory symptoms had ended [49,50]. Makeup of the gut microbiome may be linked to a person's risk of developing 'long COVID', suggests recent research findings [51]. According to the findings of this study, at 6 months, 76% of patients had PACS and the most common symptoms were fatigue, poor memory and hair loss. Gut microbiota composition was associated with occurrence of PACS. Patients without PACS, showed recovered gut microbiome profile at 6 months, comparable to that of non-COVID controls. ACE2 expression is approximately hundred-fold higher in the digestive system, than in the respiratory system [52]. COVID is infamous for wreaking havoc, in almost every body organ. COVID signs and clinical symptoms, can be related to the dysfunction of vascular system, resulting in the injury of multiple organs such as heart, brain, liver, lungs, kidney, skin, gut and in the digestive system.

Discussions

SARS-CoV-2 leverages the ACE 2 receptor, to enter host cells. Since ACE2 is widely distributed in various organs, including, oral and nasal mucosa, nasopharynx, lung, vascular endothelium, small intestine, colon, kidney, spleen, liver, heart and brain. PACS, includes symptoms that affect various organ systems, with neurocognitive, autonomic, gastrointestinal, respiratory, musculoskeletal, psychological, sensory and dermatological clusters. An analysis of nearly 154000 US veterans with SARS-CoV-2 infection, reveals the long-term effects of COVID

on cardiovascular outcomes [43,53]. According to the principal investigator, Al-Aly, "it does not matter if you are young or old, it doesn't matter if you smoked, or didn't, the risk was there". Even though coronavirus is considered a respiratory virus, a large portion of Covid patients, report neurological symptoms, especially the so called 'brain fog,' as well as cognitive symptoms. Furthermore, some studies have reported loss of gray matter in multiple regions of brain [54]. Chinese researchers have reported that incidence of liver injury in patients with COVID-19, ranges from 14.8 to 53%, manifesting as abnormal glutamic-pyruvic transaminase, glutamic-oxalacetic transaminase and bilirubin levels [55]. Kidney involvement is common in patients with acute SARS-CoV-2 infection and subclinical inflammation and injury persists for months, resulting in a progressive decline in kidney functions [56].

All viruses change over time and SARS-CoV-2 is no exception. Total genome sequencing has facilitated the identification of new variants, their lineage, rate of transmissibility and the severity of the coronavirus disease that they can cause. It is essential to distinguish between different, potentially more transmissible SARS-CoV-2 variants and their lineages, to curb the spread of this killer virus worldwide (Figure 1 and 2). The COVID-19 is in the third year of the coronavirus pandemic, globally the number of daily cases and hospitalization has been declining. The first variant designated in the UK and identified in 192 locations was Alpha. This variant was 50% more transmissible, than the original Wuhan strain. The Beta variant was first detected in South Africa in December 2020. Again, this strain was considered 50% more transmissible than the previous strains. Gamma strain was first identified in Brazil, but later was detected worldwide. The Delta variant was first identified in India, in May of 2021 and has been detected in 176 locations. This variant is estimated to be 40 - 60% more transmissible than the Alpha variant. The Omicron variant (BA.1), which was first identified in South Africa in November of 2021, has quickly spread worldwide. This BA.2 variant has a 1.4-fold higher reproduction than BA.1. According to public health experts, the viral fitness and efficacy is due to 53 mutations, 29 of which are in the spike protein. Two other variants, BA.4 and BA.5, have recently emerged in South Africa and appear to be significantly more transmissible than previously identified Omicron variants. These variants do not seem to cause severe disease than previous variants, such as Beta and Delta variants (Figure 3).

The novel virus, SARS-CoV-2 can infect a wide range of human cell types. However, its ability to use ACE2 as the preferred receptor for entry to host endothelium, provides it an easy access to all types of tissues and organs. Hence in reality, coronavirus disease is a multisystem disease, due to the vascular endothelium injury [19,21,39]. We and others believe that lasting effects and long -term sequelae could persist, after the infection and may be due to persistent endothelial dysfunction. A recent study by researchers from the University Hospital Sfax, Tunisia, focused on the evaluation of endothelial quality index (EQI) by finger thermal monitoring, in a large cohort of long COVID-19 patients, to determine whether long COVID-19 symptoms are associated with endothelial dysfunction. This cross-sectional multicenter observational study demonstrated that long COVID-19 symptoms, specifically non-respiratory symptoms, are due to persistent endothelial dysfunction [39]. Position paper of the European Society of Cardiology (ESC) Working Group for Atherosclerosis and Vascular Biology and the ESC Council of Basic Cardiovascular Sciences, stated that, "It seems relevant to follow the endothelial dysfunction, in convalescent patients for early detection, management of symptoms and prevention of long-term cardiovascular complications [57,58].

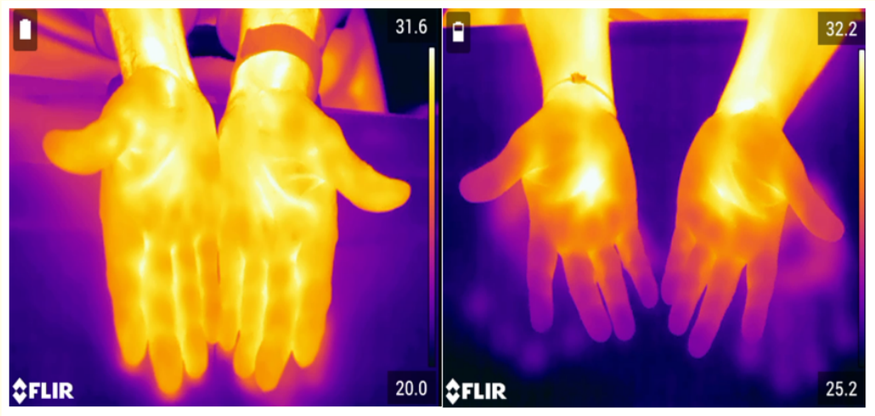

Figure 4: *Thermal Images of low-risk (left) and high-risk (right) individuals. (Courtesy Gayathri Choda and Rao GHR: J. Clin. Cardiol and Diagnostics 3(1), 2020).*

Tunisian researchers report that Sulodexide, a highly purified mixture of glycosaminoglycan that includes fast-moving heparin and dermatan sulfate, had beneficial effects on the fibrinolytic system, platelets, endothelial cells and inflammation. Sulodexide used in the early stages of COVID-19 was associated with a limiting disease progression, a decreased need for oxygen support and hospital care [58].

In an earlier study, we described a method for monitoring vascular dysfunction using thermal imaging techniques. At the Aarca Research Pvt Ltd, Bengaluru, India, we used FLIR-E85 series Video Camera, to obtain thermal scans of body surfaces, for monitoring thermal variations due to vascular dysfunction. In a routine thermal imaging process, we shot the video at 30 frames per second for 1 minute and captured 1800 frames. The data thus collected, were computed and using proprietary software, analyzed for vascular risk stratification. As shown in figure 4, image on the right side is showing asymmetric temperature pattern for the high- risk subject, compared

to the image on the left side (normal subject). In an earlier article on blood flow velocity and fluid dynamics, we have discussed several available technologies, for monitoring vascular dysfunction (endothelial dysfunction) [59]. We compared the Periscope (Genesis Medical System, Hyderabad, India), which is used for monitoring arterial stiffness with TM-Oxi system developed LD Technologies, Miami, Florida [60,61]. We would like to emphasize, that development of a simple cost-effective mobile diagnostic device, for determining vascular dysfunction, will go a long way to address clinical complications associated with vascular dysfunction. Since endothelial dysfunction, is the earliest marker for the development of cardiovascular disease (CVDs), such hand-held devices, will be very useful for early detection of metabolic disease and CVDs. Several earlier studies, have used non-invasive methods (flow-mediated dilation), for monitoring endothelial dysfunction in adults as well as children [62].

Mechanisms underlying endothelial dysfunction are complex, include altered endothelium derived vasodilators, enhanced endothelium derived vasoactive compounds, excess production of reactive oxygen species (ROS), reactive nitrogen species, activation of inflammatory and immune reactions and altered activation mechanisms of blood platelets, coagulation and fibrinolysis [63].

In the TREND study, ACE inhibitor quinapril improved endothelial dysfunction [64]. Lacidipine, Nifedipine, tetrahydrobiopterin, pravastatin, 5-methyltetrahydrofolate, selective COX2 inhibitors and a variety of supplements like ascorbic acid, folate, homocysteine, flavonoids, polyphenols, resveratrol, cocoa products, pistachios, black tea components, green tea, red wine, dark chocolate diet rich in fruits and increased exercise have been shown to restore endothelial function [65,66]. When discussing management of endothelial dysfunction or vascular dysfunction, it is important to consider the severity of damage to the endothelium and the biochemical mechanism involved, so that appropriate management strategies can be implemented. Injury to endothelium leading altered function, may be the result of multiple molecular mechanisms, we have not discussed the role of inflammation or cytokine storm in this review.

Much of our discussion has been on the ill effects of COVID-19 on vascular dysfunction, leading to the endothelial injury and dysfunction. Endothelial injury may lead to altered arachidonic acid (AA) metabolism, leading to an imbalance in vasoactive metabolites of platelets (thromboxanes) and vessel wall endothelial cells (prostacyclins). Such an alteration in the vasoactive metabolites of AA, may lead to a prothrombotic state. In addition to vasoactive metabolites of AA, endothelium derived nitric oxide (NO), has important antithrombogenic properties. Nitric oxide enhances vasodilation, inhibits platelet activation, inhibits leukocyte migration, inhibits smooth muscle proliferation, inhibits expression of adhesion molecules and serves as an antioxidant. In view of these observations, any damage to the endothelium or apoptosis of these cells, alters many cellular signaling mechanisms, as well as exposes extracellular components, which

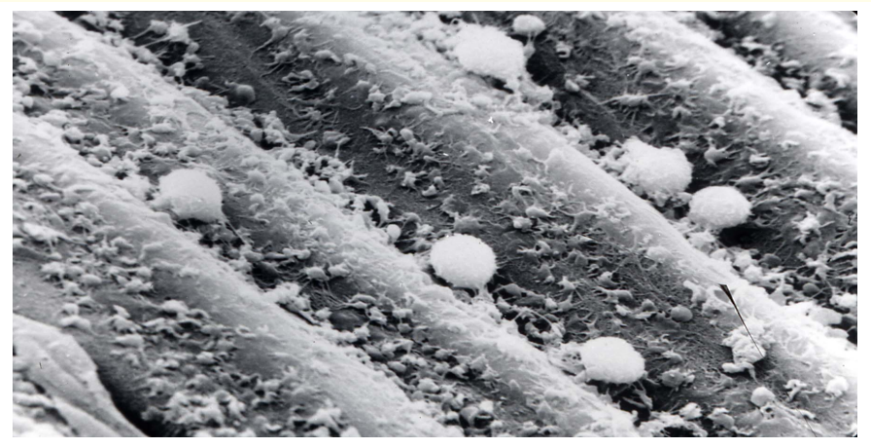

Figure 5: *Platelet interaction and activation on a dysfunctional endothelium. (Courtesy: Prof (Late) James G. White).*

activate circulating platelets. Either way, damaged or dysfunctional endothelium, activates circulating blood platelets which become sticky, change shape, express adhesion molecules and adhere to the dysfunctional vascular endothelium (Figure 5). In this review, we have not discussed the role of chronic inflammation related long COVID. Post-acute COVID syndrome is an ongoing inflammatory state following SARS-CoV-2 infection. This would be the topic of a separate review.

While discussing COVID-19 pandemic, it is important remember the role of the press, academics and the social media. In less than five months more than 15,000 publications appeared and exceeded 80,000 by the end of 2020. The need to compile available scientific knowledge was so huge, Christian Hoffman and associates presented daily Top COVID-19 papers from the major medical and scientific journals (*NEJM, Lancet, JAMA, Ann Intern Med, Nature, Science, Cell* etc.) (https://covidreference.com/top-papers-by-topic). On 7 January 2022, 21 months after the first Covid Reference (CR) edition and after 647 daily updates, they decided to stop working on CR [69]. What is out of the ordinary when considering COVID publications is, that a team of patients formed the Patient-Led Research Collaborative and conducted a first of a kind research on long COVID [70]. The authors of this report call for action: "The acknowledgment of long COVID as an illness, an accurate estimate of the presence of long Covid, publicly available basic symptom management, care and research not be limited to those with positive polymerase chain reaction and antibody tests and aggressive research and investigation into the pathogenesis of symptoms". Many professional societies, regulatory agencies, newspapers and support groups have published their own guides, COVID resource references and handbooks [71].

Prevention strategies for long COVID

In the absence of a cure for coronavirus disease, we have left with no better choices than, to develop robust prevention strategies. Public health experts recommend, wearing masks, observing social distance when in public places, washing hand frequently with soap, avoid places where people congregate or crowded places, follow travel safety guidelines, get your flu shots and COVID vaccinations and seek routine medical care. Jonathan Grein, Director of Hospital Epidemiology, Cedar's Sinai, says: "We are not going to rid of COVID-19, and so continues, the furious hunt for new ways to save lives, manage the disease and stop transmission of the virus". The most eagerly anticipated antiviral drugs are oral antivirals. Pfizer (Plaxovid) and Merck (Molnupiravir) have developed antivirals and they are currently approved, for emergency use to treat COVID-19 positive patients. National Institutes of Health (NIH) researchers have isolated a set of promising, tiny antibodies, or 'nanoantibodies' (CoVnb-112) against SARS-CoV-2, that were produced by a llama named Cornac. These nanoparticles, prevent infections and detect virus, by grabbing hold of SARS-CoV-2 spike proteins. These nanoantibodies, seem to work equally well in either liquid or aerosol suspensions, suggesting it could remain effective after inhalation. Researchers at the Catholic University of Louvain, Belgium, reported that they have managed to identify the key, that allows the COVID-19 virus to attack cells. This has sparked hope, that an aerosol antiviral therapy can be developed, that would eradicate the virus, in the case of an infection or a high-risk contact [67]. SARS-CoV-2 preferentially binds to sialic acid (SA) residues. The researchers have demonstrated that this virus specifically binds to 9-0-acetylated-SA and based on their observations, they have developed novel blocking molecules, with enhanced affinity to a multivalent effect.

At the time of this writing, we are in the third year of coronavirus pandemic and we are not sure how long this will last, or whether much severe variants would evolve, or it will just become a lingering endemic or vanish like some other earlier variants did. Omicron variant in South Africa so far has shown, that it is much less severe than the earlier variants. Like other variants, BA.4 and BA.5 appear to be significantly more transmissible, than previously identified variants. People have reached a point of exhaustion, with increased anxiety and continued stress. In addition, with no mask mandate in most of the places, it is now left to the individuals as to how they protect themselves from the virus. The data clearly suggests that one-way masking is still effective, but misinformation and politicization has polarized many people, to oppose any kind of masking. In view of the declining protection against systemic symptomatic infections, additional doses of mRNA vaccine, have been recommended for high-risk individuals. Despite the robust protection offered by vaccines, against the earlier variants Alpha, Beta and Delta, the emerging data suggests, limited protection against Omicron. Questions are many and answers very few, misinformation is abundant on the social media and large number of people remain unvaccinated and do not

care to take any precautions. Which brings us to the important Question, COVID-19 in 2022, The beginning of the END or the End of the Beginning [68]. Then what about the long COVID?

More than 100 new COVID vaccines are in clinical development, including shots that work differently, than the currently approved vaccines. Inhaled vaccines that exist for flu, are designed to train memory cells in the nose to create antibodies that detect and attack invading viruses. In a guest essay titled "The Answer to the Coronavirus May be Up the Nose" in The New York Times of May 16, 2022, Akiko Iwasaki, a professor of Immunology at the Yale School of Medicine writes that, "By catching viruses at the right site of infection, antibodies induced by nasal vaccines can give the body a head start, at combating the virus before it causes symptoms". They have demonstrated in animal studies, that by spraying the spike proteins to the host's nose, they could prevent the infection of the virus. The potential immunological and public health benefits of nasal spray vaccines are worth focusing on now, and for years to come.

Conclusion

Coronavirus-2019 (SARS-CoV-2), a novel respiratory virus, which emerged from patients suffering from pneumonia in Wuhan, China, in December of 2019, responsible for coronavirus disease (Covid-19), has caused unprecedented healthcare crisis worldwide. According to the Johns Hopkins covid tracker, globally, 532 million cases have been reported with 6.3 million deaths. In the USA alone, 8 million individuals had COVID-19, with more than a million deaths. The Alpha variant, which emerged from Wuhan, China, has evolved over the time, to a more transmissible Beta, Delta and Omicron strains. Currently, the Omicron variant is taking over in most of the countries. The fifth viral surge is emerging, with no sign of an end for these waves of new infections. Public health experts predict that the COVID-19 in one form or the other, is going to stay with us, for quite some time to come. Some people who have been infected with virus, that causes COVID-19, can experience long-term effects of their infection, known as post COVID conditions, or long COVID. Many long COVID or 'long-haulers' suffer from COVID symptoms even two years after initial infection. National Institutes of Health, USA, has launched a new initiative to study "long COVID". SARS-CoV-2 virus gains entry to the host cells through ACE2 receptor, which is found on most of the tissues. Since it is abundant on the vascular endothelium, the virus will get easy access to all the tissues and organs of the human body. We and others feel that damage to the vascular endothelium, may very well be the leading cause for long COVID. In an earlier article in this journal, we discussed the role of metabolic diseases such as hypertension, obesity, diabetes and vascular diseases in promoting the severity of the coronavirus disease. In this overview, we have expanded our discussions to include the emerging post-acute coronavirus disease sequelae of symptoms which includes, long COVID.

The COVID-19 pandemic is not over, social, health and economic losses continue to grow. It is now quite evident that COVID-19 will be with us for the long-term. International Monetary Fund on April 5, 2022, published their Working Papers, which included a 'Global Strategy to Manage the Long-Term Risks of COVID-19. They suggested four strategies: 1. First, we need to achieve equitable access beyond vaccines, to encompass a comprehensive prevention strategy (CPS). Second, we must monitor the evolving virus, dynamically upgrade the genomic profile, sequence newer variants, their transmissibility and severity. Third, we must transition from the acute phase to a sustainable strategy toward COVID-19, balanced and integrated strategies, including other health and social priorities. Fourth, we need a unified risk-mitigation approach, to future infectious disease threats beyond COVID-19. As Joshua Lederberg has described, it is going to be a continuing war -"Man against the microbes".

The Health Foundation's Covid-19 impact team, has reviewed emerging evidence on long Covid

The World Health Organization has established, 'The Independent Panel' and has come out with a comprehensive report: "COVID-19 Make it the "Last Pandemic". The Independent Panel's recommendation to make the COVID-19 the last public health pandemic, includes following recommendations: 1. Elevate and maintain political commitment to pandemic prevention, preparedness and response over time, in the service of a vision of a world without pandemics. 2. Monitor progress towards the goals and targets set by WHO, as well as against potentially new scientific evidence and international legal frameworks. 3. Draw the world's attention to gaps in pandemic

preparedness and response through high level advocacy and reporting to the UN General Assembly, the World Health Assembly and the IMF board. 4. Contribute to the mobilization of funding and oversee the allocation of resources by the International Pandemic Financing Facility. 5. Hold actors accountable including through peer recognition and pressure as well as the publishing of analytical progress status reports.

Despite these and other recommendations, by various global organizations, many COVID Long-haulers express their frustrations, which indeed are real, "When medical diagnoses miss the mark and their families don't believe in them and their COVID symptoms, some COVID long-haulers turn online groups for help". Shruti Mehta, a professor in the department of epidemiology at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, said that physicians are still learning how to cope with long COVID as patients experience wide variety of symptoms and do not yet know, what the likelihood or time frame for recovery is. She strongly believes online support communities, as an important part of recovery. She further elaborates, "We need more of what has already started to happen from support groups, to specialized care centers. And we urgently need research, to better understand how common long COVID is, who is at risks, why they are at risk and what the course of the disease is?" According to an article by Erics Carbajal and Cailey Gleeson in Hospital Review dated February 9th, 2022, 66 hospitals and health systems have launched post-COVID-19 clinics https://www.beckershospitalreview.com/patient-safety-outcomes/13-hospitals-health-systems-that-have-launched-post-covid-19-clinics.html.

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Volume 5 Issue 8 August 2022