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RESEARCH ARTICLE
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A Holistic Review of COVID-19: Epidemiology, Pathogenesis, Diagnostic Innovations, and Future Treatment Approaches

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Abstract

COVID-19 is still a threat to global health since SARS-CoV-2 mutation and ongoing transmission across the globe. As Covid-19 moves from a pandemic response to an endemic, more research needs to be done in how to manage and develop response strategies for subsequent strains. The present paper offers an extensive literature review regarding the current state of knowledge about COVID-19 epidemiology and pathogenesis, with a focus on the new emerging strains of SARS-CoV-2 and the increasing trend of long COVID, or post-acute sequelae, after infection. Finally, the paper reviews the progress in diagnostics and detection, multiple RT-PCR, which is used to detect multiple genes in SARS-CoV-2 to increase the sensitivity and specificity of the test. Another form of antigen tests, the ELISA-based, used for identification of viral proteins in clinical samples, are also being considered for detection of COVID-19, as easy, quick, and inexpensive diagnostic option, especially in LMICs(low- and middle-income countries). The paper also reviews the present management measures and SARS-CoV-2 vaccine development. These range from discovering new antiviral agents, use of Monoclonal antibodies, modifications needed in vaccine composition as a result of the current emerging forms of the SARS-CoV-2 virus. Booster doses have been of great importance when it comes to continuing protection against variants that show immune escape like Omicron. In addition, more advanced cell therapies, including T-cell and stem cell therapies are in consideration as potential treatments of worse cases of COVID-19 in immunocompromised patients. Due to further mutation and unpredictable transmission patterns of the virus, the development and the actual rollout of vaccines, therapies, and diagnostics are needed to address the consequences of COVID-19 and any descendants. Therefore, the present study supports the hypothesis that the further advance of SARS-CoV-2 warrants a lasting qualitative continuation of investigation and the updating of data pertinent to COVID-19 to enhance the global control of the disease and lessening of infected populations' morbidity and mortality.

Keywords: SARS-CoV-2, SARS-CoV-2 variants, Diagnostic advances, post-pandemic, review

Introduction

Since the peak of the COVID-19 pandemic, there has been a noticeable decline in SARS-CoV-2 infectivity and related mortality rates. This progress is largely due to public health interventions, medical advancements, and the widespread distribution of vaccines. However, the pandemic is far from over. The emergence of new SARS-CoV-2 variants, such as KP.2, KP.3, and LB.1, presents a serious

threat to global health (CDC, 2020). These variants often carry mutations that could increase their transmissibility, enhance their ability to evade immunity, or potentially reduce the effectiveness of existing treatments and vaccine (Chung *et al*., 2024).

Additionally, a growing number of individuals are experiencing long-term health issues following recovery from the acute phase of the disease, a condition now commonly referred to as 'long COVID.' Symptoms of long COVID, such as persistent fatigue, respiratory difficulties, and neurological impairments, underline the extended impact of the virus on individuals and healthcare systems worldwide.

While early efforts in developing diagnostic tools, treatments, and vaccines were pivotal in combating the initial waves of the pandemic, the continued evolution of the virus challenges the efficacy of these measures. This highlights the need for ongoing innovation and adaptability.

This paper offers a detailed examination of COVID-19's progression, including advancements in diagnostics, detection techniques, and treatment approaches. It emphasizes the importance of continuous research and updated strategies to mitigate the risks posed by new variants and to better manage the current endemic situation. A vigilant and proactive response remains essential in addressing the long-term challenges of COVID-19 and safeguarding public health.

1. Epidemiology

a) Coronavirus

COVID-19 is an illness resulting from the SARS-CoV-2 virus which is a positive-sense single-stranded RNA virus (Tsang *et al.*, 2020). Coronaviruses are classified into four primary genera: Alpha (α), Beta (β), Gamma (γ), and Delta (δ) all in lower case letters. Of all these, Alpha and Beta are of clinical importance since they are known to infect humans, while Gamma and Delta mostly infect birds. The experts began to think that Alpha and Beta coronaviruses jumped directly from bats, while Gamma and Delta coronaviruses developed from birds (Woo *et al.*, 2009).

Human coronavirus was first discovered in the mid-1960s with strains of the virus discovered later. To date, seven types of coronaviruses have been identified as having the ability to infect people. These include four common human coronaviruses: Four subtypes recognized include; the Alpha-coronavirus subgenus 229E and NL63 and the Beta-coronavirus subgenus OC43 and HKU1. These seasonally occurring common coronaviruses usually present upper respiratory tract infections, and may present as flu-like symptoms (Ogimi *et al.*, 2020).

However, there are three human coronaviruses that have a reputation for causing dangerous respiratory diseases. Due to scientific classification, they are the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and SARS-CoV-2. All three are of the Beta genus. Among these pathogens, SARS-CoV-2, which causes COVID-19, seem to be particularly prominent owing to its ability to spread rapidly, high R0, and ability to cause severe symptoms and death.

These aspects of coronavirus identification and pathogenicity offer core information on the animal-to-human transmission of this virus, its ability to spread and the different clinical presentation of the disease that is associated with it. Such knowledge is paramount in developing ways of managing, treating and preventing coronavirus associated diseases (Peiris at al., 2003).

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b) **Origin of COVID-19**

The COVID-19 can be traced from the last quarter of December 2019 when a number of pneumonia cases of unknown causes surfaced in Wuhan city, Hubei province, People's Republic of China. The first few cases were reported to be associated with the Huanan Wet Seafood Wholesale Market, which sale live animals such as bats and snakes and thus pointed to possibility of zoonotic transmission. First, the outbreak was believed to be caused by viral pneumonia and further studies pointed out that the culprit is the novel coronavirus, now known as SARS-CoV-2 because of its genetic and phylogenetic relationship with SARS-CoV which caused the 2002/2003 SARS epidemic (Ludwig et al 2020). When studying SARS-CoV-2, researchers assumed that it also spread from animals, and the contact with wildlife or consumption of animals could be the ways of transmission. This prompted the Chinese authorities to close wet markets considered unsanitary undertaking that constituted an initial measure to curb the epidemic (Horton *et al.*, 2020). However, the virus remained widespread and went from one being contained in specific geographical regions to being a worldwide pandemic.

COVID-19 cases started to increase earlier in the year 2020 globally thus being declared by the World Health Organization (WHO) a global health emergency. Thus, on March, 11, 2020 the WHO officially defined COVID-19 as a pandemic, and it became an important step generating various attempts to contain a virus presence and impact all over the world.

The Figure 1 shows the world's ten most affected countries by COVID - 19 up to 17 November 2024 based on the information provided to the WHO. In the United States there are 103 million cases while in China there are 99.4 million cases. India is placed third to report 45 million cases. He explained that other countries with a high number of cases include France 39 million, Germany thirty eight point four million, Brazil thirty seven point five million, Korea thirty four point six million, Japan thirty three point eight million, Italy twenty six point eight million and United Kingdom and Northern Ireland twenty five million. These countries subsequently summarize the situation with the COVID-19 and its impact on the countries worldwide and it is rather negative (WHO, 2024).

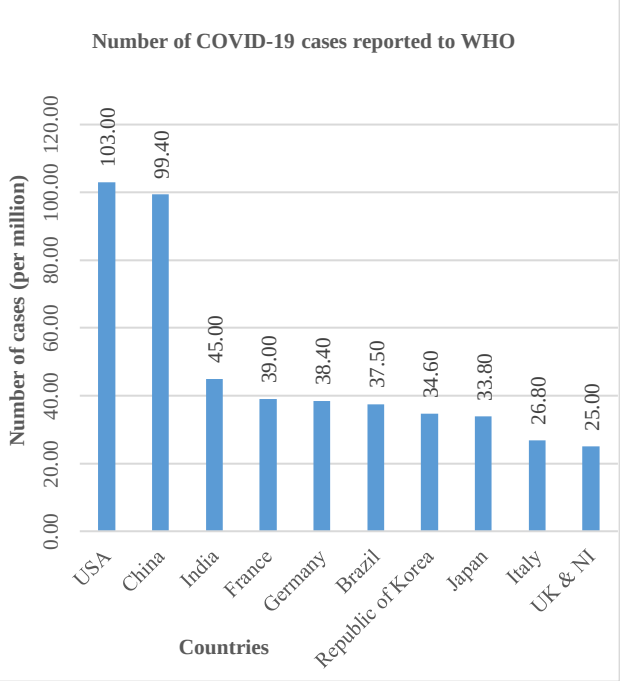

Figure (1): The top 10 countries having the highest number of cases reported to the WHO (cumulative total), as of 17 November 2024

c) **Routes of Transmission**

SARS-CoV-2, the virus responsible for COVID-19, is primarily transmitted through three major modes: droplets, aerosols, and large droplets that may result from direct or indirect contact. Keeping in view the role during pandemic, each mode contributes much in the transmission of the virus (Belser *et al.*, 2013).

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In contact transmission, direct as well as indirect modes are involved. Direct contact transference is informed through the use of contact with body parts and mainly the ocular, auricular or buccal mucous membranes. This was especially quite evident among the health care givers during the pandemic to mention, because they were exposed to the diseases because of contact with their clients. Indirect contact transmission occurs in contact with viruses when an object with infected body fluids is considered as fomites. A person gets infected when he or she comes into contact with the virus on the surface and then touches his or her mucous membranes (Lu and Shi, 2020).

Aerosol transmission refers to a method by which small particles filled with the virus are dispersed through the air. These particles result from actions such as coughing, sneezing, speaking, or even breathing and can remain in the air for longer hours in shut environments, hence posing a great spread of the virus. They found that SARS-CoV-2 can survive in the aerosol form for up to three hours. Correct the chimneying and the air conditioning with good quality filters will help in minimizing the chances of the long range aerosols (Chen *et al.*, 2021).

Droplet transmission takes place through those large droplets that are produced when an individual coughs or sneezes. These droplets usually are emitted short distances and can infect those nearby when one inhales or swallows such droplets. A physical distancing of at least 1.5 meters has been proposed as suitable measure to prevent transmission through this mode. Knowledge of these modes has been valuable in formulating measures to constrain COVID-19 infections within communities (Chen at al., 2021).

d) **SARS-CoV-2 Variant**

The new coronavirus SARS-CoV-2 is an RNA virus (Denison *et al.*, 2011), which produces a relatively high rate of mutations due to mistakes during replication. Hence, the character produces changes now and then which include the appearance of new strains of the virus. Such last ones are capable of rising the virus's infectivity, transmissibility or ability to evade an immune system. In Shuaibi (2021), the author described five primary types of Covid-19 major variants of concern between 2020 -2022 with unique qualities and consequences.

There are various examples, including the Delta variant, which manifested a rather significant rising in the capacity to overcome neutralizing antibodies (Mlcochova *et al.*, 2021). These antibodies are normally found in those who previously had the COVID illness or those who received the vaccine. This led to increased infections, this time even affecting partially immune groups – this was a new challenge in controlling Covid-19 as the virus persists to mutate.

These mutations prove the need to study these new strains because they inform future course of action for public health interventions as well as the development of vaccines. It also places a lot of importance on the need to work together with other countries in genomic sequencing and research with the view of counter adapting to the virus. Learning how these mutations affect the virus's functions remains central when combating COVID-19 to date.

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WHO Label	Pango Lineage	First Outbreak	Number of Cases Worldwide
Alpha	B.1.1.7	United Kingdom	11,41,525
Beta	B.1.351	South Africa	35,651
Gamma	P.1	Brazil	73,495
Delta	B.1.617.2	India	2,88,894
Omicron	B.1.1.529	South Africa	1,895*

Table (1): Five WHO-Labelled Parent Lineage Variants of Concern During 2020–2022 (outbreak.info, 2024)

As new subvariants of SARS-CoV-2, including XBB.1, BA.2.86.1, and JN.1, appear on the scene, COVID-19 has become less deadly than initially feared (Planas *et al.*, 2024). Vaccination has been instrumental in lowering not just the intensity but also the death toll arising from COVID 19. Some through vaccination and others by experiencing the disease, such measures have phased out mortality rates in a step-down formation over the years. Vaccination for instance has been seen to reduce the death toll which has been declining since the first raise of the pandemic (Haider *et al.*, 2023). In addition, the broad variety of diagnostic techniques has advanced and new therapeutic approaches developed to contain the virus and lessen the prevalence of the disease.

Ever since May 5, 2023, The WHO announced that COVID-19 no longer qualifies as Public Health Emergency of International Concern (WHO, 2024). This shift was to open a new phase of long-term management and containment of covid-19. Moreover, due to the ongoing mutations, new types of SARS-CoV-2 virus appear annually. By June 5, 2024, three variants of interest (VOI) has been recognized globally and they are EG.5, BA.2.86 and JN.1 and all the variants originated from the Omicron lineage (B.1.1.529). No Omicron variants were defined as VOCs in 2023 and 2024 as compared to the period 2020–2022, suggesting a reduced capacity of VOCs to cause significant public health interventions (WHO, 2023). There are mutations that change the pathogenicity of the virus, its ability to invade new susceptible populations and its effect on vaccines, and can propagate across countries (WHO, 2023). Unlike previous VOCs, most Omicron sub-lineages primarily infect the upper respiratory tract, not the lower respiratory tract. Pulmonary diseases especially LRI are generally severe because they may cause pneumonia or affect lung function (Rodriguez *et al.*, 2016).

The new Omicron variants expected to be dominant in America are KP.2, KP.3, and LB.1, all derived from JN.1 (CDC, 2020). These variants are also under observation, because the new mutations may lead to changes in either the severity of the disease, the rate of transmission, or the effectiveness of vaccines. The CDC also proving its proportionate conclusions that by June 2024, at least seventy percent of the total COVID-19 patients will correspond to KP.2, KP.3, and LB.1. Sequence comparison of these variations suggests that KP.2 and KP.3 have evolved the new substitution in the spike protein, LB.1 and KP2.3, have substituted mutated and deleted thirty first position of the spike protein (Kaku *et al.*, 2024). Work employing Lentivirus-based pseudo-virus assays and neutralization tests reveal that these mutations improve

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immunodominance and, in certain instances, promotion of pathogenicity. Interestingly, LB.1 and KP.2.3 that has resulted from this lost segment exhibited increased ability to evade the immune response and therefore Still, these variants may pose a significant threat to efforts to manage the current pandemic.

e) SARS-CoV-2 Updated Infection and Mortality Trends in Different Regions

The new COVID-19 cases reported to the WHO from February to November 2024 also depict a shift in the regions obviously due to changes in pandemics behaviour as well as course and measures undertaken to restrict it in a particular region (WHO, 2024). In Africa, actual reported cases of COVID- 19 reduced from 501 cases recorded on February 4, 2021, to 78 cases recorded on 3 rd of November, 2021, although there are slight variations in the confirming trend (WHO, 2024). The epidemic cases in the Europe was also sawed and saw surge, in February, saw 51,700 then in may saw 16,500 then again rose and in October saw highest 75,400 then in November saw 37,900. The Americas region dipped significantly in the first months – from 21,700 reported in February to 2,100 in May, while the new cases stagnated between 1,200 and 2,800 in the following months. South-East Asia was also low with its record of the number of cases, beginning with 2,700 in February, creeping down to 518 in October then rising slightly in November to 622. The Western Pacific region was also generally downward with cases falling from 23 400 in February to 1500 by November. These trends give a picture of the various trends arising from different regions' vaccination success, measures employed, and the new strains that arise. Higher rates in Europe over the past month demonstrated that focus on new outbreaks can be regional, whereas consistent reduction of daily cases in Africa and the Western Pacific indicates successful suppression measures can be taken. It therefore becomes important to understand these patterns in order to guide the on-going pandemic management and the specific response in a particular region (WHO, 2024).

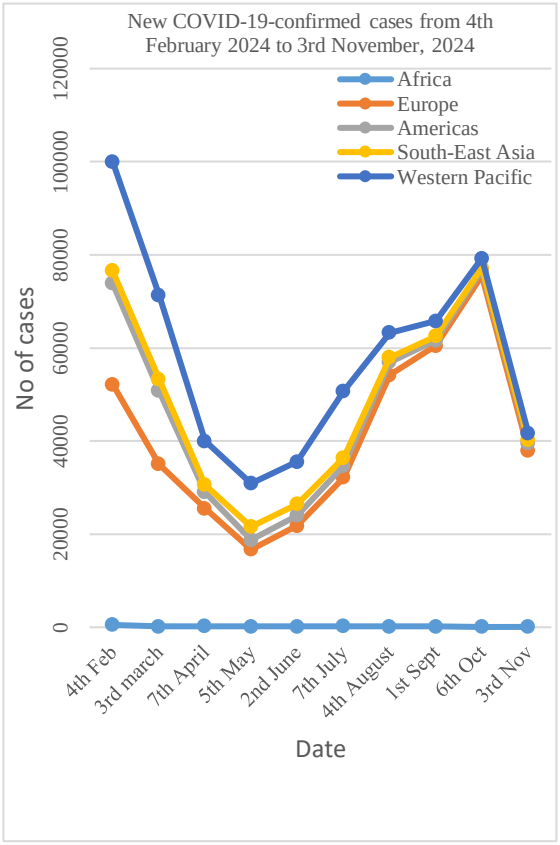

Figure (2): New COVID-19-confirmed cases from 4th February 2024 to 3rd November, 2024

SARS-CoV-2 Updated Mortality Trends

Daily mortality of SARS-CoV-2 from February to November 2024 WHO report demonstrates the geographical differences of the pandemic (WHO, 2024). It is important to mention that the fact reported deaths in Africa were low and constant all year long starting with two in February and went down to zero in September with better control of the disease and control measures.

In Europe, drastic change in the death rate was recorded from 448 deaths in February and 82 in May. This was however succeeded by a rise to 277 in the month of

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August and despite dipping to September, subsequent months data showed more than 230 deaths signifying the persistent threat of new variants and possible seasonality.

The region where the worst hit by initial fatalities was the America that showed 1,900 deaths in February but a decline to 358 in June. But it had a spike in August with 1,000 deaths, and again a steep drop again to 575 in November. Such variation persists because of SARS-CoV-2 in the region, even with increased public strategies regarding health.

In South-East Asia the reported deaths were pegged throughout, reducing gradually from 30 in February to 2 in November as evidence of regional positive pandemic management measures. Likewise in the Western Pacific region, there were steady decrease up to 11 deaths in October with a surge to 14 in November but generally, lowest mortality (WHO, 2024).

These patterns show differential mortality trends by region depending on the vaccination levels, available health care capacity and containment strategies in relation to new variants. The global mortality rates have gradually reduced but occasional milestones in some area reinforce the need for constant surveillance and effective intervention measures program.

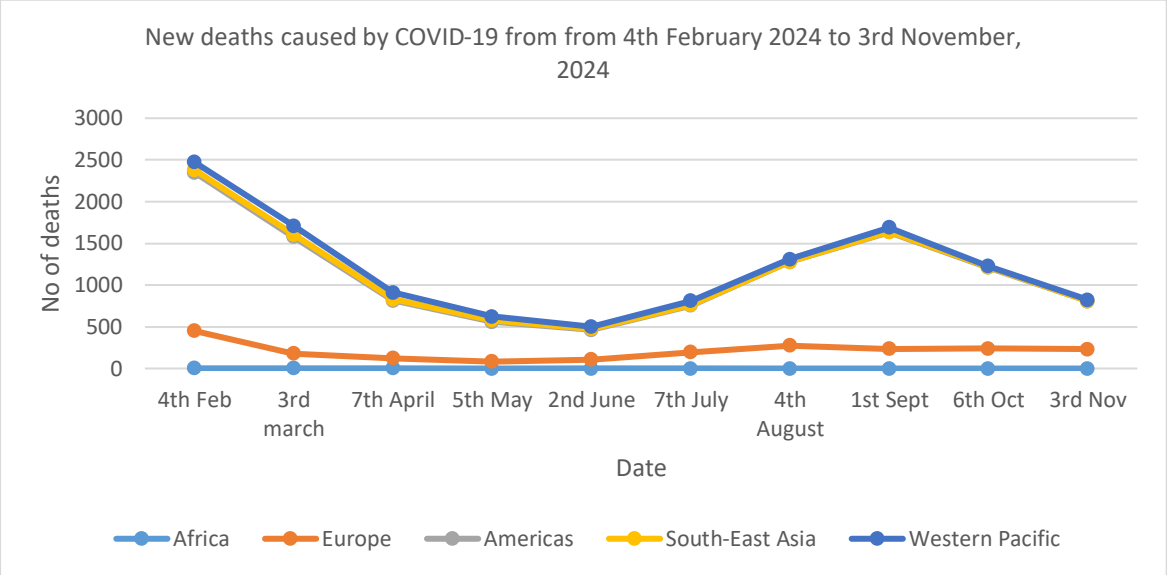

Figure (3): New deaths caused by COVID-19 from 4th February 2024 to 3rd November, 2024.

f) SARS-CoV-2 New Transmission Pattern

The practice is to measure wastewater viral activity in India as it helps identify new infectious diseases such as COVID 19. The move helps health authorities to understand how the SARS-CoV-2 virus is spreading in communities. Figure 4 presents the national trend of SARS-CoV-2 viral precursors in wastewater of Ahmedabad, India along with the active COVID-19 cases. Two critical metrics are tracked: The two lines on the graph represent cases among active patients (blue line above) and RNA copy levels in the wastewater (red line below). Higher peaks in active case counts can be observed to have a strong positive correlation with rises in wavelengths of RNA in wastewaters proving the existence of a relationship between covid 19 viral genetic material in wastewaters and the number of confirmed cases in the

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community. This concern is exemplified by active cases of contagious diseases, which reached a peak in September 2022 and fell afterwards, compared to the over 125000 cases. Outburst two was smaller than the first one and occurred in the last week of July 2022, while another peak in RNA activity was identified in April 2023. Eventually, numerical values of active cases and RNA copy levels decreased, with low viral activity in the course of the studied period by mid 2024. These trends underscore why surveillance in sewage is an effective, nonintrusive, and low-cost solution to track emerging waves of COVID-19. These two trends are in congruence to the current lack of intense pandemic due to which both of the parameters have declined and thus corroborating the usefulness of WSM specifically in guiding the public health measures (CDC, 2020; WHO, 2024).

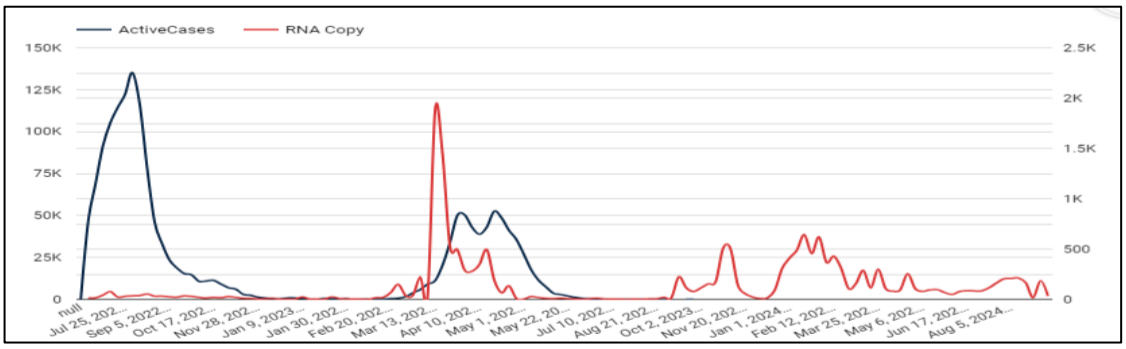

Figure-4: National trends of SARS-CoV-2 viral activity levels in wastewater from the India, Ahmedabad (accessed on 4th December, 2024).

g) SARS-CoV-2 Reinfection Rate

Infection with the same virus had been a worrying factor, even more so with the identification of omicron variants, which are highly infectious and can evade the immune system (Pulliam et al, 2022). Although the total reinfection probability with different variants of the virus is around 0.94 %, it was lower, at a level below 0.6 % until the discovery of Omicron (25). Currently, the reinfection rate has increased to 4.1% that comes from Omicron's multiple mutations particularly in the spike protein that led to the lowered neutralising antibodies. Some of these include mutation of the virus, and decline in immunity after sometime, and the fact that the virus can overcome defences from natural infection and even the vaccines. While vaccination, and more specifically with booster doses, and hybrid immunity help one a degree, still, they cannot shield a person from reinfection. Higher reinfection rates with Omicron mean that there is a question of public health, having enough hospital beds, adapting testing and isolation measures. All these challenges point to the need for variant-specific vaccines and constant assessment of virus evolution in order to reduce the effects of reinfection (Chen *et al.*, 2024).

2. Pathogenesis

SARS-CoV-2, the virus responsible for COVID-19, is composed of four structural proteins: cleavage and polyprotein precursors, spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (Akkiz *et al.*, 2021). Spike protein that is necessary for entering the host cells is composed of two major structural domains, S1 and S2. The S1 domain of the spike protein is responsible for the receptor binding and S2 domain is with the

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membrane fusion of viral with host cells. In S1Domain, there is a large variation in the Receptor Binding Domain (RBD) that further binds with the host cell receptor. Because of the existence of similarity between SARS-CoV-2 and SARS-CoV, researchers were able to confirm that SARS-CoV-2 requires the receptor, angiotensin-converting enzyme 2 (ACE2) for host cell entry (Jiang *et al.,* 2020). TMPRSS2 helps in the cleavage of the spike protein to enhance membrane fusion and viral entry into the host cells. MERS-CoV prefers ACE2 and these have been reported in varying density in organs such as the lung, hear, kidneys and intestines etc and the region where the virus binds to ACE2 determines the symptoms manifested such as lung inflammation or myocarditis (Wu *et al.,* 2020).

The initial response of the whole organism to combat SARS-CoV-2 is inflammation. Viral entry is sensed by pattern recognition receptors, PRR, detecting pathogen-associated molecular pattern, PAMPs and leads to the release of pro-inflammatory cytokines such as IL-6 and chemokines such as CCL2. IFN-1 is an important element in antiviral activity: enzymes participate in the degradation of viral nucleic acids and proteins and perform the release of viruses. Still, through its non-structural proteins that interfere with signalling pathways while degrading mRNA for IFN-1, SARS-CoV-2 can suppress this response (Chen *et al.,* 2020).

One of the grave immunopathological reactions that occur in the course of SARS-CoV-2 disease include the cytokine storm characterised by elevated levels of IL-6. This is a common with the Acutely Ill clients and if not well managed; it can result in complications such as tissue damage and organs like the heart, liver and kidneys may fail. Macrophages involvement in cytokine storms is suggested by the direct binding of the viral spike protein to ACE 2 receptors in the cells (Deng *et al.,* 2017).

Regenerative immune responses to SARS-CoV-2 consist of antibody synthesis and T-cell dependent cytolysis. CD4+ lymphocytes are involved in the humoral response and produce IgM, IgG and IgA antibodies. The neutralizing antibodies can also specifically target the S protein or RBD without entry into cells apart from inhibiting viral entry, it can also induce ADCV and ADP. CD8+ lymphocytes are engaged in the destruction of the infected tissues thus shed light on the importance of adaptive immune responses in the regulation of SARS-CoV-2 infection (Channappanavar et al 2017; Zohar *et al.,* 2020).

i.Infection Stage of SARS-CoV-2

SARS-CoV-2 infection has been described in three phases according to the severity of COVID-19 it causes. First stage is the incubation period which starts right from a time an individual contracts the virus and the virus multiplies within the host. In this phase, people are usually asymptomatic and there is no clinical manifestation. The second stage is called the dissemination stage after onset of acute pneumonia and typical manifestations of the disease, such as cough and fever (Vetter *et al*., 2020). In patients with chronic diseases, such as diabetes or cardiovascular disease, this stage can be accompanied by the development of hypoxia. In case of non-recovery, the disease goes through to the advanced third stage that is dominated by systemic hyper inflammation. This stage can cause multiple organ dysfunction particularly to the kidneys, liver and G.I tract (Mehta *et al.,* 2020; Gupta *et al.,* 2020).

Consideration of comorbidity in COVID-19 patients was attributed to higher death incidences. Co-morbidity means the

pre-existence of another disease apart from the main disease that is diagnosed in a patient. Symptoms of COVID-19 include fever, cough, sore throat, tiredness, chest pain or pressure, loss of smell or taste, difficulty breathing and confusion, muscle or joint pain, skin changes, high blood pressure, kidney problems, and diabetes (Singh *et al.*, 2021). They also greatly raise the risk for severe disease and mortality, because they increase ACE2 expression, thereby vulnerability and disease severity with SARS-CoV-2 infection. For patients with multiple comorbidity, or multimorbidity, are at even higher risk, with mortality rates that are double those of patients without the conditions (Agrawal *et al.*, 2021).

ii.Long COVID

i.Definition of Long COVID

Long COVID also called post-acute sequelae of SARS-CoV-2 infection (PASC) is a condition of ongoing symptoms, new symptoms, or worsening symptoms occurring four weeks or later following the initial phase of COVID-19 (Carfì *et al.*, 2020). These symptoms may persist for anything from weeks and months to years or even indefinitely and recipients continue to suffer from organ dysfunction and decreased quality of life. Long COVID refers to symptomatic COVID-19 within the 4–12 weeks' window and beyond the initial 12 weeks. Some present signs include; dizziness, weakness, general malaise, confusion, chest pain, joint pain and concentration difficulties. Long COVID symptoms can persist irrespective of the form and severity of the primary infection phase and is not limited to specific age demography (Greenhalgh *et al.*, 2020).

ii.Epidemiology of Long COVID

Diagnosis of long COVID also presents a problem due to the fact that it cannot be based on one's viral status because most of the patients who suffer from this condition test negative when examined with a PCR test (van et al 2019). Recovery time also differs with each person depending on the first attack and response to the disease. For the symptoms were never present, or at least starting from this moment, tests for COVID-19 were not carried out, diagnosis is much more difficult. Long COVID is thought to affect 10–30% of individuals with mild symptoms of the disease and 50–70% of those with severe symptoms. The protected people look completely different: out of 100 immunized patients, only 10-12 get long COVID (Ayoubkhani *et al.*, 2022).

Long COVID is characterized by a wide range of symptoms which affect the respiratory, gastrointestinal, neurological, musculoskeletal, hematopoietic, and endocrine systems. Some may experience one or more of the signs that are, tiredness, headache, and depression. Furthermore, long COVID has overlapping characteristics with post-acute sequelae of SARS-CoV-2 infection (PASC), including ME/CFS, during and after exertion (Singh *et al.*, 2022).

iii.Pathogenesis of Long COVID

This is why fatigue and hypoxia in patients with long COVID can be explained by innate SARS-CoV-2-mediated hypercoagulation (Fogarty *et al.*, 2021). It sparks platelet and endothelial cell activation and causes clotting that leads to blockade of blood vessels and hence poor tissue oxygenation. The SARS-CoV-2 viral spike protein enlarges the inflammation signalling by activating platelets and enhancing the fibrinogen clumping resulting in micro-clots (Grobbelaar *et al.*, 2021). In case these micro-clots do not dissolve through fibrinolysis, hypoxia ensues, decaying tissue function.

Mitochondrial dysfunction is another reason people, experiencing long COVID symptoms, might be facing. There

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is a strong association between disease severity and impaired mitochondrial function in PBMCs of COVID-19 patients (Ajaz *et al.*, 2021). This impairment affects ATP generation which in turn affects cellular energy metabolism and as a result various symptoms seen in long COVID.

Neurological signs include loss of smell in patients with damage to the olfactory bulb or the olfactory mucosa. Using MRI, investigations have evidenced that acute COVID-19 leads to stern cell odontology, olfactory stem cells that are developed to accept ACE2 receptors (Vaira *et al.*, 2020). These stem cells become damaged and are unable to help regenerate the olfactory epithelium which leads to anosmia even after the infection has cleared. This reduced regenerative capability is the basis for the chronic loss of sensation that can be seen in some patients.

iv.Treatments for Long COVID

There is no universal cure for long COVID and the treatments depend on the symptoms presented by the patient and therefore should be done clinically. Treatment involves drug therapy, counselling, vocational rehabilitation and physiotherapy. The goal of treatment is to work with given symptoms and try to deal with the reasons for them (Davis *et al.*, 2023).

Preventative remains the most effective measure – cutting the likelihood of contracting long COVID symptoms by a highly significant extent if given prior to SARS CoV2 exposure. However, vaccination does not cure the already existing long COVID symptoms (Watanabe *et al.*, 2023). Various research has proved that early vaccination will reduce the chances of developing long COVID, especially in adults.

The diabetes type drug known as Metformin has also been seen to minimize the possibility of long COVID in patients diagnosed with COVID-19 and comorbidity of diabetes (Mccarthy *et al.*, 2023). Long COVID is still being researched, and many potential treatments for patients can be found at that institution's RECOVER trial (Mccarthy *et al.*, 2023). For instance, RECOVER-VITAL looks at the use of Paxlovid for long COVID, and RECOVER-NEURO is analyzing approaches for neurological manifestations, including online training and non-invasive brain stimulation. Other trials planned in the future include RECOVER-SLEEP for sleep disturbances, and RECOVER-AUTONOMIC for dysfunction of the autonomic nervous system (Zimmerman *et al.*, 2024).

Thus, long COVID continues to complicate what is already a burden to healthcare systems anywhere in the world. The following should be done in order to reduce the infections, hospitalizations, and long COVID cases which can help to ease this burden; Getting more people for booster doses especially for the new variants.

3. Diagnostic Methods

i.Nucleic Acid Amplification Test (NAAT)

The Nucleic Acid Amplification Test (NAAT), which detects viral RNA and has excellent sensitivity and specificity, is a key diagnostic tool for SARS-CoV-2 infection (Gao *et al.*, 2021; Ravindra *et al.*, 2021). These tests are essential for diagnosing acute COVID-19 and for tracking the existence of the virus in people who may have chronic COVID. RT-qPCR, multiplex RT-qPCR assays, RT-dPCR, and other cutting-edge technologies are important forms of NAATs (Wu *et al.*, 2020).

ii.RT-qPCR

The gold standard to detect SARS-CoV-2 infection is Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR),

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which has a high sensitivity and specificity (54). Through the use of reverse transcription (RT) of viral RNA into complementary DNA (cDNA) and real-time PCR amplification, SARS-CoV-2 RNA could be detected and evaluated. It performs most effectively in the very initial stages of infection, when the viral load is at its highest level, which allows prompt action to stop the virus's spread. Samples are first collected, usually from nasopharyngeal or oropharyngeal swabs, which usually have a higher viral load. After extracted RNA is reverse-transcribed to create cDNA, primers and probes that target particular SARS-CoV-2 genes, including the N (nucleocapsid), S (spike), E (envelope), and RdRp (RNA-dependent RNA polymerase) genes, are used to amplify the cDNA. Fluorescent probes enable for real-time measurement during amplification by releasing signals according to the amount of DNA produced. The cycle threshold (Ct) value that RT-qPCR yields helps determine the severity of the disease by reflecting the viral load. RT-qPCR is resource-intensive and depends on the stage of infection, and it may produce false negative results due to poor sample collection, low viral loads, or genetic alterations, despite its quick turnaround time and versatility. However, RT-qPCR continues to be the mainstay of SARS-CoV-2 diagnosis, and new developments are expanding its use in pandemic management (Akkiz *et al.*, 2021).

iii. Multiplex RT-qPCR Assays for Detecting SARS-CoV-2 and Other Respiratory Pathogens

SARS-CoV-2 and other respiratory pathogens can be identified in a single reaction by multiplex RT-qPCR tests, which are technically advanced diagnostics tools. This technique is particularly useful in differential of COVID-19 from other viral diseases such as flu, RSV or adenoviruses which often have similar symptoms. To identify certain genomic portions of SARS-CoV-2, N, E or S gene or any specific genes associated with the other infections, primers and probes are required. It is the detection of nucleotide sequences within several targets at once at the end of which in a single reaction tube, viral RNA isolated from a patient sample is transcribed into cDNA. Quantification and identification in real-time are possible due to the incorporation of fluorescent labelled dyes which emit different signals that are unique for the pathogen discovered. As a result of our study, it can be concluded that the advantages of multiplex RT-qPCR include the increased epidemiological activity, shorter time to diagnosis, wider possibilities of identifying co-infections, and efficiency. However, there are drawbacks associated with this method; assay design is complex, costs are higher and data interpretation becomes difficult when multiple infections are present. Nevertheless, multiplex RT-qPCR tests have been essential in the COVID-19 pandemic response as it may facilitate faster and accurate diagnosis of respiratory diseases and enhance the care of patients in areas that are afflicted by overbearing respiratory pathogen epidemics (Hashemi *et al.*, 2021).

iv. RT-dPCR (Reverse Transcription Digital Polymerase Chain Reaction)

SARS-CoV-2 RNA may be found and measured using RT-dPCR, a sophisticated and extremely sensitive molecular diagnostic method. By dividing the reaction into thousands of separate droplets or wells, RT-dPCR enables absolute quantification of viral RNA, in contrast to conventional RT-qPCR, which offers relative quantification. Each partition acts as a microreactor containing either zero or one template molecule of the target RNA. Following reverse transcription to cDNA and amplification through PCR,

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fluorescence signals are measured for each partition to determine whether the target RNA is present.

This digital strategy has a number of clear benefits. Particularly for samples with low viral loads or when the viral RNA is degraded, it offers remarkable sensitivity and accuracy. The method is very dependable for clinical diagnostics as it also reduces the impact of inhibitors found in patient samples. Additionally, RT-dPCR is less likely to be inconsistent, providing accurate data that are perfect for tracking the dynamics of viral load over time, especially in prolonged COVID cases, or for identifying leftover viral RNA after recovery (Suo *et al.*, 2020).

RT-dPCR has been used increasingly for SARS-CoV-2 research and diagnostic applications, such as determining vaccination response, discovering new variations, and assessing treatment efficacy. Its drawbacks, such as increased expenses, intricate procedures, and the requirement for specialist equipment, might prevent the technology from being widely used in standard diagnostic settings (Shafie *et al.*, 2023). For high-precision viral RNA quantification, RT-dPCR is a potent technology that offers substantial advantages in research and certain clinical applications, notwithstanding these difficulties.

v. Other Nucleic Acid Amplification Tests (NAATs)

In addition to RT-qPCR and RT-dPCR, several other NAAT colourgens have been designed for the identification of SARS-CoV-2 (FDA, 2024). These techniques aim at increasing the usability, modularity and productivity of diagnosis in various care and population health approaches.

A. Loop-Mediated Isothermal Amplification (LAMP):

LAMP is one of the quickest and least expensive NAAT that doesn't expect dynamic thermal cycling since it cycles the viral RNA at a stationary temperature. The assay yields results within one hour using specific primers and a strand-displacing DNA polymerase. For this reason, given that these tests are easy to perform, require little equipment, and are highly sensitive, they are very useful in low resource settings (CDC, 2023; Sagar *et al.*, 2023). Subsequently, to ease interpretation, several LAMP tests undergo further enhancements utilizing colorimetric or fluorometric detection.

B. Transcription-Mediated Amplification (TMA):

Another sensitive and accurate isothermal system targeting SARS-CoV-2 RNA is TMA. It is particularly valuable in the high-throughput testing and is associated with high sensitivity. TMA method can be used extensively in labs and diagnostic centres since it is applied on automated platforms (Dierks *et al.*, 2021).

C. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Based Detection:

CRISPR has been adapted to identify SARS-CoV-2 by applying guide RNA sequences toward viral RNA. A measurable signal is generated when CAS proteins – including Cas12 or Cas13 – bind to the target and activate and digest the reporter (Deol *et al.*, 2022). These assays are ideal candidates for point-of-care testing because they are the following: rapid, adaptable, and selective.

D. Helicase-Dependent Amplification (HDA):

Primers may then attach and amplify DNA or RNA using Helicase enzymes in HDA; an isothermal technique that unwinds DNA. This kind of method is best used in field applications because of its

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simplicity and compatibility with simple equipment (Zasada *et al.*, 2022).

E. Nicking Enzyme Amplification Reaction (NEAR):

Enzymes capable of nicking at specific sites help to create single stranded DNA at that locations, NEAR is a very fast nucleic acid amplification method that enables the polymerase to elongate the strand for amplification. The NEAR-based assays are used in many portable diagnostic devices since the results can be obtained in a very short time, in minutes (James *et al.*, 2020).

F. Rolling Circle Amplification (RCA):

Standard Bacterial DNAs are circularized and kept in checked throughout RCA, creating lengthy successive sequences which may be identified through various methods. Other studies have shown that RCA has high specificity and that it is useful when used in multiplex testing but it is not as widely used as other NAATs. All these alternative NAATs offer the following unique and valuable characteristics for SARS-CoV-2 related diagnostics: versatility in terms of platforms, design, equipment, rapidity, and resource requirements (Gu *et al.*, 2018). Each of these methods involves its own optimizing factors and constraints so that healthcare systems can select according to organizational need.

vi. Serological Tests

The existence of antibodies or antigens in blood samples is detected by certain tests known as serological tests. These tests are beneficial in analyzing the immunological reactions, identifying the levels of immunities in a population and in identifying previous infections. In particular, they complement the measurements based on nucleic acids for the detection of immunological reactions to SARS-CoV-2 (CDC, 2023).

i.RAT

Rapid Antigen Tests (RATs) are rapidly used for screening infected with SARS-CoV-2 antigens which are portions of viral proteins in specimens such as nasal or throat swabs. Antigen tests mainly use what is known as immunochromatographic assays whereby sample is applied on a test device and in presence of the SARS-CoV-2 antigens, a visible signal is generated. RATs have numerous benefits including; being fast with results taking 15-30 minutes, easy to use and inexpensive making them fit for use during mass screening in the community, and at home. They are most useful for the quick identification of persons who have a contagion; which is critical in preventing the spread of an illness. However, their main drawback is suboptimal sensitivity when compared with the increased specificity of other molecular techniques, including RT-PCR. This implies that, compared to RT-PCR, RATs are inclined to deliver negative outcomes even in persons who truly have COVID-19 but with low viral loads inclusive of asymptomatic or early-stage patients (Sagar *et al.*, 2023). In addition, reactions with other coronaviruses or pathogens can lead to false-positive results, as such these tests can be highly inaccurate at times. However, RATs are useful in high throughput testing where speed is of essence, although follow up testing through more precise techniques is advised.

ii.ELISA

Symptoms also have limitations with tests like the PCR test, Antigen test and Enzyme-Linked Immunosorbent Assay (ELISA) which are highly sensitive and specific laboratory tests

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that are mostly used for the detection of covert antibodies against SARS-CoV-2. ELISA function in that viral antigens or antibodies are attached to the surface of a plate and then incubated in a medium and reacted with another reagent that produces color change when the target antibodies or antigens are bound. This type of quantitative test has more data outcomes compared to that of antigen tests that separate tests of different antibodies such as IgM, IgG, and IgA that is representing of recent infection and immunity levels. ELISA has been employed usefully in various large-scale epidemiological surveys to identify seropositivity or effectiveness of immunization and the amount of results is useful for a long-term antibody response evaluation. Nonetheless, ELISA and other methods mentioned above have drawbacks as follows: ELISA demands specific equipment and highly professional personnel; it requires much greater reaction time, often measured in hours and days, compared to other techniques, which makes it less appropriate for speedy point of care diagnostics. Also, when comparing ELISA with other types of methods, it should be noted that although this method allows determining the presence of antibodies in samples with high specificity and sensitivity, this method can fail to detect viral infection in patients during the acute phase of viral infection, when titter of detectable antibodies is usually low or absent (Castellanos *et al*., 2022). Hence ELISA is best used in examining samples collected after infection or after vaccination and not prognostically.

iii. Shortcomings of Antigen Tests

Shortcomings of Antigen Tests are perhaps more observed when compared with the more accurate nucleic acid amplification tests, (NAATs). Compared to antigen tests, PCR tests, and antibody tests, there are many benefits to tests that use antigens: they are fast and inexpensive, but they are less accurate when the viral load is low, as occurs in asymptomatic patients or those who are beginning to recover from the virus. The minimally derisked RATs enhance the prospects of false negative, a situation which prolongs the time one has to isolating and therefore prolonging transmission. Further, antigen tests are less informative and rarely give quantitative values of viral loads or antibodies indicating severity of the disease or immunity respectively. In addition, there are disadvantages in taking antigen tests which are the ability in identifying the new variants of SARS-CoV-2 in cases there are mutations occur in the viral proteins used in the tests. The fact is that the same antibodies associate with other coronavirus strains, including those potentially causing colds, may give a positive result, making diagnosis more challenging. These weaknesses explain why antigen testing should be complemented by other diagnostics or confirmatory tests when a negative test is given in patients with symptoms or outbreaks in high-incidence areas. Consequently, such tests are less sensitive than more elaborate serologic tests, such as ELISA or molecular tests, such as RT-PCR, even though the antigen tests are relatively faster (Xin *et al*., 2021).

Molecular tests like RATs and ELISA provide the diagnostic utility and information about immunity to SARS-CoV-2 infection. This is the case since RATs are particularly useful in cases of large-scale screening, avenues with a high population influx besides other large-scale tests; albeit less sensitive than antigen tests. Compared to ELISA, it is more time consuming and expensive, but offers information about

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the duration of immunity, which is crucial for the epidemiological observation. However, there are some restrictions of both tests which are important to consider while analysis the results (Johnson *et al.*, 2022). When used alongside molecular testing such as the RT-PCR these serological tools may prove useful in improving diagnostic outcomes as well as assist the public health sectors in addressing COVID-19 pandemic.

4. Ancillary Tests for COVID-19

These additional tests of COVID-19 give valuable information on the virus's genome, mutation, and the immune response to the disease other than basic diagnostic approaches like the RT-PCR and antigen tests. The two key supplementary tests adopted in the detection and management of COVID-19 are Sequencing and Antibody Serology Tests. These tests are central to the characterization of the viral transmission dynamics, identification of emerging strains, as well as antibody response upon recovery or upon vaccination.

i.Sequencing

Sequencing is a visually highly sophisticated method for resolving the genetic map of SARS-CoV-2 viruses, allowing researchers and clinicians to learn more about the pathogens. This test entails identifying the sequence of all nucleotides which make up RNA in the virus' genome. There are two primary types of sequencing used in the context of COVID-19: WGS and targeted sequencing. Sequencing in methods such as whole genome sequencing means decoding all the 6 bases of the virus genome which gives detailed information regarding the virus mutation and variability. This method is invaluable for surveillant viral evolution and identifying new variants as well as mutations that could alter transmissibility, disease severity, and vaccine effectiveness (El-Daly *et al.*, 2024).

The sequencing efforts are most relevant to new VOCs such as Delta and Omicron variants that emerged and proven to have partial immune breakout and altered disease impact. Sequencing also enables refinement of spike protein or other locations and showcase which mutations can affect recall of vaccines or therapeutic entities. It also tracks transmission of variants and offers epidemiological intelligence that shapes public health approaches on variants and COVID-19 Surges. Although sequencing gives useful data, it has not been applied to daily Covid-19 detection because it is time-consuming, expensive, and not easy to perform. But it is essential for surveillance, studying the way the virus spreads and its effect, as well as for the development of a vaccine and antiviral plan (WHO, 2021).

ii.Antibody Serology Tests

Serology tests are used to diagnosis an antibody in the blood which is an immunoglobulin produced by the body's immune system due to an infection such as COVID-19. These tests are meant to reveal the presence of such proteins as IgM, IgG and IgA that arise at different periods of an infection or after the administration of a vaccine. Detection of antibodies often means that the person experienced and was infected by the virus in the past through natural infection or vaccination, but the results can give some clue about the level of immunity the person has against the virus.

There is no role for serological testing in diagnosis of active SARS-

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CoV-2 disease as antibodies take several days to weeks to become detectable. However, they are of greater value in the context of the epidemiological investigations, such as the overall prevalence of COVID-19 antibodies in the given population, the evaluation of the immunogenicity following the COVID-19 vaccine administration, as well as in the development of further public health interventions. These tests are useful to determine a subject that may not show any symptoms or had very mild symptoms that they never took seriously during the pandemic.

Antibody testing is also used in research especially in determining the longevity of protection concerning COVID-19 immunity as well as the effectiveness of vaccines against the virus. For example, it can be used to assess which kind of vaccines are more likely to provoke an immune response in the organism. Nevertheless, serology tests are not ideal for all other forms of SARS-CoV-2; some forms may affect the immune response. However, antibody detection does not preclude subsequent episodes because reinfection may occur, particularly with the circulating strains that have mutations associated with immune escape (Dimech *et al*., 2024).

5. Treatment Strategies

Despite the spike of the COVID-19 cases, different approaches in treatment have been invented to address the impacts of SARS-CoV-2 virus. The distinctive therapeutic strategies include the possibility of interaction with the virus (antiviral treatment), cytokine storm inhibition (modulation of the immune response), and innate tissue regeneration and immune reinforcement (stem cell therapy). Further below, we discuss these treatment options in details.

i.Antiviral Therapy

Antiviral drugs are used with the purpose of interfering with the replication of SARS-CoV-2, so that the viral burden does not become too high in the body and therefore does not cause severe and widespread COVID-19. These treatments are very important in the initial phases of the infection because they can possibly lower the chance of serious illness and hospitalization.

i.Remdesivir

Remdesivir is none specific antiviral drug, which belong to class of RNA polymerase inhibitors and acts by blocking RNA dependent RNA polymerase (RdRp) synthesis which is required for the RNA viruses replication including SARS-CoV-2. This inhibition in actuality stops the process of replication and limits the viral quantity that continues vying for tissue possession within the body. Though initially invented to treat Ebola, remdesivir was later used for the treatment of COVID-19 and received authorization as the first antiviral for COVID-19 (Kalil *et al*., 2021).

Another clinical trial, which has been conducted comparing the effectiveness of remdesivir among patients with Covid-19, demonstrated that the drug was more efficient if it had been used in the initial stage of the disease, during the first week after the beginning of symptoms in particular. That is why its usage was said to have reduced time taken to recover, mainly among the hospitalized patients with moderate symptoms, though its effect on the mortality rates is still undeclared. Remdesivir is given intravenously and is employed mainly on severely affected

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patients with COVID 19 that needs oxygen to assist with their breathing but is not used in mild cases or patients with mild symptoms who can take treatment at home. However the drug has some drawbacks, one of which is possible renal toxicity and hence should not be administered to patients with chronic kidney disease (Cao *et al*., 2023).

ii.Nirmatrelvir–Ritonavir (Paxlovid)

Paxlovid is a combination of two antiviral drugs: nirmatrelvir, a protease inhibitor, and ritonavir, an pharmacokinetic booster of nirmatrelvir because it selectively inhibits the liver enzymes that metabolize the drug. Specifically, Nirmatrelvir work against SARS-CoV-2 main protease (Mpro) enzyme which play vital role in replication process of the virus. This reshape at the end of the polyproteins has been blocked by nirmatrelvir to prevent further development and replication of the virus (Greasley *et al*., 2022; Takashita *et al*., 2022; Imai *et al*., 2023).

Paxlovid is a medicine that is prescribed to patients with mild to moderate COVID symptoms with high risk of developing severe form of the infection. Clinical trials have shown that Paxlovid provides protection against hospitalization and deaths by nearly 88% if administered early within five days of developing symptoms. However, computerized processing is contraindicated in severe renal or hepatic impaired patients due to drug interaction with other drugs especially those that are metabolized by the enzymes in the cytochrome P450 complex. Although Paxlovid has proven highly effective at reducing the risk of severe disease, it does not appear to help patients who are already presenting severe symptoms or those admitted to hospital with significant organ dysfunction (Perelson et al., 2023).

ii.Immunomodulators

Immunomodulation too targets at controlling immune cascade overdrive to SARS-CoV-2 leading to occurrences of cytokine storms, ARDS and multiple organ dysfunction syndrome. These therapies aim directing the immune system to focus on elements that provoke inflammation thereby enabling body to heal itself from the effects of the infection without having to damage the tissues irreparably.

i.Baricitinib (JAK Inhibitor)

Baricitinib is an orally active Janus kinase (JAK) inhibitor which inhibits the activity of JAK-STAT pathway is known to activate the inflammatory cytokines. This inhibition reduces proinflammatory cytokines in the levels like IL-6,and IL-1 βwhich are in the inflammatory cascade of COVID-19 especially in severe cases. As JAK inhibitors, baricitinib decreases inflammation that leads to lung injury and organ failure and puts patient at risk of poor survival (Huang et al., 2022).

Baricitinib is indicated for the treatment of COVID-19 in patients with moderate, severe or severe COVID-19 symptoms who will likely require supplemental oxygen or mechanical ventilation. Randomized controlled trials have shown that baricitinib as an adjunct therapy with corticosteroids decreases the mortality and the risk to require invasive mechanical ventilation in severe COVID-19 patients. But it can also lead to infections because it alters the patient's immune system, thus making proper monitoring crucial during treatment. Furthermore, baricitinib is contraindicated in patients with active

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infection or with past history of cancer, since the drug increases the risk of malignancy and serious infection (Wolfe et al., 2022).

ii. Tocilizumab (IL-6 Inhibitor)

Tocilizumab is a monoclonal antibody acting selectively on and blocking the IL-6 cytokine molecule, which is released in excessive amounts during a cytokine storm. Increased levels of IL-6 are associated with high inflammation, organ dysfunction, and poor outcome in COVID-19 infected patients. As an 'antagonist' to the IL-6 receptor, tocilizumab works to decrease inflammation and precludes the deterioration of certain organs like the lungs, heart and kidneys in particular (Rezabakhsh *et al.*, 2024; Zhang *et al.*, 2020). Tocilizumab is usually administered to those severe COVID-19 patients admitted to the hospital with elevated IL-6 levels and who need oxygen or mechanical ventilation. It was established that adding tocilizumab to the regimen of high steroid action has a better effect on the treatment of severe COVID-19 cases, decreasing mortality rates and the risk of mechanical ventilation. However, patients treated with tocilizumab should be regularly checked for infections and gastrointestinal perforations and exhibit liver enzyme abnormalities (Lu *et al.*, 2024).

iii. Cell Therapy

Continued discussion has been made on cell-based therapies as an option for critical COVID-19 patients or those with organ injury or no response to conventional interventions. These therapies aims to enhance the immune response mechanisms, treat molecular and tissue injuries and promote healing from viral initiated organ failures.

i. T Cell Therapy

T cell therapy is based on administration of T lymphocytes (T cell), which are among the components of adaptive immunity. These are important in medicating virus infected cells in the body Deng *et al.*, (2006). SARS-CoV-2 clearance by T cells is critical in COVID-19, but T cells are exhausted in critically ill or immunocompromised patients. T cell therapy is the process of augmenting the activity of T cells whether autologous T cells obtained from the patient's blood or allogeneic T cells from a donor, to increase the fight or response to SARS-CoV-2.

The early experiments have indicated that T cell therapy can have benefit in patients with the severe COVID-19, in particular, those who have dangerous prolonged viral replication or immunocompromised condition. This is shown to have an advantage of aiding the body reach a means to clear the virus and avoid reinfection. However, T cell therapy is relatively new today, and more efforts are required in order to establish the best administrations, the safety as well as the efficacy of the therapy (Wang *et al.*, 2023).

ii. Mesenchymal Stem Cell (MSC) Therapy

MSCs (Mesenchymal stem cells) are a type of partially characterized multipotent cell population derived from mesodermal tissues possessing tissue repair/ regeneration capabilities as well as immune regulation. MSCs release molecules that have various effects including promoting tissue remodelling, reducing inflammation and promoting healing of injured organs. This makes MSC therapy appealing to patients with

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the severe COVID-19 related injuries like ARDS, myocarditis, or affected liver and kidneys (Sengupta *et al.*, 2020).

In human clinical trials MSC treatment has demonstrated effectiveness in the amelioration of lung pathology and inflammation as well as boosting tissue repair in COVID-19 patients who experience severe pneumonia (Ringden *et al.*, 2022). MSCs are generally given intravenously and in evidence that they are useful in reconstructing damaged lung tissue, shortening time on the ventilator, and increasing overall survival. However, the ongoing studies have reported an immediate benefit of the MSC therapy and there is still so much more to be learned regarding the safety issues, the way MSC therapy works, and the long-term impact it has on COVID-19 (Dilogo *et al.*, 2021).

6. Vaccines

i. Impact of Vaccines on Epidemiology of COVID-19

The current COVID-19 approved vaccines were designed primarily for the basic strain of SARS-CoV-2. For the vaccines, the mRNA vaccine BNT162b2 (Pfizer BioNTech) was 95\% effective for preventing symptomatic infections, and the protein subunit vaccine was 90\% effective in a study done among participants. Efficacy against both hospitalization and death was near complete for both vaccines. But due to high rates of mutation in SARS-CoV-2, newer strains appeared which lead to so-called breakthrough cases. For instance, these mutation possess the latitude to avoid the neutralizing antibodies like JN.1, which is featured in the Omicron variant (Dunkle *et al.*, 2022).

Essential to vaccine protection are neutralizing antibody titres that, however, wane rapidly and this is why boosters are required. A new mRNA booster for the Omicron XBB.1.5 variant has been endorsed and does certainly enhance the neutralizing antibody titers against the new strains, and hence assists in sustaining the protection. Likewise, the hospitalization and death rates persist at constant levels in vaccinated populations to show that getting vaccinated helps to prevent severe disease sequelae (Wang et al ., 2024).

The research has also demonstrated that the proportion of patients more than seventy-five years old and individuals with immunocompromising diseases rose during the Omicron wave; nevertheless, the severity of COVID and mortality dropped thanks to the vaccine. This implies that preventing measures are very important for quantifying the impact of COVID-19 in high-risk populations (Kojima *et al.*, 2023).

ii. Disparities in COVID-19 Response between High-Income and Low-Income Countries

Resource-rich countries in the developed world—say, the United States—were in a position not only financially and infrastructurally to guarantee large-scale vaccination but also to do so where these options have simply not existed for low-resource settings. Developed countries could have huge COVID-19 vaccine inventories, put up large vaccination centres, and use apps to administer vaccines. On the other hand, lower income country especially those in Africa were shaded off due to financial enablers and poor health systems (Zaoui *et al.*, 2023).

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To avoid this, COVAX has been developed to distribute vaccines across the globe by the end of 2023 in 2 billion doses to save many lives (Sign *et al.*, 2024). However, there is still an issue of vaccine bequeathal and transportation even in the low income countries after making arrangement of acquiring vaccines. Some of these difficulties have been addressed by solutions such as extension of vaccines to normal immunization schedules, and establishment of mobile immunization stations. Non-governmental organizations (NGOs) also collaborate with government in delivery of these vaccines to harder to reach areas (Med *et al.*, 2023).

iii. Pfizer-BioNTech COVID-19 Vaccine (mRNA Vaccine)

Pfizer-BioNTech's BNT162b2, introduced in 2020, is an mRNA form of COVID-19 vaccine first to receive an emergency use authorization. BioNTech's Comirnaty works by using adapted mRNA to carry out the genetic plan of the spike glycoprotein of SARS-CoV-2 and delivers it encapsulated in lipid nanoparticles. Early large-scale outcomes exposed the vaccine to have 95% efficacy in stopping symptomatic illness and no severe side effects. Efficacy was found to be reduced gradually, which suggests that booster doses are required (Vogel *et al.*, 2021).

They said that the vaccine has great efficiency against some variants such as the Beta and the Delta, with approximately 90 % effectiveness in preventing hospitalization due to the virus but the efficacy of the vaccine in preventing infection in the first place is lower and wanes over time (Sahin *et al.*, 2020). Research has also indicated that a booster dose increases protection and that it protects especially against serious outcomes such as hospitalization and death. The research show during the Omicron wave that the booster lessened the effectiveness and substantially hindered developing severe disease but had a comparatively lesser efficiency in preventing breakthrough symptomatic infection. Though it weakens human body more than usual flu, it still afforded substantial degree of safeguard against hospitalization and severe infection (Polack *et al.*, 2020).

To address new variants, Pfizer-BioNTech come up with adapted vaccines, monovalent and bivalent targeting specific Omicron subtypes (BA.1, BA.4/BA.5 and XBB.1.5). The variant-adapted vaccines demonstrated increased immunogenicity compared to the primary titer, and bivalent boosters provided further protection concerning severe diseases and hospitalization (Moreira *et al.*, 2022).

The tolerability of the vaccine is generally acceptable, although some severe side reactions have been noted even though they are rare. This list comprises myocarditis especially in men, coagulation disruptions such as CVT and thrombocytopenia. Nonetheless, the research indicates that vaccine-associated myocarditis often seems to have a more favourable prognosis for the patient than myocarditis with other origins (Martinelli *et al.*, 2023).

The vaccine's safety was comparable to that observed in the general population in immunocompromised populations, including transplant recipients, there were no reports of organ rejection or serious adverse effects. This implies that, there is no harm with regard to increased risk associated with

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immunization with patients with compromised immune systems.

iv. Novavax COVID-19 Vaccine (Protein Subunit Vaccine)

The NVX-CoV2373 (Novavax) is a recombinant spike protein COVID-19 vaccine, developed with the Matrix-M adjuvant to promote broad immune response ("Novavax and Serum Institute of India Announce World Health Organization Grants Emergency Use Listing for NVX-CoV2373 COVID-19 Vaccine - Dec 17, 2021). It has been proven very effective in the prevention of COVID-19 disease from the clinical trials because it has overall efficacy of about 89-90% and efficacy against its variants such as Alpha and Delta. It also provided confidence about its ability to act as a booster shot as post-vaccination antibody levels rose sharply against several SARS-CoV-2 variants (Hotez et al. 2022). The data from phase III trials show that NVX-CoV2373 is relatively safe; only minor to moderate side effects such as headache and pain at the injection site. Despite the myocarditis and pericarditis side effects, the number was few than the other vaccines side effects. The vaccine proved real-world efficacy, protection comparing to comparator vaccines depending on variants, NVX-CoV2373 offered generally high protection (Hotez et al. 2022). The new version of the vaccine is NVX-CoV2601 approved for booster dose use in the US and appears to protect against the XBB.1.5 but more research is needed on its ongoing safety and effectiveness. In general, the mainstay is Novavax's vaccine, which provides an additional non-mRNA way to prevent COVID-19, based on reputable data on its safety and effectiveness (Heath *et al.*, 2021).

Conclusions

Early on in the pandemic, the cooperation of scientists around the globe made it possible to get a clear picture of this new coronavirus. Many new detection techniques and treatment approaches have been developed new and made available thereafter to help contain the spread and enhance management of COVID-19. While continuing the research and controversial COVID-19 is no longer considered a pandemic by the World Health Organisation. They further ensure continued and renewal of vaccines and treatments to counter any new variants of SARS-CoV-2 which will make the current endemicity of COVID-19 worse.

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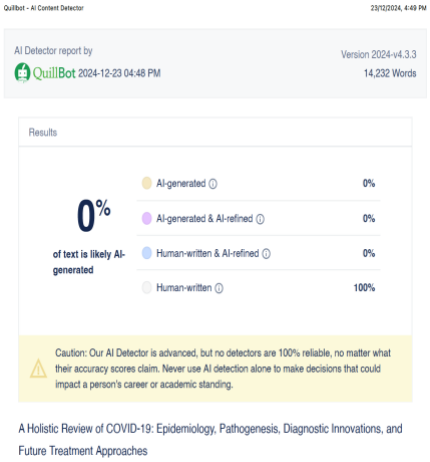

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