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Understanding COVID-19 - A Molecular Perspective

Michael O. Okpara[1,*], Miebaka Jamabo[2]

[1]Department of Biochemistry, Federal University of Technology, Akure, P.M.B. 704, Akure, Ondo State, Nigeria
[2]Department of Biochemistry, Rivers State University, Nkpolu-Oroworukwo, P.M.B 5080, Port Harcourt, Rivers State, Nigeria
*Corresponding author: okpara87michael@yahoo.com

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Abstract Coronavirus disease (COVID-19) is an infectious disease caused by a novel coronavirus now identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV). COVID-19 was first identified in Wuhan, China in December 2019 but has spread globally. As of May 11, 2020, over 4 million people have been infected with over 280,000 deaths reported globally. This pandemic has severely affected the global economy as most countries had to take pro-active measures to curb the spread of the disease by shutting their borders, making this one of the most devastating health crises in the past century. Coronavirus epidemics are not new to the human populace. The severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) caused epidemics in 2002 and 2012, respectively. These three coronaviruses belong to the beta-coronavirus genus. Despite the past experience from the previous coronavirus epidemics, the world was unprepared for this new outbreak. Therefore, it is important to understand the biology of the virus and the possibility of targeting its components for developing therapeutic drugs and vaccines. This review gives an overview of the biology, transmissibility, and genome organization of SARS-CoV-2. Furthermore, we described the available diagnostic, therapeutic and vaccine strategies for COVID-19.

Keywords: *COVID-19, coronavirus, SARS-CoV-2, diagnostics, therapeutics, vaccines*

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1. Background

The index case of coronavirus disease 2019 (COVID-19) was reported in Wuhan, Hubei, China in December 2019 [1]. COVID-19 was originally believed to be transmitted to humans from animals in the local wet markets. However, subsequent widespread of the viral infection, even to people who never had any exposure to the Huanan seafood wholesale market in Wuhan suggested that the virus could be transmitted from human-to-human [2]. The means of transmission of the virus can either be via close human-to-human contact or respiratory droplets (from sneezing or coughing) or fomites or airborne droplets [3]. More so, the transmission of the viral infection from asymptomatic carriers to non-carriers is also very possible thereby making the spread of the disease very difficult to curtail [4]. As of May 11, 2020, COVID-19 has spread to at least 210 countries and territories with over 4 million confirmed cases and at least 280,000 deaths recorded [5].

The causative organism of COVID-19 has been identified and its complete genome sequenced by independent laboratories [6,7]. According to the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV), the name of the causative organism of COVID-19 is the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [8]. On March 12, 2020, the World Health Organization (WHO) declared the disease a global pandemic that requires global attention [9]. The asymptomatic transmissibility of SARS-CoV-2 infection will, perhaps, be one of the biggest challenges the world will face in trying to curtail the spread of the virus or develop a quick therapeutic intervention for the disease. COVID-19 patients have been reported to show some of the following symptoms - fever, headache, lymphocytopenia, dry cough, severe pneumonia, sputum production, myalgia, acute respiratory distress syndrome (ARSD), fatigue, acute cardiac injury, haemoptysis, diarrhoea and acute ground glass opacity (GGO) [10,11]. Presently, there are no clinically approved antiviral drugs or vaccines for the cure or prevention of COVID-19 as the disease can only be managed by treating the symptoms shown by the patient. However, concerted efforts have been made by affected countries to limit both local and/or international transmission of SARS-CoV-2 by implementing relevant preventive/control measures such as physical distancing and national lockdown. Consequently, the global economy has been severely affected with many countries recording a fall in GDP and increase in unemployment rate [12]. Therefore, a timely therapeutic intervention - especially

with a vaccine - for SARS-CoV-2 infection becomes imperative. The purpose of this review is to provide a brief overview of the taxonomy, biology, transmissibility, and genome organization of SARS-CoV-2. In addition, we described the potential diagnostic, therapeutic and vaccine strategies for COVID-19.

2. Taxonomy and Biology of Coronaviruses

Coronaviruses belong to the *Nidovirales* order, which also include *Arteriviridae*, *Mesoniviridae*, and *Roniviridae* families. They can be divided into four genera including the alpha-, beta-, gamma- and delta-coronavirus. Amongst these four genera, alpha- and beta-coronaviruses are only capable of infecting mammals, gamma-coronavirus infect only birds while delta-coronavirus can infect both mammals and birds [13,14]. The severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 all belong to the beta-coronavirus genus and are the aetiological agents of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19, respectively.

According to ICTV, coronaviruses are a large family of pathogenic agents that possess a single-stranded positive-sense RNA genome which is between 26-32 kilobases (kb) long and contain several open reading frames (ORFs). The first ORF represents about 67% of the entire genome and encodes the non-structural proteins (nsps) while the remaining ORFs in the viral genome encode the accessory and structural proteins. Morphologically, coronaviruses are spherical in shape with a size ranging from 120-160 nm and they depend mostly on vertebrates as their hosts for survival [15,16]. Structurally, coronaviruses are described as being pleomorphic. They possess four major structural proteins that are key to their survival and virulence. Their large genome is well-packaged inside a helical nucleocapsid (N) protein. Then there is a glycoprotein called the membrane(M) protein which spans the length of the virus bilayer membrane. The envelope (E) protein is found in small quantity within the virus bilayer membrane. And lastly, the club-like spike (S) protein is found in large quantity on the surface of the virus (Figure 1). The S protein is the most prominent structural protein which is key for viral entry into the host cell [13].

2.1. Entry and Life Cycle of Beta-coronavirus

The complete genome analyses of SARS-CoV-2, SARS-CoV and MERS-CoV indicate that SARS-CoV-2 is more similar to SARS-CoV with about 80% similarity compared to a 50% similarity with MERS-CoV [6]. Even the host cell receptor through which SARS-CoV-2, SARS-CoV and MERS-CoV enter the host cell are different. While SARS-CoV-2 and SARS-CoV S proteins bind to angiotensin-converting enzyme 2 (ACE2) receptor, MERS-CoV S protein binds to a dipeptidyl peptidase 4 (DDP4) receptor on the host cell surface [14,17,18,19,20]. This suggests that the mode of infection and/or transmission of SAR-CoV-2 and SARS-CoV are more likely to be similar compared with that of MERS-CoV. Upon attachment on the host cell surface, SARS-CoV and SAR-CoV-2 S proteins bind to the host cell ACE2 receptor through their respective receptor-binding domains (RBD) [21]. A recent study by Wan *et. al.* (2020) demonstrated that there is at least 76% sequence similarity between SARS-CoV and SAR-CoV-2 S proteins and at least 73% sequence similarity between their respective RBD, suggesting that their host cell receptor could be similar [22]. Further investigations have also implied that the viral entry process of SARS-CoV-2 and SARS-CoV is via endocytosis and could be similar [20,23]. A recent study identified a host cell serine protease, called transmembrane protease serine 2 (TMPRSS2), as a very critical factor for SARS-CoV-2 S protein priming and subsequent viral entry and spread in the host cell [24]. Similarly, TMPRSS2 was previously reported to play a key role in SARS-CoV entry into host cells during infection [23,25]; further confirming the similarity between SARS-CoV and SARS-CoV-2.

Some recent studies reported that SARS-CoV-2 is capable of binding to a wide range of cell types including oesophagus keratinocytes, lung alveolar type II cells, liver cholangiocytes, ileum and rectum enterocytes, and other respiratory epithelial cells through ACE2 receptor lining the cell membrane [26,27]. However, lung alveolar type II cell had a 4.7-fold lower expression of ACE2 compared to the average expression level of all the ACE2 expressing cell types. Despite the very low expression of ACE2 receptor, lung alveolar type II cell was still infected by SAR-CoV-2 [26]. In another independent study, SARS-CoV was reported to gain entry into the host cell via an endosomal pathway fusogenically activated by cathepsin L when TMPRSS2 was inhibited [23]. Similarly, Ou *et. al.* (2020) in their study revealed that the inhibition of cathepsin L affected SARS-CoV-2 entry into host cell [20]. Taken together, these indicate that there could be other host cell co-receptors/auxiliary proteins which mediate the entry of SARS-CoV and SARS-CoV-2 into the host cell and may contribute to SARS-CoV-2 infection [20,26]. The binding affinity of SARS-CoV S protein to human ACE2 receptor is about 10-20 folds lower than that of SARS-CoV-2 S protein to human ACE2 receptor [28]. This could possibly explain why SARS-CoV-2 is much more contagious and transmissible than SARS-CoV. Once inside the host cell, the virus particle is uncoated, and the single-stranded positive-sense viral RNA genome is released for replication. Subsequently, the host cell protein translation machinery is used to translate viral genomic RNA into viral polyproteins. These viral polyproteins are eventually cleaved into multiple nsps by viral proteases and new virions are assembled and released for onward infection [29,30].

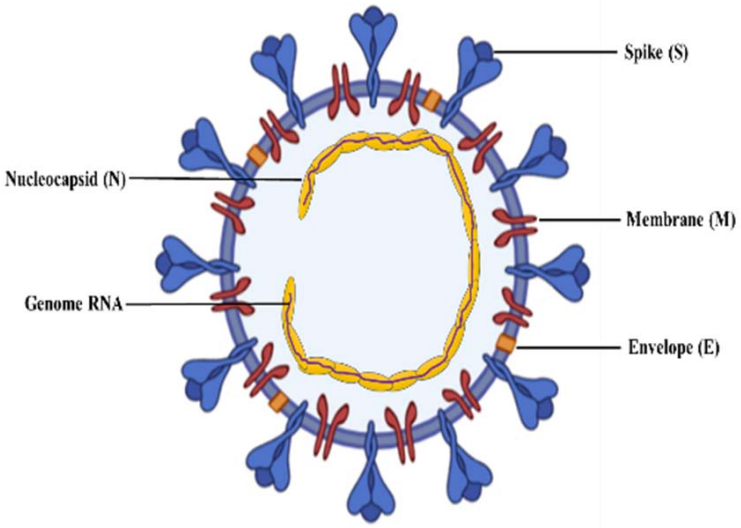

Figure 1. Schematic diagram of coronavirus particle. The 26-32 kb long viral genome RNA is encapsidated in nucleocapsid (N) protein which is enclosed by the bilayer membrane. The membrane (M), envelope (E) and Spike (S) proteins are located and interspersed on the bilayer membrane.

2.2. Genome Organization and Protein Synthesis in Beta-coronaviruses

Coronavirus RNA-dependent RNA synthesis involves a conserved genome replication step which yields several copies of subgenomic RNA (sgRNA) and the transcription of sgmRNAs which encode the viral structural and accessory proteins. The whole genome replication process takes place in the cytoplasm of the host cell. Coronavirus genome replication is a process of continuous synthesis while its transcription involves a discontinuous stepmodulated by transcription regulatory sequences (TRSs) [31,32]. TRSs are conserved nucleotide sequences located close to the 5'-terminus of the viral genome and at the
5'-terminus of every structural or accessory gene of the virus. A leader sequence and untranslated region (UTR) are also located at the 5'-terminus of the viral genome. The 3'-terminus is characterized by the 3' UTR which contains RNA structures for viral RNA replication and synthesis [13]. Generally, the genome organization of coronaviruses is 5'-leader-UTR-replicase region-structural and accessory protein region-3' UTR-poly (A) tail.

The viral genome is segmented into different ORFs which encode for the nsps, structural proteins and accessory proteins. MERS-CoV has 11 identified ORFs that encode for 11 proteins [33]. SARS-CoV has 14 functional ORFs and more than 14 proteins [34,35]. SARS-CoV-2 possesses 14 ORFs which encode 27 proteins [36,37,38]. In coronaviruses, a single large ORF identified as ORF1 occupies about two-thirds of the entire genome and is approximately 20 kb long. ORF1 is located at the 5'-terminus and subdivided into two large partially overlapping ORFs, designated as ORF1a and ORF1b genes. ORF1a and ORF1b encode for two large polyproteins called pp1a and pp1ab proteins, respectively. Together, pp1ab and pp1a make up at least 15 nsps (nsp1-10 and 12-16) fused together without any intervening stop codon with most of the nsps forming the replicase-transcriptase complex upon their cleavage by viral proteases [31,38,39]. The papain-like protease (PLpro) and 3-chemotrypsin-like protease (3CLpro) are the main proteases that cleave the replicase polyproteins in coronaviruses. Cleavage by PLpro takes place at the boundaries between nsps1 and 2, 2 and 3, 3 and 4 and 4 and 5 to give 4 nsps. While 3CLpro cleaves the boundaries between the remaining nsps to produce another 11 nsps [38]. Perhaps the most important enzymes in the replicase-transcriptase complex in coronavirus are the exoribonuclease (ExoN), RNA helicase and RNA-dependent RNA polymerase (RdRp) which are represented by nsp14, nsp13 and nsp12, respectively. ExoN functions as a proofreading exoribonuclease by reducing the number of mutations in the viral genome during replication. RNA helicase is essential for viral RNA capping. While RdRp plays a critical role in viral RNA replication and sgmRNA synthesis during transcription [34].

During viral RNA synthesis, both genomic and sgRNAs are produced. RdRp promotes the synthesis of negative-sense genomic RNA from the single-stranded positive-sense genomic RNA of coronavirus. The synthesized negative-sense genomic RNA can either undergo continuous replication to yield another positive-sense genomic RNA or undergo discontinuous transcription to yield several copies of positive-sense sgmRNAs which will eventually be translated into structural and accessory proteins by the host's translational machinery [13,40]. The genes which encode the four structural proteins (N, M, E and S) and the accessory proteins are located on the 3'-terminus of the sgRNA. While the four structural proteins are synthesized in all coronaviruses, the accessory proteins are species-specific. SARS-CoV-2 possesses 8 identified accessory proteins which include 3a, 3b, p6, 7a, 7b, 8b, 9b and 14 [38]. In SARS-CoV, there are also 8 accessory proteins (3a, 3b, 6, 7a, 7b, 8a, 8b, and 9b) [35,41] while MERS-CoV possesses only 4 accessory proteins (3, 4a, 4b, and 5) (Figure 2) [13,33,42]. The structural proteins are assembled to form the structural component of the new virus progeny with the viral genome encapsidated in the N protein. The new viral progeny is eventually released from the host cell via the secretory pathway for onward infection.

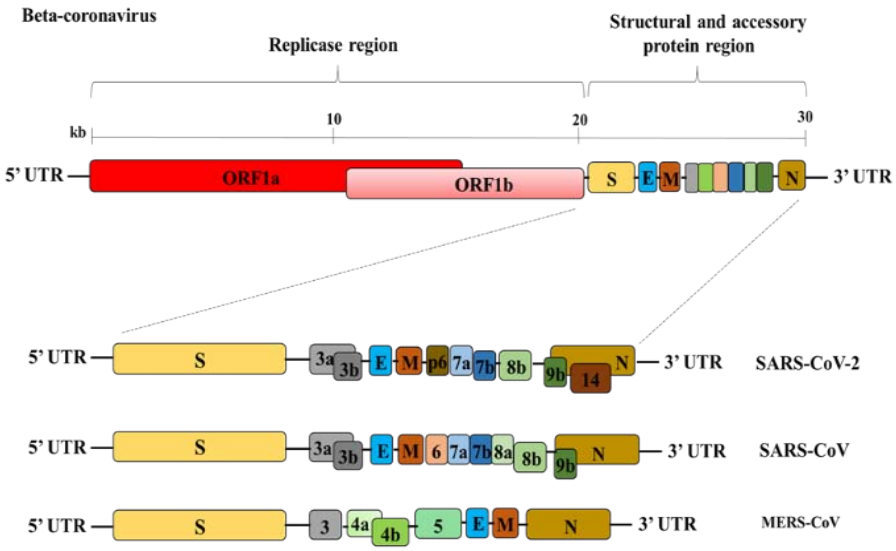

Figure 2. Genome organization of beta-coronavirus. The general gene order is 5' UTR-replicase region-structural and accessory protein region-3' UTR. The three beta-coronavirus species possess ORF1a, ORF1b, S, E, M and N genes alike but have different genes for accessory proteins. SARS-CoV-2 has ORFs 3a, 3b, p6, 7a, 7b, 8b, 9b and 14. SARS-CoV has ORFs 3a, 3b, 6, 7a, 7b, 8a, 8b, and 9b while MERS-CoV has ORFs 3, 4a, 4b, and 5.

3. Transmissibility of SARS-CoV-2 infection

SARS-CoV-2 is a very contagious virus that has spread rapidly across the world. The mean incubation period of SARS-CoV-2 is estimated to be 5.2 days with a range of 2-14 days depending on certain factors [43]. The basic reproductive ratio (R_0) of SARS-CoV-2 was estimated to be between 2.68-3.58 and is higher than the estimated R_0 of SARS-CoV (0.80) and MERS-CoV (0.69), respectively [44,45,46,47]. R_0 is the average number of previously uninfected and non-vaccinated people who could possibly get infected by a contagious individual.

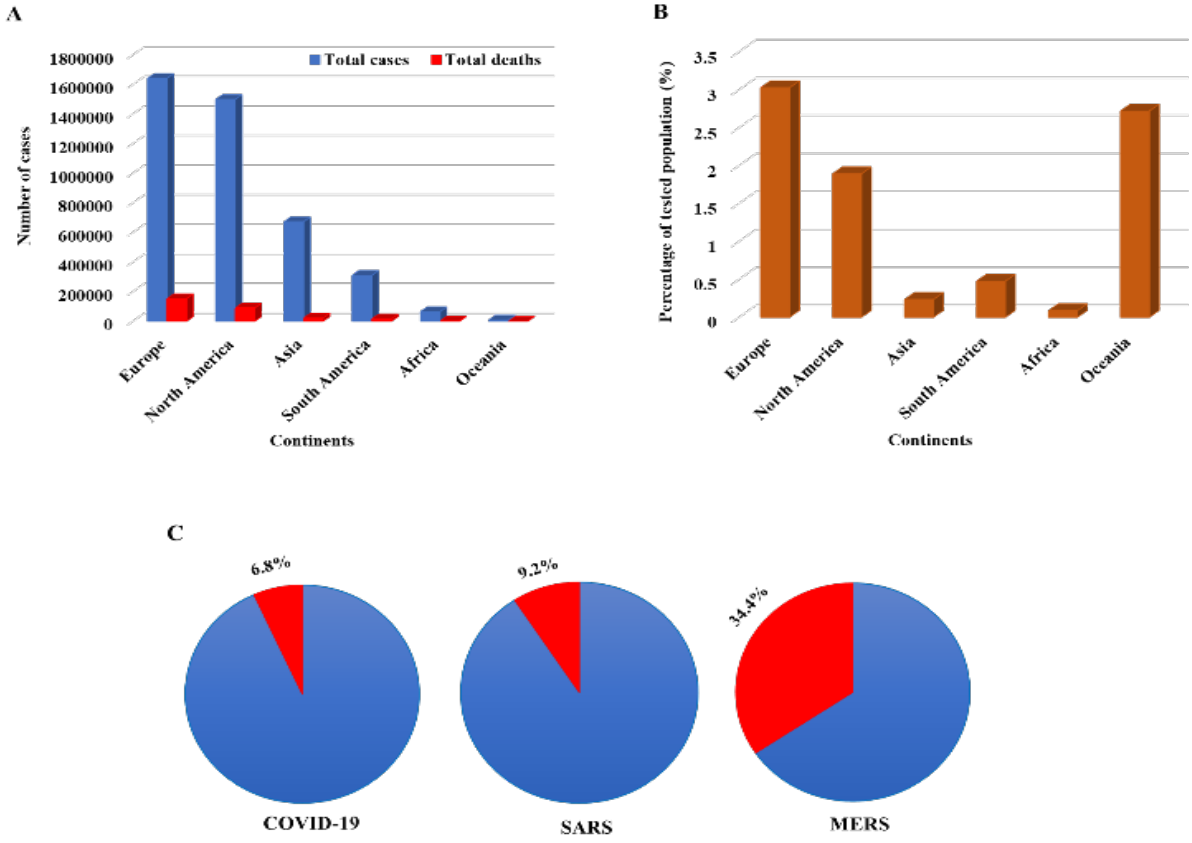

Figure 3. Graphical representation of beta-coronavirus pathogenesis. (A) The total number of confirmed cases and deaths from COVID-19 in Europe, North America, Asia, South America, Africa and Oceania. (B) The percentage of the total population already screened for SARS-CoV-2 infection in Europe, North America, Asia, South America, Africa and Oceania. The data was accessed on May 11, 2020 from reference [5]. (C) Mortality rate of COVID-19 (6.8%), SARS (9.2%) and MERS (34.4%).

As of May 11, 2020, at least 4 million confirmed COVID-19 cases have been reported globally with over 280,000 deaths recorded, amounting to a case-mortality rate of approximately 6.8%. The most affected region is Europe with about 1.64 million cases and 153,000 deaths. Followed by North America with about 1.5 million cases and 90,000 deaths. Then Asia with approximately 672,000 cases and 22,000 deaths, South America with about 310,000 cases and 16,000 deaths, Africa with approximately 65,000 cases and 2,300 deaths, while Oceania has the least number of cases (8,550) and deaths (118) (Figure 3A). However, Africa (0.09%) has the least percentage of tested population, followed by Asia (0.23%), South America (0.48%), North America (1.89%), Oceania (2.72%) and Europe (3.03%), in that order (Figure 3B) [5]. The percentage of the tested population is the number of tested individuals per 100 persons in a population. This statistics implies that there is a need to increase testing across the globe especially in developing and under-developed countries. An improved testing capacity would help countries to identify infected/contagious individuals and have them isolated from uninfected individuals. With this in place, the R_0 is expected to drop and the transmissibility of SARS-CoV-2 infection would drop. Compared to SARS and MERS, COVID-19 is more contagious but least deadly. In 2002/2003, 8096 confirmed cases of SARS with about 744 deaths (9.2% mortality rate) were recorded during SARS outbreak [46]. While in 2012, 2494 confirmed cases with about 858 deaths (34.4% mortality rate) were recorded during the MERS outbreak (Figure 3C) [48].

4. Diagnostic Strategies for COVID-19

With the very high contagious nature of COVID-19, a quick diagnostic test to identify infected individuals is needed to manage the spread of the disease. Once identified, infected individuals are isolated from uninfected individuals, thus limiting the spread of the disease and potentially reducing the R_0. Amongst the numerous testing techniques that were urgently suggested for diagnosing SARS-CoV-2 infection, real-time reverse transcription polymerase chain reaction (RT-PCR) is the most widely accepted and is presently the gold standard. Over the years, RT-PCR has been widely applied in diagnostic virology for diagnosing viral infections. RT-PCR can quantitatively and/or qualitatively detect unique sequence(s) of a viral genome; however, it can be laborious and time-consuming. The targeted genes for diagnosing COVID-19 using RT-PCR can be any of SARS-CoV-2 N, E, S or RdRp genes or a combination of 2 or more of the genes to increase the specificity and sensitivity of the test. Corman *et. al.* (2020) developed a testing kit and showed that the kit is very sensitive and discriminatory in detecting SARS-CoV-2 E gene and RdRp genes without any cross-reactivity with SARS-CoV genes. They extracted SARS-CoV-2 RNA from respiratory samples collected from COVID-19 patients and recommended that SARS-CoV-2 E gene assay should serve as the first-line screening tool while SARS-CoV-2 RdRp gene assay serves as validation [49]. Other groups, including multinational companies, have also developed diagnostic kits for SARS-CoV-2 using RT-PCR technique. BGI Global Genomics Co., LTD. have developed a Real-Time Fluorescent RT-PCR which can give test result in a few hours. This fluorescent-based RT-PCR kit is widely used in hospitals and disease control centres in China, Hong Kong, Taiwan, Brunei, Thailand, South Africa and Nigeria [50]. BGI Global Genomics Co., LTD. also developed a 2019-nCoV PMseq® kit for diagnosing SARS-CoV-2 and other respiratory tract infections in a relatively shorter time than the fluorescent-based detection kit. The 2019-nCoV PMseq® kit is a metagenomic sequencing kit based on combinatorial probe-anchor synthesis that is capable of monitoring mutations. Both the Real-Time Fluorescent RT-PCR and 2019-nCoV PMseq® kits have officially passed the emergency approval procedures of the National Medical Product Administration in China [51]. Recently, a US-based molecular diagnostics company, Cepheid, obtained an Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA) for Xpert® Xpress SARS-CoV-2 test kits. This real-time RT-PCR kit was developed to detect specific genes in SARS-CoV-2 genome from nasopharyngeal swabs or nasal wash of COVID-19 patients especially during the acute phase of the infection [52]. Though very efficient, the use of a molecular diagnostic test for COVID-19 is not without some challenges. Running COVID-19 RT-PCR-based diagnostic tests require the use of sophisticated equipment and highly trained personnel thereby making the availability and accessibility of testing kits in remote locations very difficult.

Consequently, some academic laboratories and organizations have developed immunoassay-based rapid diagnostic tests for the diagnosis of COVID-19. Upon SARS-CoV-2 infection, the body's immune system secretes antibodies into the bloodstream in response to SARS-CoV-2 antigens. Thus, the immunoassay-based technique - which is based on antigen-antibody interactions - can either be used to detect SARS-CoV-2 antibodies in indirect immunoassay or SARS-CoV-2 antigens in direct immunoassay technique. In a recent study, Okba *et. al.* (2020) developed an immunoassay for detecting SARS-CoV-2 S and N proteins in COVID-19 patients' sera [53]. On April 25, 2020, an Italian multinational biotechnology company, DiaSorin announced that it has received an EUA from the US FDA for the LIAISON® SARS-CoV-2 S1/S2 IgG diagnostic kit. This SARS-CoV-2 diagnostic kit is an immunoassay-based kit that specifically identifies IgG antibodies directed against the S1 and S2 domains of the SARS-CoV-2 S protein. The LIAISON® SARS-CoV-2 S1/S2 IgG diagnostic kit is a high throughput diagnostic kit that is capable of processing 170 samples in one hour [54]. Other pharmaceutical and diagnostics companies have also developed immunoassay-based SARS-CoV-2 diagnostics kits with improved sensitivity and specificity. On April 27, 2020, a US health care company (Abbott Laboratories) launched an immunoassay-based SARS-CoV-2 diagnostics kit after receiving an EUA from the US FDA. Abbott's SARS-CoV-2 diagnostic kit can specifically detect the IgG antibody to SARS-CoV-2 and is capable of analysing 100-200 blood samples in an hour [55]. On May 3, 2020, a Swiss-based multinational

healthcare company (F. Hoffmann-La Roche AG) announced that it has obtained an EUA from the US FDA for its Elecsys® Anti-SARS-CoV-2 diagnostics test kit. This immunoassay-based diagnostics kit can detect antibodies specific to SARS-CoV-2 in human serum and plasma samples with a 99.81% specificity and 100% sensitivity [56]. These immunoassay-based diagnostic tests can also help to determine if an individual was previously infected by SARS-CoV-2 as the antibody can remain in the blood for up to 3 months even after recovery from the infection.

The use of immunoassay-based rapid diagnostic kits also has its shortcomings with the possibility of false-positive and false-negative results. Also, cross-reactivity with SARS-CoV antibodies/antigens is not impossible due to the high degree of similarity between SARS-CoV and SARS-CoV-2 S and N proteins. However, it should be noted that the transmission of SARS-CoV has not been reported since its outbreak about 17 years ago. There are several other techniques that have been applied to develop diagnostic kits for SARS-CoV-2. They include the CRISPR/Cas based specific high sensitivity enzymatic reporter unlocking (SHERLOCK) technique [57], the visual/colorimetric reverse-transcription loop-mediated isothermal amplification (RT-LAMP) technique [58,59] and the use of artificial intelligence (AI) deep learning methods to interpret computed tomography (CT) scan of patient' chest [60,61]. However, for the purpose of this review, we focused on the techniques that have been applied to develop diagnostic kits approved for use in clinical settings.

5. Therapeutic Strategies for COVID-19

With effective diagnostic/testing kits already available and approved for detection of the novel SARS-CoV-2, the search for quick therapeutic intervention becomes the next challenge in the fight against COVID-19. Due to the high estimated R_0 of SARS-CoV-2 infection, it is very important to discover a therapeutic drug for COVID-19 especially from the drugs that have been clinically approved for SARS, MERS or other viral infections through drug repurposing. We, therefore, highlight some therapeutic drugs that are either in clinical trials or have shown potential in animals as inhibitor(s) of key proteins for SARS-CoV-2 infection. Like every other viral infectious agent, SARS-CoV-2 depends on some viral and/or host cell components for its entry, protein synthesis, viral assembly and egress for onward infection of other cells. One of such proteins is the SARS-CoV-2 S protein which requires a host cell serine protease (TMPRSS2) to facilitate viral entry upon binding to ACE2 receptors on the host cell. Camostat mesylate is a known serine protease inhibitor and has been shown to be effective against some viral infections [24,25,62]. In Japan, camostat mesylate has been clinically approved and is used for the treatment of pancreatitis [63,64] suggesting that it is potentially safe for humans at the recommended dosage. Hoffman *et. al.* (2020) showed in their *in vitro* study that camostat mesylate is a potent inhibitor of TMPRSS2 and prevented SARS-CoV-2 entry into mammalian cells [24]. This suggests that camostat mesylate could be repurposed for SARS-CoV-2 treatment.

Viral entry is not the only therapeutic target that is currently explored in the search for therapeutic intervention for COVID-19. The possibility of an alternative pathway for SARS-CoV-2 entry into the host cell cannot be completely ruled out. A recent study has revealed that SARS-CoV-2, just like SARS-CoV, could potentially achieve host cell entry through cathepsin L-mediated endosomal pathway [20,23]. Therefore, targeting other viral proteins which are essential for viral reproduction has been explored as well. The antiviral drug, arbidol, which inhibits the binding of influenza virus haemagglutinin to host cell membrane receptor [65] was shown to possess direct antiviral effects in SARS-CoV by suppressing its reproduction *in vitro* [66]. Considering the similarity between SAR-CoV and SARS-CoV-2, arbidol could elicit similar antiviral effect in SARS-CoV-2. So, it is not surprising that arbidol, in combination with lopinavir and ritonavir is currently under clinical trials for SARS-CoV-2 infection [67,68]. Lopinavir and ritonavir are clinically approved HIV homodimeric aspartyl protease inhibitors [69] and were used in combination for the treatment of SARS-CoV infection in 2003/2004 [70]. In SARS-CoV-2, 3CLpro and PLpro are the key viral proteolytic enzymes that cleave SARS-CoV-2 polyproteins into smaller functional proteins thereby facilitating the production of new viral progeny. Using a virtual screening approach, Chen *et. al.* (2020) identified lopinavir and ritonavir as potential inhibitors of SARS-CoV-2 3CLpro although the scores for the two compounds were slightly below the mean score for the study [36]. Consequently, arbidol is presently under phase IV clinical trials with lopinavir and ritonavir as potential therapeutic intervention for COVID-19 [68,71]. Also, independent clinical trials for lopinavir together with ritonavir as therapeutics for COVID-19 are ongoing in China [72].

The key enzyme in SARS-CoV-2 replicase-transcriptase complex, RdRp, can also be a potential therapeutic target for COVID-19. Therapeutic agents against RdRp could potentially inhibit SARS-CoV-2 RNA replication and sgmRNA synthesis during transcription. Remdesivir is an adenosine nucleotide analogue which was originally discovered as a therapeutic agent against Ebola virus by Warren *et. al.* (2016). In their study, they reported that remdesivir inhibited RNA synthesis in the Ebola virus by targeting the viral RdRp [73]. Several studies - using cell culture and animal models - showed that remdesivir has potential as a therapeutic agent against coronavirus by inhibiting the activity of viral RdRp thereby causing a decrease in viral RNA production [74,75,76]. This is an indication that remdesivir could be repurposed to treat COVID-19 by using it as a therapeutic agent to inhibit the activity of SARS-CoV-2 RdRp. On May 1, 2020, the US FDA issued an EUA for remdesivir to be administered for the treatment of COVID-19 after it showed promising results during clinical trials [77,78]. There are scores of therapeutic compounds which are in different phases of investigation as drugs for COVID-19. We have only described a few with huge potential due to their reported inhibitory effect(s) on key SARS-CoV-2 proteins. Nevertheless, each of these potential therapeutic drugs must show clinical effectiveness and their safety in humans must be proven before they can be clinically

approved. The process of getting a drug approved could take as long as ten years [79] and as such, an alternative intervention - such as vaccines development - could prove to be more timely. Moreover, vaccines for infectious diseases have greater success rates (20-40%) than therapeutic drugs against infectious diseases (10-15%) during their developmental journey from preclinical trials to clinical approval [80,81,82,83].

6. Potential Vaccines for COVID-19

Vaccines are biological substances that can elicit an immune response through the production of antibodies thereby providing immunity against a disease. The biological substance is usually made from either an attenuated form of the pathogen or part(s) of the pathogen or product(s) of the pathogen or a synthetic substitute. In the wake of the previous SARS epidemic, many vaccine studies exploring different parts of the virus were initiated by various groups and they included virus-like particles, spike protein preparations, plasmid DNA, inactivated whole virus and a couple of vectors containing different genes for the SARS-CoV virus. However, some of these studies came with different challenges especially as they were mostly carried out in mice and not tested in a large cohort of human subjects [84,85,86,87,88]. Also, the early eradication of SARS in the world prompted many researchers and pharmaceutical companies to discontinue the development of SARS vaccines. Perhaps one of the biggest challenges the world will face in developing a vaccine for COVID-19 is that there is no vaccine for other coronavirus-associated diseases which could berepurposed for COVID-19. Consequently, the search for COVID-19 vaccine has led to the application of different strategies/ platforms for vaccine development. Live-attenuated whole virus vaccine, killed-whole virus vaccine, subunit vaccine, nucleic acid vaccine, vectored vaccine or virus-like/ nanoparticle vaccine could be developed to provoke a protective immune response against SARS-CoV-2 in humans. Many research groups and/or multinational pharmaceutical companies are working round the clock to develop vaccines for COVID-19 with many of the potential vaccines already in different phases of clinical trials. Table 1 presents the list of potential COVID-19 vaccines which are already in different phases of clinical trials.

Table 1. Summary/Overview Of Vaccines Currently In Clinical Trial

S/N	Name	Identifier number	Platform	Target	Sponsor	Start Date	End Date	Trial Phase	Location	Ref
1	2019-nCov vaccine (mRNA-1273)	NCT04283461	RNA vaccine Lipid nanoparticle (LNP)-encapsulated	Spike protein	Moderna TX National Institute of Allergy and Infectious Diseases (NIAID)	March 2020	September 2021	I	USA	[89]
2	Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)	NCT04313127	Vector-based	Spike protein	CanSino Biologics Inc	March 2020	December 2022	I	China	[90]
3	Recombinant vaccine for Covid-19 (Adenovirus vector) (CTII-nCoV)	NCT04341389	Vector-based	Spike protein	Institute of Biotechnology, Academy of Military Sciences, PLA of China	April 2020	January 2021	II	China	[91]
4	Covid-19 vaccine (ChAdOx1 nCoV-19	NCT04324606	Vector-based	Spike protein	University of Oxford	April 2020	May 2021	I/II	UK	[92]
5	Covid-19 aAPC vaccine	NCT04299724	Vector-based	Viral proteins	Shenzhen Geno-Immune Medical Institute	February 2020	December 2024	I	China	[93]
6	Covid-19 synthetic minigene vaccine	NCT04276896	Vector-based	Viral proteins	Shenzhen Geno-Immune Medical Institute	March 2020	December 2024	I/II	China	[94]
7	RNA vaccine candidates	NCT04368728	RNA vaccine		Biontech SE Pfizer	April 2020	January 2023	I/II	USA	[95]
8	bac-TRL spike vaccine	NCT04334980	DNA vaccine	Spike protein	Symvivo corporation	April 2020	December 2021	I	Canada	[96]
9	SARS-CoV-2 inactivated vaccine	NCT04352608	Inactivated vaccine		Sinovac Research and Development Co., Ltd.	April 2020	December 2020	I/II	China	[97]
10	SARS-CoV-2 recombinant spike (rS) protein nanoparticle vaccine with or without Matrix-M adjuvant	NCT04368988	Recombinant protein subunit	Spike protein	Novavax	May 2020	July 2021	I	Australia	[98]
11	INO-4800	NCT04336410	DNA vaccine Electroporation		Inovio pharmaceuticals	April 2020	April 2021	I	USA	[99]

*Information was extracted from **ClinicalTrials.gov.**

In addition to the vaccine candidates in clinical trial, some researchers hypothesized that there is reduced COVID-19 mortality in areas with high Bacille Calmette-Guérin (BCG) vaccination rate. Several trials with BCG vaccines have moved to Phase III/IV in Brazil, Egypt, USA, Australia and Columbia and most of these trials are targeted to protecting health care workers (ClinicalTrials.govIdentifiers: NCT04369794, NCT04350931, NCT04348370, NCT04327206 and NCT04362124) [100,101,102,103,104]. In addition to BCG vaccine, there are also trials with measles vaccine and Influenza vaccine to ascertain cross-protectivity (ClinicalTrials.gov Identifiers: NCT04357028, NCT04367883) [105,106]. Finally, in Pakistan, there is a clinical trial on the use of convalescent plasma for passive immunization (ClinicalTrials.gov Identifier: NCT04352751) [107]. Most of these vaccines would take some months or even years in clinical trials before any clinical approval can be granted as their safety and tolerability in humans must be guaranteed.

7. Concluding Remarks

Highlighted in this review are the similarities amongst the beta coronaviruses. A molecular grasp of these details forms the foundation for intervention, whether prophylactic or therapeutic. This understanding can also give foresight to intending researchers as they make attempts to predict how the virus is mutating for gain of function studies. Since the outbreak of the pandemic, a lot of resources have been invested in therapeutics and vaccines research. If the resources had been made available earlier, perhaps the pandemic would have been better managed, and many lives would have been saved. The COVID-19 pandemic is the third time in the last 3 decades that a virulent strain of the coronavirus family would affect the human population, and it is unlikely that this would be the last epidemic. The unavailability of clinically approved vaccines from the last two coronavirus epidemics coupled with the length of time it might take to develop a therapeutic drug or vaccine for COVID-19 makes physical distancing measures the best approach to limit the spread of the SARS-CoV-2 virus for now. In the meantime, concerted efforts must remain in place to develop vaccines for COVID-19 even if the pandemic is eradicated through public health and physical distancing measures. The COVID-19 pandemic is one of the most tragic public health crises of the 21st century. However, we can take advantage of better communication networks and cutting-edge technology at our disposal to prioritize health care and research. Hopefully, the world has learned from the COVID-19 pandemic and would be better prepared to tackle any epidemic/pandemic in the future.

Author Contributions

The authors contributed equally to the review article.

Conflict of Interest

The authors have no conflict of interest to disclose.

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