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Appraisal of COVID-19 infection and suggestive approaches for candidate vaccine and novel therapeutic development

Olufemi Emmanuel Bankefa[1,*], Seye Julius Oladeji[1], Olubunmi Evelyn Ajayi[1], Gbenga Victor Kayejo[1] and Lawrence Ehis Okoror[1,2]

[1]Department of Microbiology, Federal University Oye-Ekiti, Ekiti-State, Nigeria;
[2]Biosolution Technologies, Akure, Ondo-State, Nigeria.

ABSTRACT

Since the emergence of COVID-19 in Wuhan, China in December 2019, the world concern has raised owing to the increasing and rapid spread of the virus across the globe. As of 26 May 2020, 5, 495, 061 confirmed cases with 2, 916, 236 active cases and 346, 232 deaths were reported across 188 countries. From the data reported so far, it can be deduced that COVID-19 pandemic still continues to spread across the globe at an alarming rate. At present, there is no specific antiviral treatment or vaccine against COVID-19; however, HIV-protease inhibitors and nucleoside analogues are currently being used for the treatment of COVID-19 infection. In addition, researches aimed at developing nonhuman primate models for better understanding virus-host interactions for possible evaluation of candidate vaccine and development of novel therapeutics are underway. Studies have shown that about 81% of all COVID-19 cases are mild illnesses, suggesting a strong connection between natural recovery and a competent immune system of the discharged patients. In light of this, it is without gainsay that the implicated immune parameters could be of great importance in the development of candidate vaccine and/or novel therapeutics for COVID-19 infection. On this note, this paper highlights the overview of COVID-19 infection, current epidemiology, routes of transmission of COVID-19 and suggests novel approaches for candidate vaccine development and/or novel therapeutic antivirals against COVID-19 infection.

KEYWORDS: COVID-19, candidate vaccine, competent immune system, coronavirus, epidemiology.

*Corresponding author: femibankefa@gmail.com, olufemi.bankefa@fuoye.edu.ng

INTRODUCTION

Coronaviruses (CoVs) belong to the genus Coronavirus in the family *Coronaviridae* [1] and have been recognized as one of those pathogens whose primary target is the human respiratory system. Middle East respiratory syndrome (MERS)-CoV and severe acute respiratory syndrome (SARS)-CoV are notable examples of coronaviruses whose outbreaks have previously caused a lot of havoc, and hence regarded as major public health concerns [2]. All CoVs are regarded as pleomorphic RNA viruses with typical crown-shape peplomers of 80-160 nM size and 27-32 kb positive polarity [1]. They are zoonotic pathogens [3] with the ability to inflict different forms of illnesses, ranging from asymptomatic to symptomatic conditions depicted by respiratory failure and/or multi-organ and systemic manifestations in the form of multiple organ dysfunctions, septic shock and sepsis among others [4]. Since the emergence of coronavirus in Wuhan, Hubei province, China in December 2019, the high mortality and morbidity coupled with high transmission capability of the virus have raised the world concern [4, 5]. Moreover, following the declaration of the pathogen as severe acute

respiratory syndrome (SARS)-CoV-2 by the World Health Organization (WHO), the virus has received great attention from researchers worldwide due to its high virulence.

As of 26 May 2020, 5, 495, 061 infected cases with 2, 916, 236 being active and 346, 232 deaths were reported across the globe [6]. Studies have shown that individuals with underlying health conditions such as hypertension, diabetes, cardiac-related diseases etc. are at high risk of being infected by the virus [4], owing to their weakened immune system. Upon the declaration of the COVID-19 as a pandemic by the World Health Organization, efforts were made to unravel the human-human transmission and pathogenicity, which has significantly led to preventive approaches. At present there is no specific antiviral treatment or vaccine against COVID-19 infection, however, antiviral drugs with broad-spectrum activity including HIV-protease inhibitors and nucleoside analogues with the capacity to render viral infection attenuated are currently considered the only treatment option [7]. Nevertheless, researches aimed at developing nonhuman primate models for better understanding virus-host interactions for possible evaluation of candidate vaccine and development of novel therapeutics are underway [2].

Studies have shown that 81% of all COVID-19 cases are mild [4, 8, 9] and this probably suggests a strong connection with a competent immune system, hence, justifying the report of Thevarajan *et al.* [10] on the suggestion of immune parameters as key towards vaccine development. This review therefore aims at providing the populace with the general overview of the disease, up-to-date epidemiology, routes of transmission of COVID-19 and to suggest novel approaches for candidate vaccine development and/or novel therapeutic antivirals against COVID-19 infection.

Epidemiology of COVID-19 pandemic

The outbreak of corona virus disease (COVID-19) originated from Wuhan City, China in December 2019 and began with the identification or documentation of the first known case of pneumonia of unknown origin on 8 December 2019 followed by a cluster of 27 pneumonia cases of unknown etiology which were reported in the city and eventually spread to the rest of Mainland China within 30 days [11, 12], which thus led to the quest to identify the causative agents. Interestingly, Chinese scientists successfully identified the culprit on 7 January 2020 as a novel coronavirus coupled with a successful genomic characterization and test method development for the pathogen [13-17]. As of 20 February 2020, the number of confirmed cases in China had skyrocketed to 74, 675 with 2121 deaths, from 27 cases reported on 31 December 2019 [12].

Global travel of symptomatic and asymptomatic individuals to countries outside China could be said to be an important factor that has contributed to the worldwide spread of the pathogen. Recent data on the epidemiology of COVID-19 pandemic as of 26 May 2020, revealed a total of 5, 495, 061 confirmed cases with 2, 916, 236 active cases and 346, 232 deaths in 188 countries [6] as compared to 87, 317 cases that was reported on 3 March 2020 by Sahin *et al*. [18], indicating exponential rise in the spread of the pathogen globally on a daily basis. Moreover, according to a recent report, the deaths from COVID-19 in the US (99, 462), UK (36, 914) and Italy (32, 877) individually have surpassed those reported in China (4, 634) [19, 20], hence augmenting the number of COVID-19 cases in North America and Europe, respectively (Table 1). It is therefore on this note that WHO declared Europe as the new center of COVID-19, following the improved situation in China [21] and as of 25 March 2020, 33 African countries had reported more than 2, 400 confirmed cases and 63 deaths due to COVID-19 pandemic according to the WHO [22].

Virology and etiology

Coronaviruses (CoVs) are a large family of positive-sense, single-stranded RNA viruses found diversely in animal species, which belong to the order *Nidovirales* which comprises of *Arteriviridae*, *Rinoviridae* and *Coronaviridae* families. The *Coronaviridae* family is subdivided into *Torovirinae* and *Coronavirinae* subfamilies while *Coronavirinae* is further classified into four genera as alpha-COV, beta-COV, gamma-COV and delta-COV [33]. Gene characterization has revealed that the gene sources of alpha-COV and beta-COV are bats and rodents. Conversely, avian species are considered as genetic sources of gamma-COV and delta-COV [34].

Table 1. Epidemiology of COVID-19 pandemic in a few countries as of 26 May 2020.

Country	Region	Confirmed Cases	Death cases	Recovered	Reference
United States	North America	1, 697, 361	99, 462	352, 984	23
United Kingdom	Europe	261, 184	36, 914	No data	24
Italy	Europe	230, 158	32 ,877	141, 981	19
Germany	Europe	180, 808	8, 432	163, 681	25
France	Europe	145, 279	28, 432	65, 199	26-27
Iran	Asia	137, 724	7, 451	107, 713	28
China	Asia	82, 992	4, 634	78, 277	20
South Africa	Africa	23, 615	481	11, 917	30
South Korea	Asia	11, 225	269	10, 275	29
Nigeria	Africa	8, 068	233	2, 311	31
Ghana	Africa	6, 808	32	2, 080	32

The high mutation rates observed in CoVs have been attributed to high recombination rates owing to their ability to frequently develop transcription errors and RNA-dependent RNA polymerase (RdRP) jumps [35]. Hence, the classification of these viruses into subtypes is based on their phylogenetic clustering accounts; consequently, CoV classification is continually changing. According to the most current classification of the International Committee on Taxonomy of Viruses (ICTV), there are four genera of thirty-eight unique species [36]. SARS-CoV-2, a type of beta-COV, is responsible for the COVID-19 pandemic and genomic characterization studies of this novel virus have indicated an 89% nucleotide match with bat SARS-like CoVZXC21 [26, 37] and also, there is an 82% nucleotide match with the human SARS virus [17]. Thus, the new strain was called SARS-CoV-2 on the basis of these findings. The full genomic length of the virus is 29, 891 to 29, 903 nucleotides. Additionally, the virus is sensitive to ultraviolet light and heat and also efficiently inactivated with the use of ethanol (60%), ether (75%), and chlorine-containing disinfectants [34].

Routes of transmission

Consumption of wild animals or direct contact with intermediate host animals was suspected as the main route of SARS-CoV-2 transmission since the first cases were presumably linked to direct exposure to infected animals (animal-human transmission) at a seafood market in Wuhan, China. Nevertheless, there are still no sufficient evidences so far that the origin of SARS-CoV-2 was from the seafood market as bats are not available for sale in the seafood market [38]. However, bats are the natural reservoir of a large variety of CoVs, including SARS-CoV-like and MERS-CoV-like viruses [39-41]. Alignment of the full-length genome sequence of COVID-19 was analyzed *via* genome sequencing throughout the genome showing 96.2% overall genome sequence identity to Bat CoV RaTG13 [42], suggesting that bat CoV and human SARS-CoV-2 may share the same ancestor.

Conversely, clinical cases with diversity in exposure history have emerged with human-to-human transmission, now considered the main form of transmission and this may be through respiratory droplets from coughing or sneezing of an infected person [34, 43]. Recent data has revealed that this virus has an incubation period of one to fourteen days and asymptomatic individuals could also transmit the virus but the most common source of infection is through the symptomatic carrier and that the virus may also be transmitted in closed spaces owing to elevated aerosol concentrations [34]. It has also been documented that 31.3% of

infected persons (patients) who recently travelled to Wuhan and 72.3% of patients who came into contact with people from Wuhan were among the patients of non-residents of Wuhan thus implicating close contacts as the most dominant mode of COVID-19 transmission [44].

Pathogenesis of COVID-19 infection

The major pathogenesis of COVID-19 infection includes RNAaemia, severe pneumonia, coupled with acute cardiac injury and incidence of ground-glass opacities [4]. COVID-19 infection is characterized by elevated LDH (lactate dehydrogenase), prothrombin time, ALT, D-dimer, creatine kinase, C-reactive protein (CRP) [34] coupled with decreased levels of CD4 and CD8 lympocytes and increased concentrations of GCSF (granulocyte colony-stimulating factor), interleukin (IL) 2, IL-7, IL-10, MCP1 (monocyte chemotactic protein 1), TNF-α (tumor necrosis factor-α), IP10 (interferon gamma-induced protein 10) and MIP1A (macrophage inflammatory protein alpha) [4], all of which have been considered as prognostic markers for COVID-19 infection.

Coronaviruses are characterized by four structural proteins, including nucleocapsid (N), spike (S), membrane (M) and envelope proteins (E) [45, 46]. The notable protein responsible for attachment, fusion and entry of these viruses is the spike protein or S protein [47, 48]. The viral entry ensues following the successful binding of S protein to the specific host cell receptor *via* receptor-binding domain (RBD) present in the S1 subunit coupled with subsequent fusion of virus and host membrane *via* S2 subunit [48]. MERS-CoV and SARS-CoV initiate infection by binding specifically to cellular receptors dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme 2 (ACE2), respectively [49]. Moreover, like SARS-CoV, SARS-CoV-2 also binds to ACE2 through the viral S protein [42].

Although there is paucity of information regarding the pathogenesis of SARS-CoV-2, literature has it that upon the internalization of MERS-CoV and SARS-CoV genetic material (RNA) in the cytoplasm of a host cell, it becomes encapsulated and polyadenylated with subsequent encoding of different structural and non-structural polypeptide genes [42, 50] which are later separated by proteases with chymotrypsin-like activity, leading to RNA production *via* both replication and transcription processes which are driven by the resulting complex derived from the splitting of structural and non-structural polypeptide genes by proteases [50, 51].

In addition, studies have shown that S protein is essential for the development of antibodies, entry inhibitors and vaccines against coronaviruses [47, 48]. In this regard, Tai *et al*. [52] unraveled an RBD fragment in SARS-CoV-2 S protein and discovered that the recombinant RBD protein aids the attachment of the virus to the human ACE2 (hACE2) receptor. Surprisingly, it was also shown that the RBD could block or inhibit the entry of SARS-CoV-2 into hACE2-expressing cells [52], which thus implies that it could serve as a novel inhibitor for attachment. Hence, we strongly recommend that researchers should harness the antiviral potential of the RBD fragment for rational designing of a novel therapeutic antiviral agent against COVID-19.

Clinical manifestation

COVID-19 infection is characterized by an array of clinical spectrum, ranging from asymptomatic to symptomatic conditions [34]. In asymptomatic condition, the patient or carrier does not exhibit any noticeable signs and symptoms of the disease but can infect a healthy person when close contact ensues between the asymptomatic patient and a healthy individual or when a healthy individual has direct contact with the saliva or discharge from the nose of the asymptomatic patient. The symptomatic condition is depicted by respiratory failure and/or multi-organ and systemic manifestations in the form of multiple organ dysfunctions, septic shock and sepsis [34]. Huang *et al*. [4] showed that COVID-19 symptomatic patients could also be challenged with fever, malaise, dry cough, dyspnea and pneumonia; however, the WHO reported that the most common symptoms of COVID-19 infection are fever, cough, myalgia or fatigue, pneumonia, and complicated dyspnea, whereas less common reported symptoms include headache, diarrhea, hemoptysis, runny nose, and phlegm-producing cough [4, 53].

The Chinese Center for Diseases Control had classified clinical manifestations of COVID-19 based on severity, from mild to moderate, to

severe and to critical illnesses. The mild illness which constitutes about 81% of all COVID-19 infections may manifest as mild fever, cough (dry), sore throat, nasal congestion, malaise, headache, muscle pain, or malaise with the absence of dyspnea and diarrhea and patients recover after one week [9, 34, 54], provided that they are given early supportive health care. The moderate illness is characterized by tachypnea, cough and shortness of breath [34]. A patient with this kind of illness does not exhibit any signs and symptoms of severe disease [54]. Patients with severe manifestation of COVID-19 have been reported to experience progressive respiratory failure due to alveolar damage from the virus, which may lead to death [9].

Diagnosis

Diagnostic criteria, including detailed history of contact and travel, and precise laboratory testing are employed for proper diagnosis of COVID-19 infection [18]. Laboratory testing involves the exploitation of diagnostic tools such as molecular methods, serology and viral culture for the detection of either the viral particle or antibody (notably IgM and IgG) mounted by the body of the infected individual against the pathogen, in clinical specimens such as nasopharyngeal and oropharyngeal swabs, bronchoalveolar lavage, endotracheal aspirate, nasopharyngeal or nasal wash or aspirate, sputum, tissue from biopsy or autopsy from lung, serum, whole blood, stool and urine [54, 55]. Molecular methods such as real-time reverse transcriptase polymerase chain reaction (rRT-PCR) has gained a great deal of attention and to date, it is the most widely used method, probably owing to the fact that it is less time consuming and more sensitive compared to other methods such as serology and viral culture. Real time polymerase chain reaction operates by detecting the genetic material of COVID-19 (RNA) in respiratory samples [18].

A recent key milestone in the rapid diagnosis of COVID-19 infection is the development of rapid Cepheid's GeneXpert Xpress point-of-contact diagnostic system. Following the authorization of this system by US Food and Drug Administration (FDA) on 21 March 2020, the system promised to provide a test with results within hours, rather than days like the existing tests with the assurance that it will be rolled out by March 30 2020. The under-utilization of serology as a diagnostic tool for detecting COVID-19 infection has been attributed to low sensitivity as compared to molecular methods [18]. Nevertheless, the WHO appraised serological testing by asserting that serological survey could support diagnosis with respect to aiding investigation of an ongoing outbreak and retrospective diagnosis of COVID-19 infection once validated serology tests are available [56]. Interestingly, studies with COVID-19 serological data on clinical samples have been published [57] and according to the WHO, the use of viral culture for routine diagnosis of COVID-19 infection is not recommended [56], because it is more time consuming compared to other diagnostic methods [54]. Nevertheless, the role of viral culture *in-vitro* and *in-vivo* antiviral treatment and vaccine evaluation trials cannot be under-estimated [3].

The use of chest CT scan for diagnosing COVID-19 infection has been reported in several studies with the capacity to provide some level of sensitivity in regard to the identification and characterization of lung pathology due to COVID-19 [58, 59]. In a study carried out by Salehi *et al*. [58], early manifestation of COVID-19 was observed to have bilateral multilober ground-glass opacification with a peripheral or posterior distribution. Hence, improved usage of chest CT scan in the laboratory in addition to other diagnostic tools is encouraged in order to further enhance proper diagnosis of COVID-19 infection.

Antiviral regimen/management

So far, specific antiviral drugs or vaccine for the treatment of COVID-19 infection are currently not available, hence, symptomatic treatment, oxygen supplementation and supportive care are strongly advocated for treatments [4, 34]. As majority of COVID-19 cases are mild, patients with mild illnesses should be cared for *via* early supportive care and monitoring through the use of nutritional supplements, external cooling, oxygen supplementation, anti-bacterial therapy and acetaminophen. Furthermore, extracorporeal membrane oxygenation (ECMO), high flow oxygen, convalescent plasma and glucocorticoid therapy are strongly recommended for critically ill patients [60]. In addition to the aforementioned management strategies, there are laid down guidelines that

must be followed strictly in order to avert negative consequences that may surface with respect to antimicrobial resistance among others. For instance, unnecessary and indiscriminate use of antibiotics by patients should be avoided [54] coupled with total avoidance of systemic corticosteroid administration in patients with acute respiratory distress syndrome (ARDS) while extracorporeal membrane oxygenation (ECMO) should only be considered as a treatment of choice in patients with refractory hypoxemia [34].

For therapeutic purposes, albeit there is no specific antiviral treatment or vaccine against COVID-19 infection, hence as an alternative in this context, antiviral drugs with broad-spectrum activity including HIV-protease inhibitors and nucleoside analogues with the capacity to render viral infection attenuated are currently considered the only treatment option available [61]. On this note, the laid-down guidelines with respect to antiviral regimen for COVID-19 infection include oral administration of 500 mg lopinavir, 75 mg oseltamovir, 500 mg ritonavir twice a day coupled with the intravenous administration of 0.25 g ganciclovir for 3-14 days, and these are all broad-spectrum antivirals [7].

In addition to the aforementioned anti-virals, other antiviral drugs that have shown remarkable potency against COVID-19 infection include, ribavirin, abidor [60], chloroquine and remdesivir [62], neuraminidase inhibitors, RNA synthesis inhibitors, peptide (EK1), inhalational alpha- and beta 1a intereferon and a combination therapy involving lopinavir and ritonavir [2, 12, 61], hence engendering more treatment options. It should be noted that aerosol administration of beta 1a intereferon has been observed to be among the potentially interesting approaches for therapy or prophylaxis for COVID-19 infection [35].

Prevention and control

The best preventive measures to stop or slow down the spread COVID-19 virus is by the sensitization of the populace about the virus, the disease it causes and more importantly how it spreads. To prevent infection and to slow transmission of COVID-19, the WHO recommends washing of hands regularly with soap and water, or cleaning them with alcohol-based hand rub (sanitizer), maintaining at least 1-meter distance from a person coughing or sneezing. Also, avoid touching of face (eyes, mouth and nose), cover mouth and nose when coughing or sneezing and stay home when feeling unwell. But it must be reported that refraining from smoking and avoiding other activities that weaken the lungs is key to preventive measures. In addition to this, practicing respiratory etiquette such as coughing into a flexed elbow or disposable tissue is paramount in curbing its spread [34].

Suggestive approaches for candidate vaccine and/or novel therapeutic antiviral development for SARS-CoV-2

Without refute, vaccines represent the most potent medical intervention for combating infectious diseases. In this regard, the rapid spread and enormity of COVID-19 pandemic have strongly necessitated the swift need for the development of vaccine for COVID-19, thereby making this aspect a humanitarian and scientific priority. At present, no specific antiviral treatment or vaccine against COVID-19 infection has been documented, hence sprouting the necessity for suggestive approach(es) for developing candidate vaccine and/or novel antiviral(s) for SARS-CoV-2.

Following the instance reported by Thevarajan *et al.* [10] about a 47-year-old patient whose recovery was observed to be largely dependent on the immune response to the pathogen as follicular helper T cells (TFH cells), SARS-CoV-2-binding immunoglobulins IgM and IgG, increased antibody-secreting cells (ASCs), activated CD4+ T cells and CD8+ T cells were detected in her blood, despite the fact that she was only subjected to intravenous fluid rehydration with no oxygen supplementation or administration of steroids, antibiotics and antiviral agents. The report therefore signifies the potential usage of previously mentioned immune parameters in the evaluation of new interventions that might engender the development of protective candidate vaccine and/or minimization of severity of COVID-19 infection. Nevertheless, the characterization of these immune parameters in larger cohorts of individuals with COVID-19 infection of varying severities is recommended to further justify their promising features with respect to candidate vaccine development among other benefits.

As stated earlier, the pathogenesis of COVID-19 is still poorly understood, however, researchers are of the opinion that the pathogenesis of SARS-CoV and MERS-CoV could still provide an insight into COVID-19 pathogenesis [63], probably owing to the striking similarity between the viruses. Antigen-presenting cells (APCs) have been implicated in the processing and presentation of antigen peptides of SARS-CoV and MERS-CoV [64] with little or no clue on the antigen presentation of SARS-CoV-2. However, revitalizing this aspect coupled with disentangling of induction potential capability of APCs on T-cell lymphocytes against SARS-CoV-2 could provide more insight into the development of candidate vaccine. For instance, success stories have been documented on the development of vaccine for viral infections through proper understanding of viral pathogenesis with respect to the induction of T-cell lymphocytes by APCs [65]. On this note, DNA sequence of a virus-encoding antigen is incorporated into a genetically engineered plasmid DNA, the method which has been observed to offer the advantage of endogenous (that is, within the host cell) expression of vaccine antigen coupled with subsequent antigen processing and expression of major histocompatibility complex (MHC) class I in APCs, thereby culminating into the induction of T-cell responses [65].

Interestingly, the antigen presentation of SARS-CoV has been documented to be mainly dependent on MHC class 1 molecules [64], hence depicting the usefulness of this mechanism for DNA vaccine development for SARS-CoV-2. Moreover, it should be noted that enhancing the immunogenicity of the plasmid DNA is key to ensuring the direct intake of the recombinant DNA by APCs [66]. In this regard, several methods, including the use of needle-free delivery systems, incorporation of plasmid DNA into various particles, metals, or lipid formulations and the most popular method which involves the application of pulsed electrical currents to the region of immunization, termed '*in vivo* electroporation' have been developed in an attempt to improve the uptake of plasmid DNA into APCs while producing remarkable levels of immunity [67]. Above all, this approach could be of great significance for rational designing of a novel vaccine for COVID-19, hence, the need for researchers to direct effort into this area.

Furthermore, other vaccine strategies that could be novel approaches for SARS-CoV-2 will employ direct targeting of COVID-19 antigens such as S protein or N protein to MHC class I molecules. In light of this, soluble antigens of COVID-19 may be combined with adjuvants that directly target and/or activate APCs such as dendritic cells and macrophages among others. However, ascertaining the type of APCs that are involved in COVID-19 pathogenesis and their unique capabilities for efficient cross-presentation of soluble antigens to the class 1 pathway coupled with improved knowledge about the expression and location of toll-like receptors (TLRs) and surface antigens on APCs could promote tailoring of vaccine strategies for stimulation of the response of choice [65].

It has been documented that in an attempt to forestall the detection of ds RNA of SARS-CoV and MERS-CoV by host immune cells, the viruses induce the development of double-membrane vesicles devoid of evolutionarily conserved microbial structures termed pathogens-associated molecular patterns (PAMPS) since these conserved structures can easily be recognized by pathogen-recognition receptors (PRRs) found on APCs [68]. Interferon I (IFN-α and IFN-β) has been shown to have protective effects on SARS-CoV and MERS-CoV; however, resistance to IFN *via* blockage of IFN induction and inhibition of nuclear transport of IFN regulatory factor 3 has been documented [69]. This therefore suggests that debottlenecking immune evasion mechanism of coronaviruses, including SARS-CoV-2 could be a panacea towards the development of a novel therapeutic antiviral for COVID-19 infection.

Membrane fusion, furin activation and clathrin-dependent and –independent endocytosis have been observed to play critical roles in the internalization and infectivity of coronaviruses [70]. As this connotes an important stage in the pathogenesis of coronaviruses, including SARS-CoV-2, it could serve as a novel approach for developing a new therapeutic antiviral agent.

CONCLUSIONS AND RECOMMENDATIONS

With efforts to combat the ravaging spread of COVID-19 globally as evident by researches geared towards vaccine development, the guidelines to prevent the spread as given by the WHO should be strictly adhered to as individuals are saddled

with responsibility of managing their health towards improving their immune system by feeding on good diet. This review also recommends that researchers should focus on the effort to boost the immune system to wade off the virus by harnessing immune parameters previously mentioned coupled with the activation of T-cell responses *via* the enhancement of induction capability of APCs using DNA plasmids and viral adjuvant-coated soluble antigen and not only on drug development as this may even be a guide towards vaccine development for the virus. We also recommend that researchers should consider the possibility of arriving at the combination of modalities that can stimulate CD4 and CD8 T-cells as well as antibodies against COVID-19 infection.

AUTHORS' CONTRIBUTIONS

The research idea was conceptualized and designed by BOE and OSJ. Data acquisition, draft preparation and writing were carried out by BOE, AOE, KGV and OSJ. The final editing was done by BOE and OEL.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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