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Review Article

COVID-19 Variants, Available Treatments, and Vaccinations: An Overview Study

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Abstract

SARS-CoV-2 is the recent variation of the corona virus which is infecting people around the world and has affected more than 258 million people worldwide. Upon observation, the virus is similar to the coronavirus which spread from the horseshoe bat or wild animals to human beings. Up to date, there have been three major variants of the coronavirus which have been identified in UK, South Africa, and India which are spreading to other countries. Based on the current data, it is suggested that the incidents of repeated infection with SARS-CoV-2 is related to the level of neutralizing antibodies and the retained memory response which follows infection. Moreover, recently, a critical issue arises in relation to the association of black fungus and COVID-19, and urgent investigation is required. As a treatment method of COVID-19, FDA has recently approved the feasibility of Remdesivir to treat COVID-19 as emergency use authorization (EUA). There are also various possible antivirals which are still undergoing clinical trial. After widespread of the vaccine, the results showed that EUA vaccines have been effective in controlling COVID-19 in patients. However, these licensed vaccines ought to be reviewed to ensure they are also effective in combating the rising variants of SARS-CoV-2.

***Keywords*:** Covid-19 variants, Covid-19 pandemic, antiviral treatment, Covid-19 vaccines

المتحورات المختلفة والعلاجات المتاحة والتطعيمات الخاصة بفيروس كورونا: دراسة عامة

الخلاصة

يعد متحور السارس - كوف- 2 احدث اختلاف فى فيروس كورونا الذى يصيب الناس فى جميع انحاء العالم واصاب اكثر من 258 مليون شخص فى جميع انحاء العالم. ويشبه المتحور الجديد الفيروس التاجي الذي ينتشر من خفاش حدوة الحصان أو الحيوانات البرية إلى البشر. حتى الآن، كانت هناك ثلاثة متغيرات رئيسية من الفيروس التاجي التي تم تحديدها في المملكة المتحدة وجنوب أفريقيا والهند التي تنتشر إلى بلدان أخرى. واستنادا إلى البيانات الحالية، يقترح أن تكون العدوى المتكررة بفيروس الكورونا مرتبطة بمستوى تحييد الأجسام المضادة والاستجابة للذاكرة المحتجزة التي تعقب العدوى. وعلاوة على ذلك، في الآونة الأخيرة، تنشأ قضية حرجة فيما يتعلق باالأرتباط بين الأصابة بالفطريات السوداء و COVID-19، وهناك حاجة إلى إجراء دراسات عاجلة بهذا الخصوص. ولعلاج COVID-19 ، وافقت إدارة الأغذية والعقاقير مؤخرا على استخدام ريمديسفير لعلاج COVID-19 والترخيص بالأستخدام الطاريء. وهناك أيضا العديد من مضادات الفيروسات المحتملة التي لا تزال تخضع للتجارب السريرية. بعد انتشار اللقاح على نطاق واسع ، أظهرت النتائج أن اللقاحات كانت فعالة في السيطرة على انتشار COVID-19 في المرضى. بيد انه يتعين مراجعة هذه اللقاحات المرخصة لضمان فعاليتها ايضا فى مكافحة المتحورات المتزايدة من السارس- كوف- 2 .

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INTRODUCTION

Human coronaviruses (HCoVs)

Human coronaviruses belong to the order Nidovirales, suborder Cornidovirineae, family Coronaviridae, and subfamily Orthocoronavirinae. It comprises the alpha, beta, gamma, and delta CoVs, which are divided into four genera. Both viruses that affect the upper and lower respiratory tract are classified as human coronaviruses. HCoV-229E (Alphacoronavirus, subgenus Duvinacovirus), HCoV-NL63 (Alphacoronavirus, subgenus Setracovirus), HCoV-OC43, and HCoV-KHU1 are among the viruses that cause Upper Respiratory Tract Infections (URTIs), accounting for ten to thirty percent of all common cold infections in humans. The first two is related to Betacoronavirus subgenus. SARS-CoV and SARS-CoV-2 (Betacoronavirus subgenus, Sarbecovirus), as well as MERS-CoV, are the three coronaviruses that cause severe Lower Respiratory Tract Infections (LRTIs) (Betacoronavirus subgenus, Merbecovirus) [1].

SARS-CoV-2 variants database

Among the variants which have emerged so far; two variants have been a cause for concern. The Nextstrain classification was modified to include labels which are consistent with the rising variants and the extent to which each of the variants spike affect transmissions. Some of the new clades are inclusive of 20D, 20E, 20F, 20G, 20H/501Y.V2, and 20I/501Y.V1 (Table 1).

Table 1: The origin and distribution of SARS-CoV-2 clades based on Nextstrain clustering.

Clade	Root Clade	Main characteristics	Region
19A	The root clade		China then to the rest of Asia
19B	The ancestor Wuhan strain (Dec. 2019)		Wuhan strain
20A	19A	Spike: D614G	Europe
20B	20A	Spike: D614G	Europe
20C	20A	Spike: D614G	North America
20D	20B	ORF1a: 1246I and ORF1a 3278S	South America, Southern Europe, and South Africa
20E	20A	Spike: 222V, N: 220V, ORF10: 30L, and ORF14: 67F	Europe
20F	20B	ORF1a: 300F and Spike: 477N	Australia
20G	20C	ORF1b: 1653D, ORF3a: 172V, N 67S and N 199L	USA
20H/501Y.V2	20C	Spike: 80A, 215G, 484K, 501Y, and 701V	South Africa
20I/501Y.V1	20B	Spike (501Y, 570D, 681H) ORF8(27*)	UK

The VUI 202012/01 variant of SARS-CoV-2, which has been discovered in the UK is under study, it comes from the clade GR, lineage B.1.1.7 of the 20B. This will be referred to as the Concern Variant (VOC). This VOC has spread throughout the world, including in Africa (Gambia, Mayotte, and Nigeria), Europe (almost all countries), Asia (Bangladesh, Hong Kong, India, Iran, Israel, Jordan, Malaysia, Oman, Pakistan, Singapore, South Korea, Thailand, and the United Arab Emirates), North America (Canada, Jamaica, Mexico, and the United States of America) and Australasia (Australia and New Zealand). Variations in the spike of the viral proteins have resulted in different mutations in the VOC. S1 (deletion 69-70, deletion 144, (RBD: N501Y), A570D, D614G), S1/S2 (cleavage site: P681H), and S2 (T716I, S982A, D1118) are all present [2]. Another well-known VOC has arisen in South Africa, with 80A, 215G, 484K, 501Y, and residues of the 701V amino acid protein. This version has been found in Africa (Botswana, Ghana, Kenya, Mayotte, Mozambique), Asia (Bangladesh, Israel, Japan, South Korea, and the United Arab Emirates), Australasia (Australia and New Zealand), and Europe (Austria, Belgium, Denmark, Finland, France, Germany, and the United Kingdom). These mutations have developed rapidly due to a number of varied reasons. For example, extended periods of infections among patients with immunosuppressive conditions is a possible cause of the development of these mutations. Another possible reason is the rapid rate of mutation induced by reinfection that impacts the immune system. In addition to the incidents of an animal contracting the virus and then transferring it back to humans which is justified in the case of the mink in Denmark (deletion 69–70 and Y453F) [2-4]. Due to mutations, some viruses begin to be easily transmitted between humans and animal as their affinity for binding also increases. Mutations can also result in the virus gaining the ability to evade the responsiveness of the immune system of the host. They can also change the epitopes by neutralizing them. The initials D614G variant increased the rate at which viral cells were infected but it did not change the symptoms and the outlook of the disease. 382 nucleotide deletions in SARS-CoV-2 Singapore strains were used to establish the SARS-CoV-2 phenotype. The transcription regulatory sequence (TRS) of ORF8 was extracted as a result of these deletions, with the expectation that virus replication will be reduced. Towards the end of the 2003 outbreak, a related phenotype deletion was discovered in SARS-CoV [5-7]. One isolation combined with 81 nucleotide deletions with subsequent deletions of 27 amino acids in the ORF7a were also noted in Arizona. However, to date, these variants have since ceased to exist [8]. In a B-cell epitope; there was discovered an D614G amino acid substitution. P4715L and P323L amino acid substitutions in ORF1ab and RdRp were found in a significant number of SARS-CoV-2 strains with the D614G mutation. In the G, GR, and GH clades, the Spike D614G mutation is often linked to higher viral loads, whereas the rapidly spreading

variants are linked to Nsp12P322L. The GR clade was found to be more prevalent in patients with serious disease manifestations. Grubaugh *et al*., on the other hand, dispute this notion, questioning the likelihood of a specific position for the D614G mutation based on existing evidence and its effect on the current epidemic [4,9-11]. The impact of VUI 202012/01 mutations is still poorly understood. There is a scarcity of information on how the virus binds to cells, the rate of transmission, and the scope of the disease. It is suggested that the binding affinity to Angiotensin-converting Enzyme-2 (ACE2) is increased by N501Y, and this is gathered from evidence of a study which comprised experimentally-infected mice. While both N501Y and P681H were previously noticed in SARS-CoV-2, this is the first time they've both been found in the same virus. The ORF8 Q27stop mutation in the VUI 202012/01 virus strain decreases the ORF8 protein's versatility by limiting its activity. ORF8 deletion, on the other hand, had only a marginal effect on virus replication [12-14]. As a result, it has been established that the growth and increase of neutrophils aids in the fight against coronaviruses. L18F, A222V, N439K, G476S, S477N, T478I, V483A, E484Q, D614G, and E780Q are among the strains with various amino acid substitutions in the spike glycoprotein. As a result, an analysis may be carried out to investigate the importance of the substitutions.

India's Covid-19 variant

Scientists are trying to figure out what role coronavirus variants, including a new one known as B.1.617, are playing in India's fastest-growing Covid-19 outbreak. There is mounting evidence that it spreads faster than the B.1.1.7 strain from the United Kingdom, also known as the Kent variant, although this has yet to be proven conclusively. It was uncommon until early March 2021 when it became the most commonly recorded version. Many other countries have caught on to it, and some are seeing rapid growth. It has become more common in the United Kingdom than B.1.1.7, though overall case numbers remain poor. There's no proof that B.1.617.2 is any deadlier than B.1.1.7 or has any different symptoms. In December 2020, India was the first country to detect another subvariant known as B.1.617.1. By late March 2021, B.1.617.1 had accounted for half of all recorded sequences, but by April, the percentage had dropped [15]. It has been found in a number of other countries, but only a small percentage of cases are reported. The term "double mutant" refers to two mutations in the virus's outer spike protein that are of particular concern. These two mutations, known as L452R and E484Q, may reduce the effectiveness of antibodies to older variants or existing vaccines, but this has yet to be proven. B.1.617.2 does not have the E484Q mutation and has other mutations that B.1.617.1 does not have. The mutations E484Q and L452R are not special to B.1.617.1. Other forms of both mutations have been discovered in other parts of the world. Initial research suggests that antibodies from people who have been infected with older strains or who have received the Covaxin or Oxford/AstraZeneca vaccine (known in India as Covishield) will still protect them from B.1.617 infections. In India, B.1.617.2 has been the most popular version. The situation, however, varies from state to state. Other variants found in the second wave in India include B.1.1.7, the P.1 variant first discovered in Brazil, and the B.1.351 variant that developed in South Africa. The spike protein of certain B.1.617.1 virus has an additional mutation called V382L. This is what the word "triple mutant" refers to (15,16). This mutation has been discovered in other viruses, and there is no proof that these "triple mutant" viruses propagate faster or are more deadly (15,17). Almost all coronavirus variants can be identified solely by sequencing the virus's genome. To determine if new variants are more transmissible or deadly, researchers must examine a large number of them to see whether there are major variations in how they spread or impact people. The majority of countries, including India, do little or no sequencing, that is why there is so much debate over whether some variants are truly riskier.

COVID-19 AND BLACK FUNGUS

Some scientists feel that a severe case of COVID-19 could compromise the immune system. This could make people more susceptible to other diseases, especially if they are immunocompromised. An illness known as mucormycosis, sometimes known as black fungus, is of special concern. In India, 90 persons who recovered from COVID-19 died of mucormycosis, prompting requests for a mucormycosis epidemic to be declared by India's health officials. India has a higher rate of mucormycosis cases due to a number of causes. In India, for example, more than 30 million people have been diagnosed with diabetes. Despite this, before the COVID-19 pandemic, the number of cases of mucormycosis was quite modest, despite the fact that prevalence was rising. Eye surgeons, who frequently have to remove an eye to treat mucormycosis, have seen a significant increase in cases. Surat, Gujarat's sixth-largest city, recorded 40 cases and eight lost eyes in just 15 days [18]. About two weeks after recovering from covid-19, the majority of instances occur in diabetic individuals with poorly controlled blood sugar. Some experts attribute the spread of the fungus to overuse of steroids in the treatment of covid-19, while others believe the virus has immunosuppressive component [18,19]. Therefore, a thorough investigation is required to identify the main trigger that cause suddenly black, yellow, and white fungal infection.

Potential causes of the emergence and variation of SARS-CoV-2

Coronaviruses are prone to high-frequency recombination events. This led to the virus evolution of SARS-CoV, MERS-CoV and it was also supposed to have been a result of a recombination occurrence of the receptor binding domain (RBD) derived from Malayan pangolin coronavirus. Majority of the SARSr-CoV viruses are not

inclusive of ACE2 but they can acquire such ability through mutations and emergence of new strains of the virus. Therefore, there has been a successful synthesis of chimeric SARS coronaviruses. A bat-SCoV genome was combined with the binding domain of the SARS-CoV receptor [1,20,21]. The chimeric virus of murine containing SARS-CoV backbone with SHC014 spike bat coronavirus (BtCoV HKU5-SE) was combined with BtCoV HKU5 containing the SARS-CoV spike (S) glycoprotein (BtCoV HKU5-SE). Even without interacting with the human or mouse respiratory systems, this virus was found to replicate quickly. These findings bolstered the theory that natural recombination can occur in the human genome and increase the risk of forming other viruses derived from natural circulating beta-coronavirus strains because their effect on humans cannot yet be quantified [1,22].

Causes of reinfection with COVID-19

SARS-CoV-2 reinfection can happen for a variety of reasons. For instance, patients who have been exposed to SARS-CoV-2 and have detectable IgG+ RBD-specific plasma antibodies are at risk of reinfection for up to 90 days [23,24]. The period of seroconversion commences within 70 days in about half of symptomatic patients and within 14 days for all patients. In mildly infected patients, the IgG is undetectable. This contrasts previous findings, but it has since been rationalised noting that it could be due to the use of detection techniques with low sensitivity and the difference in the targeted. This is justified by how all patients with undetectable IgG were detected to have neutralizing antibodies using neutralisation assay [23, 25-27]. The intensity of COVID-19 is proportional to the level of IgG antibody titres because the more severe the case was; the more antibody titres were found. In patients with mild cases of COVID-19, there were specific immune memory cells which indicated the possibility of antiviral activity which lasts up to 3 months from the incident of exposure. In the initial period of three weeks; there was an eminence of IgM+ memory preceded by a light increase of IgG1+ memory B cells [28-30]. The cells reflected CD27 and were positively linked with the T follicular helper (Tfh) cell number which supposes high virulence. Furthermore, there was upregulation noted in the B cells of CD80, CD180 and TACI which would be supposedly reactivated once there is reinfection. The B Cell memory is estimated to last up to 8 months and within that period it would offer protection from any potential reinfection. Therefore, it is important to note that when there is reinfection, the symptoms and virulence would be milder [28]. The IgA^+ which works contrary to the RBD depleted sharply over a period of three months which indicates a shorter lifespan of the plasma blasts IgA, SARS-CoV-2-specific memory B-cells. Instead, there was a detection of mainly IgG^+ B cells which had lower levels of cells which reflected the IgM and Ig. These results indicate that there is an expectation for memory B cells to be quickly responsive to SARS-CoV-2 re-exposure, and they would quickly trigger the generation of protective antibodies and avert the possibility of severe forms of infection. In-vitro stimulation of CD4 + memory T cells from patients who recuperated from SARS-CoV-2 has a quick detection of Th1- and Th17- cytokines and upregulation of both ICOS and CD40L on $CXCR5^+$ cells [1,29]. There is evidence that as time progresses, there is reduction in the levels of SARS-CoV-2 antibodies. This would indicate the retrenchment of the responsiveness of the immune system. Mild COVID-19 triggers an increase in memory B-cells and $CD4^+$ memory T-cells. However, what causes the varied levels of severity of the disease is dependent on one's unique immune memory and subsequent immune protection [29,31]. There have been several incidents which reported reinfection of patients from different parts of the world. Homologous reinfection and antibody titres determine the level of protection which one could have from reinfection. However, there are not yet any drastic changes to the spike protein according to the GISAID sequence database. This would confirm that in the case of reinfection, it would be a milder case than the prior infection [1,32]. From observation, three patients who had been infected by SARS-CoV were exposed to it again but they did not fall ill. In an overnight camp where there was presence of the virus, there was previously infected person who did not get re-infected yet those who were having their first-time exposure to the virus were infected [33]. However, there have also been cases where one is re-infected and they get a severe case in comparison to their initial infection [34, 35]. A possible cause would be that the patient could be exposed to an expansive viral load, or their immune system could be poorly neutralizing or non-neutralizing antibodies which would provide a progenitor for antibody-dependent enhancement (ADE). However, it is still unknown which severe diseases one can get upon reinfection with the virus [1]. These cases were noted in both SARS-CoV and MERS-CoV, where it was thought that using antibody-dependent entry, the ACE-2 receptor could be successfully re-attacked [36]. Furthermore, ADE was identified when anti-spike protein antibodies were less potent but anti-nucleoprotein antibodies were absent. Furthermore, the mAbs that target the SARS-CoV spike epitopes (apart from RBD e). Rabbits developed ADE after being exposed to non-neutralizing antibodies against MERS-CoV [37]. Despite the presence of ADE in viruses close to SARS-CoV-2, animal models are insufficient to represent immune-pathogenesis in humans. There is currently insufficient evidence to suggest that ADE will affect COVID-19 inpatients' outcomes. Furthermore, since the majority of viruses are species-specific, the pathogenesis of a model virus strain in animals does not accurately represent how it would respond in humans. Plasma therapy improved the condition in infected patients and their survival rate by facilitating a passive transfer, where the therapy was used [1,38,39].

DEVELOPMENT OF VACCINES AND ANTIVIRAL TREATMENT

Approved COVID-19 treatment as emergency use authorization (EUA)

Remdesivir has been approved by the FDA as a treatment for COVID-19 as EUA. It is an adenosine nucleoside analogue which stops the virus from replicating itself in the host. The inhibition is done through binding to RdRp M and nsp1. Notably, the combination of M and S together with M and N facilitate the assembly of viral proteins [40,41]. Veklury® (Remdesivir) was the first drug authorized by the FDA for the treatment of COVID-19, and it was approved on October 22, 2020. The patient must be at least 12 years old and weigh more than 40 kilograms to be eligible for the prescription. The FDA granted Veklury® an EUA to treat hospitalized paediatric patients weighing less than 50 pounds. For children older than 12 years and with a minimum weight of 40kg, the drug is administered with a first dosage of 200mg then subsequent dosages of 100 mg. For children with a minimum weight of 3.5kg and maximum of 40kg, treatment is done through an initial single dosage of 5mg/kg with subsequent dosages of 2.5 mg/kg. An intravenous infusion which lasts between 30 and 120 minutes is used to administer the drug. When there is no improvement in the patients, an extension of 5 days of treatment could be provided for the patients. Veklury® has been proven to have notable side effects which include liver injury, nausea, rash, and allergic hypersensitivity [1]. Remdesivir was also proven to shorten the recovery time of patients based on a clinical trial which was sponsored by the NIH. However, a clinical trial sponsored by WHO SOLIDARITY refuted these claims [42].

Potential antiviral drugs

There are several drugs which are under clinical trial as potential antiviral drugs targeted at the treatment of COVID-19. Favipiravir (T-705), a viral RNA polymerase inhibitor, was approved for marketing in China's Zhejiang Province on February 16, 2020 [1]. Five FDA-approved drugs are currently being investigated for their effectiveness in treating SARS-CoV-2. Chloroquine phosphate (an old antimalarial drug), ribavirin, penciclovir, nitazoxanide, and nafamostat, as well as two viral RNA polymerase inhibitors, are among the five medicines. However, the drugs which were found to be more effective *in vitro* are Remdesivir and chloroquine [40]. Regarding the in vitro antiviral activity against corona virus, it will ostensibly prevent the virus from entering the body by interfering with the cell receptors for SARS CoV-2 S protein and human ACE-2, as well as TMPRSS2. It binds to SARS-CoV-2 nsp14, N, and M proteins, ostensibly interfering with cell replication and N nuclear import, which is mediated by IMP/1. It is likely that it binds to SARS-CoV-2 Mpro and PLpro, preventing post-translational cleavage of viral polyproteins [1,43,44]. Chloroquine and hydroxychloroquine block the terminal glycosylation of ACE-2 interfere to prevent viral entry and alkalinise of the endosome pH to prevent the post-entry mechanism. They would also clock the biosynthesis of sialic acid. There is increasing evidence that hydroxychloroquine would be an effective drug to treat patients infected with COVID-19 [45-47]. However, there are also multiple clinical trials which deny the effectiveness of hydroxychloroquine as either a pre- or post-exposure prophylaxis. The studies deny that this drug would have any value in the development of COVID-19 treatment. Therefore, this is still an area of ongoing study; to explore the effect of chloroquine and hydroxychloroquine in the treatment of COVID-19 thus it would be too early to either pass or dismiss the drug as a potential treatment [1,46,48]. Camostat mesylate is another potential therapy for SARS-CoV-2 (a serine protease inhibitor). In BALB/c mice, the drug inhibits TMPRSS2 and has been shown to block SARS-CoV (49). Furthermore, bromhexine hydrochloride (a mucolytic cough suppressant that inhibits TMPRSS2), which has been shown to be effective in the treatment of influenza viruses and coronaviruses, may be a possible treatment [50]. Following the treatment, there was a disappearance of the virus and a substantial decrease of different cytokines. EIDD-2801 is a ribonucleoside analogue N4-hydroxycytidine (NHC) which demonstrates high efficiency in combating viruses was found to be just as effective for the treatment of SARS-CoV-2 [51]. After 48 hours of administration, EIDD-2801 substantially lessened *in vivo* virus titres. The development of the disease was curbed when the drug was administered as a pre-exposure prophylactic therapy [52].

IMMUNOTHERAPY

Convalescent plasma therapy

Immunotherapy with the use of convalescent plasma derived from successfully treated patients has revealed success in the treatment of SARS-CoV-2 infected patients earning EUA by the US FDA. The clinical trials reveal that, regulation of the basal temperature and optimization in clinical and laboratory metrics were noted following administration of convalescent plasma. For increased efficiency, this therapy was administered in conjunction with complementary antiviral therapies. Several studies have supported that the use of COVID-19 convalescent plasma in varied amounts is successful. In one instance a dosage of convalescent plasma (400 ml, a neutralisation titre >40) helped in the regulation of body temperature and improved PaO2/FiO2 within 72 hours of treatment. The viral load was also improved and inflammation was reduced [53]. Further research showed that treatment with 200 ml convalescent serum (neutralization titre 640) improved clinical findings and laboratory biomarkers. Patients with serious COVID-19 illness improved after receiving 500 ml of convalescent plasma within 48 hours of admission. To administer to patients, a minimum of 200 ml of convalescent plasma infusion was needed [54].

Convalescent plasma helped in the reduction of the viral load of SARS-CoV-2 in patients who were treated using steroids. There are above 170 clinical trials ongoing which are being conducted to see if using plasma therapy in COVID-19 patients is successful and healthy. The US FDA revised its EUA in early February 2021, based on findings from patient care and rehabilitation, and agreed to limit the use of plasma therapy in the treatment of COVID-19 patients [1,55].

Monoclonal antibody therapy

On November 21, 2020, the FDA granted an EUA for the use of casirivimab and imdevimab as monoclonal antibody therapies (mABs) against the SARS-CoV-2 S protein. For mild to moderate COVID 19 cases, the medication is given as an intravenous infusion to patients who are at least 12 years old and weigh at least 40 kilograms. It is not recommended for patients with serious symptoms or those who are at high risk of developing severe COVID-19 together with patients aged or above 65 years and those with chronic illnesses. The cumulative therapy treatment improved the outcome of clinical cases within a month of treatment. However, this therapy is not advisable for patients who are already been hospitalized and are in need of ventilation assistance or high-flow oxygen. If such patients are subjected to the treatment, it would result in their conditions deteriorating [56].

Approved vaccines for COVID-19

There are currently five vaccines that have been authorised. The vaccines are: I BNT162b2 (Pfizer and BioNTech) and mRNA-1273 (Moderna); ii) two inactivated vaccines (SinoPharm and Bharat Biotech); and iii) a non-replicating adenovirus vector vaccine (SinoPharm and Bharat Biotech) (AstraZenca). Pfizer and BioNTech's BNT162b2 candidate vaccine (mRNA in lipid nanoparticles) was the first to be approved as it scored 95% efficacy, followed by SinoPharm inactivated vaccine, Moderna (mRNA-1273) with 94.1% vaccine efficacy and more recently the AstraZenca adenovirus vaccine with 90% efficacy in combination with Bharat Biotech's COVAXIN (the first indigenous vaccine) [57-60]. The vaccines which have been release are administered in two dosages; and these have been efficient in providing maximum protection. Furthermore, there are additional potential vaccines which are at varied phases of preclinical and clinical trials. These vaccines are inclusive of RNA vaccines, DNA vaccines, non-replicating viral vector vaccines, replicating viral vector vaccines, inactivated vaccines, live attenuated vaccines and subunit vaccines. 172 vaccines are in preclinical phases and 56 vaccines are in clinical phases [1]. Inactivated vaccines are propagated in Vero cells and chemically deactivated with propiolactone before being adjuvated with aluminium hydroxide (or other adjuvants). The non-replicating adenovirus vector vaccines include: I ChAdOx1-S; ii) ChAdOx1-S; iii) ChAdOx1-S; iv) ChAdOx1 (Oxford and AstraZeneca). They use chimpanzee adenovirus as a backbone to unleash the SARS-CoV-2 spike protein. ii) the human adenovirus 5 (Ad5)-based CanSino Biological Inc. vaccine, and iii) the non-replicating adenovirus recombinant vaccine containing both Ad26 and Ad5. The Gamaleya Research Institute was responsible for its development [61]. A potential challenge of this vaccine arises when two dosages have been administered and the presence of a humoral anti-human adenovirus antibody. This can be avoided by giving the initial dose with one vector and then supporting it with another. COVID-19 mRNA vaccine has been encapsulated in lipid nanoparticles (LNP). Moderna/NIAID produced mRNA-1273, and BioNTech/Fosun Pharma/BNT162b1 Pfizer's and BNT162b2 were derived from BioNTech/Fosun Pharma/Pfizer [62]. Another effective vaccine is Novavax, a subunit vaccine containing recombinant purified SARS-CoV-2 spike protein in combination with Matrix-M1 adjuvant. Adjuvated protein-based vaccines are the most potent, followed by mRNA vaccines, ChAdOx1-based vaccines, and AdV5-based vaccines. In terms of side effects; vectored vaccines prove to have the most intense side effects while the inactivated vaccines, protein-based vaccines and mRNA vaccines have the least. A live attenuated vaccine is effective as a vaccine for humans. This is supported by how the model has been effective for combating several diseases such as poliovirus, measles, rubella, mumps, and yellow fever. They are successful because, when given to humans, the vaccine simulates a normal infection while still ensuring that no mucosal, humoral, or cell-mediated immune response to the virus exists. However, it would take time and various stages of development to ensure that this type of vaccine is safe and effective for combating viruses in humans. At the moment, there currently exists are SARS CoV-2 live attenuated vaccines. Two of the vaccines are from India while the other one is from Turkey. Two of them are currently undergoing pre-clinical testing while Codagenix/Serum institute of India is in clinical phase I [1,63].

CHALLENGES

There is acceleration in developing a vaccine because a potent vaccine against COVID-19 is needed. However, this is curbed because in developing a vaccine there is needed to consider the long-term effects of the vaccine and to ensure that they will not compromise human safety in the long run. There are also limited studies which can quantify the effects of the different vaccines on the autoinflammatory responses such as paediatric inflammatory multisystem syndrome which are being detected inSARS-CoV-2 (PIMS-TS) [64]. There has been a sign of vaccine-associated enhanced disease (VAED) in preclinical trials of SARS-CoV and MERS-CoV vaccines which have been linked to low neutralizing antibodies. On the other hand, this issue is not yet detected with the SARS-CoV-2 and mRNA-1273 vaccine. Therefore, VAED monitoring needs to be conducted with each ongoing vaccine trial. Another essential concern is to

determine the lifespan of neutralizing antibodies and protective memory immune responsiveness. Currently, they have been noted to last for up to 90 days after the second booster dose of vaccine [65-67]. The virus has been mutating rapidly thus there is pressure to make vaccines which would cope with the ongoing viral mutations. The progressive analysis of virus escape mutation is needed to help in the formulation of appropriate vaccines which will effectively combat the virus. Similar to fellow non-replicating vaccines, it is supposed that the SARS-CoV-2 virus infection duplicates at the portal of entry of vaccinated subjects, when local immunity is not developing or progressing. This is an important consideration to avert scenarios where vaccinated individuals can spread the disease to healthy individuals around them. According to the WHO, by the end of 2021 there could be 2 billion doses of an effective vaccines will be available. The world population is at 7.7 billion thus this implies that by 2021 there would still be insufficient vaccines for the entire world population. WHO has created a priority list for those which should be the first ones to be vaccinated. The extensive list includes healthcare workers, the elderly population above 60 years of age and people younger than 60 years who have comorbidities.

LEARNT LESSONS

One of the major lessons is the inability to take the SARS-CoV outbreak in 2002-2003 seriously and allowing the virus to spread without devising combating strategies. Transmission has been supposedly facilitated through the close interaction of animals and humans which would occur through the butchering of animals and their sales. However, it is still unproven whether food can facilitate the transmission of the virus. The consumption of exotic live animals is believed to have assisted the emergence of SARS-CoV in 2002 and SARS-CoV-2 in 2019. However, there bats and wild animals are still being consumed in China, African countries and other regions of the world. This would lead to increased cases of transmission of the virus between animals and humans [68]. As a combative measure, there is need to revise the food consumption practices and limit the spread of viruses from animals to humans. When zoonotic pathogens arise, they tend to affect both consumers and the communities which they live in which is detrimental to their lives. It's difficult to predict virus evolution and natural selection patterns, as well as how the host will respond. It's also unclear whether adequate herd immunity would increase the mutation rate or evolution of immune-escape variants. As a result, the successful and rapid production of mRNA-based vaccines against SARS-CoV-2 would aid in the fight against other viruses like Ebola and Zika.

Conclusions

While it is impossible to project the future course of the SARS-CoV-2, there is now substantial information about this virus available. It is recommended to place a strict control and even a ban on the commercialisation and consumption of live wild animals, until the study on SARS-CoV is completed. This would prevent further transmission of the disease and limit the rates of reinfection. Despite the FDA approving Remdesivir as an antiviral drug for treatment COVID-19, it is still under study whether the drug can reduce hospitalization duration or mortality rate for infected patients. However, there is still a need to confirm the validity of these findings and the development of possible antivirals against the SARS-CoV-2. There has been a repeated waves of the disease worldwide which are more intense and has affected larger numbers of people and communities. This reveals the large extent of the battle which healthcare systems are facing with the virus. There has been an upregulation of both memory B-cells and Tfh cells when there is additional exposure to SARS-CoV-2. In the same light, it is supposed that a case of re-infection would be significantly milder than the first. Meanwhile, there was also a sharp decline of IgA+ after 90 days and this could be a reason for reinfection from those who suffered illness and even those who have been vaccinated. This raises priority for formulation vaccines against SARS-CoV-2 that promote mucosal immunity. However, some vaccines are proving to be moderately successful in treating coronaviruses due to limited antigenic variations in the S protein. Both immune and vaccination pressure mutations are also anticipated due to the nature of coronaviruses. Therefore, the virus must be noted to look out for the emergence of new variants of the virus.

Conflicting interests

The authors declare that there is no conflict of interests regarding the contents of this work.

Data sharing statement

N/A

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