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A review on the advancements in the development of vaccines to combat coronavirus disease 2019

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Coronavirus disease 2019 (COVID-19), the deadly disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is a global pandemic that has severely affected lives and economies around the globe. The spread of this virus will be very difficult to contain if no vaccine is ready for implementation. This is because of the high human-to-human transmission rate of this virus and the fact that the virus is in the community spread stage. As of 31st August 2020, 25.3 million individuals have been affected by this deadly virus resulting in about 850,673 deaths. To combat the spread of COVID-19, more than 100 applicant immunizations are being developed around the world. Among them, eight have begun or will be soon beginning preliminary clinical trials. This paper provides a review of the current developments of potential COVID-19 vaccines around the world. It specifically discusses the recombinant vaccine produced by the University of Oxford and AstraZeneca (Cambridge, UK), the use of novel self-amplifying RNA technique to create a vaccine and the progress made by UNAID (US National Institute of Allergy and Infectious Diseases) and World Health Organization (WHO). Furthermore, this review demonstrates the pharmaceutical prophylaxis and treatment protocols for COVID-19 by analysing the documentation set up by the WHO for up to date data with respect to the novel coronavirus of 2019–2020.

Keywords: COVID-19, SARS-CoV-2, Vaccines, ChAdOx1 COVID-19 vaccine, mRNA, Novavax, UNAID, WHO, MeSH

Introduction

As of 31st August 2020, 25.3 million individuals have been affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) all over the world and about 850,673 people have died due to the associated disease termed coronavirus disease 2019 (COVID-19) [1]. Methods employed for the prevention and control of viral spread include recommendations for social distancing, quarantine and isolation. However, a vaccine is immediately required to reduce mortality and morbidity rates of COVID-19 patients [2].

Without vaccines, current approaches to control the pandemic which requires the adoption of physical distancing, isolation and quarantine rules may not be sufficient to effectively call off the global lockdown due to the pandemic [3,4]. Compelling immunizations against COVID-19 are direly expected to lessen the tremendous weight of morbidity and mortality linked with SARS-CoV-2 disease [5]. There are more than 100 applicant immunizations being developed around the world. Among them, eight have begun or will soon begin clinical preliminaries [6]. These include Moderna's mRNA

COVID-19 antibody and CanSino's non-repeating adenovirus type-5 vectored COVID-19 immunization. Both of these entered stage 1 of clinical preliminaries on March 16, 2020. On April 3, 2020, Inovio Pharmaceuticals DNA vaccine entered clinical trials. In the same month, three inactive vaccines produced by Beijing Institute of Biological Products, Wuhan Institute of Biological Products, and Sinovac entered trials successively. This was followed by phase I and II clinical trials of BioNTech's mRNA and the University of Oxford's non-replicating chimpanzee adenovirus vaccines [2].

This paper aims to provide a review on the current developments of potential COVID-19 vaccines around the globe. To do so, four of the candidate vaccines being produced are highlighted in this paper.

Introduction to COVID-19 Vaccines

Leading scientists and researchers around the world have joined their hands to work actively on developing a vaccine for the treatment of COVID-19. Many pharmaceutical companies are working on ways to invent drugs which are useful for treating patients that have the novel COVID-19 disease. However, while progress is being made to produce necessary vaccines and medicines, the number of active patients is increasing all over the globe. Initially, doctors implemented the use of certain drugs which were useful in treating other viruses in the past. Presently, multiple vaccine candidates are in phase 1, 2, and 3 of trials. In the following sections, an update on four of these candidate vaccines is provided [7,8].

University of Oxford's and AstraZeneca's recombinant vaccine ChAdOx1 COVID-19 vaccine

The recombinant vaccine ChAdOx1 COVID-19 vaccine produced by the University of Oxford and AstraZeneca (Cambridge, UK) has received huge coverage in the media. In this vaccine production, the replication-deficient chimpanzee adenovirus is utilised to transmit DNA for the spike antigen protein of SARS-CoV-2. It is expected that the vaccine produced will be able to offer a greater protection just with lesser dosages as compared to some of its rival nominees because of the immunogenicity of adenoviruses. The Oxford team has previously been successful in the production of a safe vaccine for the well-known Middle East respiratory syndrome (MERS) virus and completed vaccine trials in 2019. Based on their success in producing a safe vaccine for MERS virus, the Oxford team is believed to have the potential to produce a vaccine for COVID-19 swiftly.

In the United Kingdom, AZD-1222 has now entered phases 2 and 3 of its trials. However, since the virus transmission in the United Kingdom is reducing, it is highly plausible that the phase 3 of the trial might take place in Brazil, later in 2020 [8]. Overall, Oxford University is on the forefront in the race to produce a vaccine for combatting COVID-19, around the world, with estimates that a functional vaccine will be available in the approaching winter season or in early 2021 through one or more of the candidates involved in this process. Although, it is possible that the vaccine produced initially is only able to assist in alleviating the symptoms of COVID-19 instead of providing complete protection, thus questioning the rationale behind their production. Because social distancing have proven to be successful in reducing the chances of infection transmission especially in the United Kingdom, clinical trial for a potential vaccine will be difficult to practice in the United Kingdom. Hence, countries such as Brazil and South Africa have been recommended as the places for vaccine trials due to the large number of active COVID-19 cases in these places. In addition to this, AstraZeneca has planned to commence a trail involving 30,000 people in the United States. However, there has been criticism about the poor pandemic planning in the United Kingdom and lack of industrial capacities for producing vaccines in the United Kingdom [9].

Using novel mRNA technique to create a vaccine

The Imperial College London team in the United Kingdom, led by Robin Shattock has received 50 million US dollars (USD) in the UK Government funding to speed up the process of providing a vaccine for COVID-19. Although this technique has not produced a vaccine yet, its utilization in vaccine production can be based on the fact that the vaccine is composed of RNA which sends messages in the body to the muscle cells for producing a distinctive spike protein which is available on the SARS-CoV-2's surface. It is anticipated that this protein can induce a response for immunity which will then be able to diminish the virus by killing it. Currently, a combined phase 1 and 2 trial involving 300 candidates is underway in the United Kingdom. Once the initial results demonstrate satisfactory results, phase 3 of the trial will commence. This is most likely to take place in October, mainly in a place where the transmission of the infection is fairly high [8].

The mRNA technology is being extensively used for the development of the vaccine mRNA-1273. This is a collaboration between Moderna (Cambridge, MA, USA) and Imperial Col-

lege. A preliminary phase 1 study on the patients who received the vaccine displayed similar or equivalent levels of immunization to those with COVID-19. Phase 2 studies plans to consist of 300 adult applicants who need to be 55 years or above while phase 3 will consist of 30,000 volunteers. These series of trials would be under the US National Institute of Allergy and Infectious Diseases known as UNAID. In a bid to develop the vaccine, Moderna received significant funding capital of approximately half a billion USD from the government to prepare the production and shipping of 1 billion doses to start early 2021.

It is expected that the vaccine by Imperial College London would be a much cost-effective vaccine due to the smaller dosage (50–100 times) compared to Moderna, due to the existing infrastructure and knowledge capital owned by Imperial College London. Furthermore, the cost of production and distribution would also be cheaper than other competitors. The Oxford University vaccine would be distributed at low cost by AstraZeneca who has received funding from the Centre for Epidemic Preparedness and Innovation (CEPI) and both the UK and US Governments. AstraZeneca has predicted and estimated the production of 2 billion units with an allocation of 400 million to developing countries [8].

Novavax

Another candidate vaccine is that financed by the CEPI which had provided 400 million USD for enhancement attempts of the vaccine Novavax (Gaithersburg, MD, USA). The CEPI's vaccine is a protein subunit which has been encapsulated using nanoparticles; thereafter, the protein is infused along with an adjuvant to boost its immunogenicity. The first phase trial of this vaccine was conducted on 130 candidates in Australia. With positive results from the first phase trial, the second phase trial will take place in other countries including the United States. It is worth mentioning that the contract has a clause that the subsequent technology will be transferred to different areas of world to make large scale production easy. As of early August 2020, Novavax intends to declare the outcomes from the first phase of the clinical studies on NVX-CoV2373. Next, phase 2 is anticipated to commence soon after [8-10]. Quite recently, Fujifilm Diosynth Biotechnologies agreed for the production of clinical supplies of Novavax vaccine for the phase 3 trial. This is anticipated to commence in fall 2020 [11]. Overall, Novavax is aimed at developing a vaccine candidate which could possibly prevent infections by the novel COVID-19. Novavax in 2020 has offered impressive gains [11].

UNAID and WHO

Analysts at UNAID and World Health Organization (WHO) are amongst those contemplating human test preliminaries for antibody applicants, in which inoculated people are directly presented to the infection to set up viability, as opposed to depending on the changing elements of the pandemic in various nations. This can be viewed as a controversial approach as queries and doubts persist over the morals of this methodology. Eventually, a fair access to an immunization will be dependent on which antibodies are endorsed, and attention will be paid to the order of the vaccine endorsement and approval. Moreover, at present, none of the bodies engaged in this procedure can offer the most significant assurance, which

Table 1. A landscape of the top 10 coronavirus disease 2019 vaccines [6]

Platform	Developer	Type of candidate vaccine	Current stage
Non-replicating Viral Vector	University of Oxford/AstraZeneca	ChAdOx1-S	Phase 3, phase 2, phase 1
Non-replicating Viral Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	Adenovirus type 5 vector	Phase 2, phase 1
RNA	Moderna/NIAID	LNP-encapsulated mRNA	Phase 2, phase 1
DNA	Inovio Pharmaceuticals/International Vaccine Institute	DNA plasmid vaccine with electroporation	Phase 1/2
Inactivated	Wuhan Institute of Biological Products/Sinopharm	Inactivated	Phase 1/2
Inactivated	Beijing Institute of Biological Products/Sinopharm	Inactivated	Phase 1/2
Inactivated	Sinovac	Inactivated+alum	Phase 1/2
Protein Subunit	Novavax	Full length recombinant SARS CoV-2 (severe acute respiratory syndrome coronavirus 2) glycoprotein nanoparticle vaccine adjuvanted with matrix M	Phase 1/2
RNA	BioNTech/Fosun Pharma/Pfizer	3 LNP-mRNAs	Phase 1/2
Inactivated I	Institute of Medical Biology, Chinese Academy of Medical Sciences	Inactivated	Phase 1

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is that they will definitely be producing a vaccine that can protect from COVID-19 [8].

Documentation protocols set up by the WHO gathers data regarding treatments employed for the novel coronavirus of 2019–2020. Generally, 18 upcoming antibodies are in clinical assessment while 129 applicant immunizations are in preclinical assessment [6]. Table 1 demonstrates a landscape of the top 10 COVID-19 vaccines, their types, developers and the respective stages of scientific assessment.

Pharmaceutical Prophylaxis and Treatment of COVID-19

Currently, various large-scale, trials are happening around the world employing groundbreaking technologies for assessing the candidates as possible COVID-19 therapeutics. These include national trials in many European Union (EU) member states and the WHO solidarity trials [12,13]. To expedite the timely and successful completion of these trials, patient enrolment is very important. The various pharmaceuticals enrolled for trials in assessing the efficacy and safety of their product for treating COVID-19 include monoclonal antibodies, the antimalarial chloroquine/hydroxychloroquine (HCQ), the antiviral combination lopinavir/ritonavir, systemic interferons and interferon β-1a and the antiviral nucleotide analogue remdesivir [14]. It is vital that the prospective therapies and medications are provided after careful assessment that takes places in randomized controlled trials.

There have been successful results obtained from drug trials including those undertaken for dexamethasone which showed a significant reduction in the 28-day mortality rate in critically ill patients who were on medical equipment support such as ventilation. However, no advantage was found for those not requiring oxygen and medical aid [15,16]. Thus, it is recommended that dexamethasone be administered to those who require ventilation or oxygen support by the National Institute of Health [17].

Recommendations for the drug Remdesivir were announced by the European Medicines Agency (EMA) based on careful and compassionate use to treat COVID-19 patients [18]. Remdesivir could be associated with a faster recovery time compared to a placebo; 11 days versus 15 days in a study consisting of 1,059 patients who enrolled in a double-blind trial. From the trial, the 14-day fatality rate is 7.1% versus 11.9% between remdesivir and the placebo group respectively [19]. As a result, it is recommended that remdesivir be administered to patients with severe pneumonia and those requiring additional oxygen support. This was overseen by the EMA's human medicines committee (Committee for Medicinal Products for Human Use) on June 25, 2020 [19]. Soon after, conditional marketing authorization for treating COVID-19 adolescents and adults was granted by the European Commission. This resulted in remdesivir becoming the first authorized antiviral treatment for COVID-19 in the EU [20].

A randomized trial of the drug lopinavir/ritonavir administered to 199 patients located in China did not display any significant improvements in comparison to a standard treatment process [21]. Another trial in the United Kingdom with a sample size of 1,596 patients who were administered lopinavir/ritonavir showed less improvement compared to the 3,376 patients on standard care [22]. The trial did not include a considerable number of patients who had to be put under ventilation due to the difficulty in studying the effect of the lopinavir/ritonavir.

HCQ has previously been used in the treatment of malaria in several countries of the world. In a very small study of patients in China and Europe during the early stages of the virus outbreak, it was found to modify and reduce the uptake of viral particles into the cells. However, this produced conflicting results when used with azithromycin. Another large randomized trial of 1,542 patients receiving HCQ was compared to those with 3,132 patients receiving usual care and it was found that there was no advantage to HCQ [23]. The results show that any significant advantage of HCQ for treating the virus has been omitted and therefore terminated randomization in the HCQ arm. As a result of these studies and trial results, the benefits of HCQ have been ruled out to treat COVID-19. The WHO announced on 17 June, 2020 that the SOLIDARITY trial would be discontinued based on the trial results and the Cochrane review [12]. HCQ was also analyzed post-exposure in 821 patients in a randomized controlled trial due to known exposures such as through occupation or households [24]. The analysis again failed to show improvements between HCQ and the placebo group.

Statements concerning the worsening of COVID-19 disease through non-steroidal anti-inflammatory medicines with heightened representation of "angiotensin-converting enzyme 2 (ACE2)", whose receptor is used by SARS-CoV-2 to penetrate the target cells, are not endorsed [25]. Patients who are treated for hypertension or renal disease are usually provided angiotensin receptors and ACE-inhibitors and are advised to not switch medication or choose alternatives [26].

In two new studies being carried out in China, convalescent plasma (obtained from fully recovered patients) are underway despite the limitations and it has shown some promise as a potential treatment for COVID-19 [27,28]. This may provide a new alternative approach to treat patients [29-31]. These studies or trials are also under investigation in the EU and the United States according to their respective protocols. Early results obtained from 670 patients who have received this treatment in the United States [32-36] as of May 29, 2020 is promising.

Conclusion

COVID-19, a global pandemic caused by SARS-CoV-2 has disrupted life as well as economies around the world. If no vaccination is produced for its control, the spread of the virus shall be very difficult to manage. As of 31st of August 2020, 25.3 million individuals have been affected by this deadly virus resulting in about 850,673 deaths. However, to combat the spread of COVID-19, more than 100 applicant immunizations are being developed around the globe. Among them, eight have begun or will soon begin clinical trials. This paper provides a review on the current developments of possible COVID-19 vaccines around the world by discussing the recombinant vaccine produced by the University of Oxford and AstraZeneca, the use of novel mRNA technique to create a vaccine and the progress made by UNAID and WHO. Four of the candidate vaccines being produced are highlighted in this paper. In addition, the paper also demonstrates the pharmaceutical prophylaxis and treatment of COVID-19 by analyzing the documentation set up by the WHO for data gathering for the novel coronavirus of 2019–2020.

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