COVID-19 vaccine: Potential candidates, achievements, and challenges

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Abstract

Severe acute respiratory syndrome [SARS]-CoV-2, which is the causative agent of Coronavirus Disease 2019 [COVID-19] disease, has engulfed more than 2.4 million people and still counting. As this pandemic is at its peak and is responsible for more than 100 million infected people worldwide, there is an urgent need to develop an effective vaccine to stop the COVID-19 disease. More than 220 vaccine candidates are in the pre-development stage while 15 candidates are in the developmental stage, from which Pfizer/BioNTech, Moderna, and some other vaccines have received approval by some countries for emergency use only. Fever, tiredness, headache, joint pain, swelling at the injection site and some other common effects have been found by using these vaccines. Efficacy, rapid mass production, and long-term immunity as well as acceptance of vaccination by society are the main challenges in developing a safe vaccine against COVID-19 despite the fact that some vaccines have over 90% efficiency against COVID-19 and are useful in developing immunity as well.

Keywords: Coronavirus disease; Major Challenges; Society perception; Vaccines; World responses

1. Introduction

Since the last month of 2019, there has been an outbreak of Covid-19 disease which was first reported in Wuhan, a city in China [1]. The World Health Organization (WHO) identified SARS-CoV-2 as the causative agent for the pandemic, which is responsible for 2.39 million deaths and more than 108.8 million confirmed cases as of 13 February 2021 [2, 3]. SARS-CoV-2 is a single-stranded, positive-sense RNA virus and contains four major structural proteins, envelop protein, nucleocapsid protein, membrane protein, and spike proteins that are found on the surface of SARS-CoV-2 [4].

A variety of vaccines are under development which include protein-based vaccines, non-replicating viral vector vaccines, and weakened virus vaccines [5, 6]. However, there is real novelty representation by Deoxyribonucleic acid [DNA] or Ribonucleic acid [RNA]-based vaccines [5]. But RNA vaccines are not approved in humans, but there are seven COVID-19 RNA vaccine candidates that are being tested in medical trials [7]. Global researchers are working hard to develop an effective vaccine against SARS-CoV-2, and most experts believe that a vaccine will be available by the middle of 2021 [8, 9]. But it requires several years to develop an effective and safe vaccine [10]. By December 23, 2020, there were two hundred and eighty-seven vaccine candidates, of which two hundred and twenty-four are in the pre-development stage while 15 candidates have reached the development stage [11]. One vaccine in the United Kingdom while two vaccines in the United States have been accepted for emergency use against COVID-19 [12]. Because of the novelty of SARS-CoV-2, some approved vaccines are available, but there is an urgent need to develop an effective and safe vaccine to prevent and control future outbreaks [13].
1.1. RNA Vaccines
It is a new generation of vaccines in which all the ingredients can be prepared chemically [14]. The mode of action of RNA vaccines is shown in Figure 1.

![Figure 1 Mode of action of RNA Vaccine](https://www.compoundchem.com/2020/12/02/rna-vaccines/)

**Source:** Royal Society of Chemistry (URL: https://www.compoundchem.com/2020/12/02/rna-vaccines/)

2. Moderna
The RNA-based vaccine which was first used for human trials on March 16, 2020, is Messenger RNA (mRNA)-1273 and it was developed by Moderna, an American company [15, 16]. The results of phase I showed that protective antibodies were developed in forty-five volunteers. The optimal dose, as well as the effectiveness of the vaccine, were also decided during the first phase [15]. 30,000 participants were involved in the third phase of testing and the vaccine showed safety for three months [17, 18]. The efficacy of this vaccine was 94.1% and it was approved by the Food and Drug Administration (FDA) in the United States for emergency use on December 17, 2020 [17].

2.1. Pfizer and BioNTech
Another RNA-based vaccine, BNT162b2 was developed by Pfizer and BioNTech [19]. In the third phase, thirty thousand healthy participants were treated, and the efficacy of the vaccine was 95%. The level of efficacy was the same in people of different racial groups, different ages, and individuals with diabetes. Canada, Mexico, and the United States have approved BNT162b2 for emergency uses due to the positive results from the third trial [20]. Frequent fatigue, muscle aches, and fever were reported due to this vaccine there were four adverse cases and six deaths as a result of this vaccine, though none of the deaths were attributed to this vaccine [19, 21].
2.2. Non-replicating Viral Vector Vaccines

2.2.1. Ad5-nCoV
Beijing Institute of Biotechnology and CanSino Biological Inc developed Ad5-nCoV, which is a non-replicating viral vector-based vaccine [21]. This vaccine utilizes Ad5 adenovirus to incorporate the genes of SARS-CoV-2 into the body of humans. In the first phase, three different doses were tested on a trial basis. The better tolerated among these doses were low and medium, while high doses resulted in fatigue, joint pain, and high fever, which is the result of a high reactive profile [21]. After that, low and moderate doses were evaluated in phase II. Vaccines with low doses provided better immunogenicity and protection results [21]. Ad5-nCoV was approved by the Chinese Central Military Commission (CMC) for military use only on 25 June 2020 [22].

2.2.2. AstraZeneca
The Oxford Jenner Institute, The University of Oxford, and AstraZeneca made a collaborative effort and developed a COVID-19 vaccine (AZD1222). During trial phase I and II, there were no serious adverse cases were reported [23]. In the third phase of trials, the vaccine was tested on almost 30,000 people in different countries of the world, including South Africa, the United States, the UK as well as Brazil [24]. According to the results of phase III, which were recently published, the efficiency of this vaccine is 90% [25].

2.2.3. Sputnik V
Another non-replicating vaccine, Sputnik V, was also developed by Gamaleya Research Institute of Epidemiology and Microbiology. Sputnik V was approved by the Russian government [26]. The results of phase III in which more than 40,000 people participated, showed more than 90% efficacy against SARS-CoV-2 [27].

2.3. Inactivated Virus Vaccine

2.3.1. Sinovac
CoronaVac is an inactivated virus vaccine made by a pharmaceutical company in China, Sinovac. In this vaccine, aluminum adjuvants are used [28]. In the 1st and 2nd phase of trials, 743 volunteers were vaccinated and there were no adverse cases. On July 03, 2020, this vaccine received approval to proceed to the third phase [29].

Table 1 Efficiency of different COVID-19 vaccines candidates

<table>
<thead>
<tr>
<th>Candidates for Vaccines</th>
<th>Vaccine Type</th>
<th>Clinical Phase</th>
<th>Efficacy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/BioNTech</td>
<td>mRNA</td>
<td>Phase 3</td>
<td>95%</td>
<td>[19]</td>
</tr>
<tr>
<td>Moderna</td>
<td>mRNA</td>
<td>Phase 3</td>
<td>94.1%</td>
<td>[17]</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Adenovirus based</td>
<td>Phase 3</td>
<td>90%</td>
<td>[25]</td>
</tr>
<tr>
<td>Sputnik V</td>
<td>Adenovirus based</td>
<td>Phase 3</td>
<td>91.4%</td>
<td>[27]</td>
</tr>
<tr>
<td>Ad5-nCoV</td>
<td>Adenovirus based</td>
<td>Phase 3</td>
<td>65.7%</td>
<td>[30]</td>
</tr>
<tr>
<td>Sinovac</td>
<td>Inactivated Virus</td>
<td>Phase 3</td>
<td>50.4%</td>
<td>[31]</td>
</tr>
</tbody>
</table>

2.4. Protein-Based Vaccines

2.4.1. Novavax
Novavax developed a protein-based vaccine which is in the III phase of testing. This vaccine contains an adjuvant in a few groups which has resulted in an increased immune response [32]. Institute of Microbiology, Chinese Academy of Sciences, and Anhui Zhifei Longcom Biopharmaceutical from China have also developed a protein-based vaccine that has entered phase III of trials [10, 33].
2.5. Threats

Eight healthcare workers experienced serious allergic reactions after receiving both mRNA-based vaccines, but the scientists speculated that these serious allergic reactions may be related to anyone from polyethylene glycol or lipid-based nanoparticles in the vaccines, which are used to prolong their lifespan [34-36]. BioNTech/Pfizer, AstraZeneca, and Moderna were approved by the European Union. On the 2nd day of vaccination, two adverse but resolved events of anaphylaxis were reported [37].

Complacency, misinformation, and lack of confidence can also lead to vaccine hesitancy, which is listed in the top ten threats to world health by the World Health Organization [38-40]. Some side effects such as tiredness, chills, joint pain, fever, swelling at the injection site, a state of being unwell, headache, and swelling of lymph nodes were also reported by using the approved vaccines against COVID-19 [41].

Almost 1.89 million doses of the BioNTech/Pfizer vaccine were given in the US till 23 December 2020. Of these, 0.2% of adverse cases were reported and the reports of these events were sent to the Vaccine Adverse Event Reporting System for further analysis [42]. A major concern that can lead to the ineffectiveness of vaccines is political pressure by governments to speed up the process of development of a vaccine. As a result of such a situation, the public may feel hesitant to accept the future vaccine [43].

2.6. Challenges

Historical and early studies on the coronavirus family, which includes SARS, Middle East Respiratory Syndrome [MERS], and SARS-CoV-2, indicate that infection does not provide long-term immunity [33, 44]. If long-term immunity is not achieved, only healthcare workers and vulnerable people can be protected by a vaccine by decreasing the quantity of the virus that a vaccinated individual produces and eliminates [45]. Previously, the use of adjuvants to improve long-lasting memory has been shown and in medical trials, the vaccine candidates have already used adjuvants [46].

One of the biggest challenges in making millions of vaccines quickly is to promote manufacturing, as the infrastructure will vary depending on the type of vaccine [47]. Combining the phases to speed up the vaccine development includes trials in small groups. It is a major concern because when the vaccine is declared for public use, it may cause severe side effects in a large population that were not previously seen in small groups [48].

Although it is unclear whether these vaccines will actually work, some countries have already secured millions of doses of vaccines from different pharmaceutical companies [49]. With many uncertainties, rapid mass production is also a big challenge to overcome the demand for vaccines against an epidemic disease [43].

It is also an important challenge that the vaccine may have limited efficacy against the virus as a result of mutations in the viral genome [50, 51]. Previous studies show that nucleic acid-based platforms like deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) could not develop an effective vaccine for diseases of human beings, and it remains to be seen how messenger RNA vaccine will be made successfully. This is because the lipid nanoparticles are sensitive to temperature and may show difficulty in increasing the production of vaccines [52].

2.7. World Responses

Different responses were received by a variety of respondents. A study was conducted to check the acceptance of a vaccine against COVID-19, in which 13,426 participants from 19 countries participated. According to this study, 71.5 percent of individuals agreed to get an effective vaccine against COVID-19 while 48.1 percent of people responded that they would take the vaccine on their employer recommendations [53].

Another survey was conducted before the approval of the Pfizer vaccine in the UK. According to this, 51 percent of individuals agreed to be vaccinated against COVID-19. Among the countries where the survey was conducted, half of the French people (from those who participated in the survey) were unwilling to be vaccinated, while 65 percent of the British people (from those who participated in the survey) were most likely to agree [54].

An online survey was conducted in China in which 2058 people participated. Out of these, 91.3% of individuals agreed to be vaccinated against COVID-19 of which 52.2% participants wanted to be vaccinated quickly while the remaining responded that they would get vaccinated after the confirmation of vaccine safety [55].

Sallam [56] reviewed various publications about the perception of society about COVID-19 vaccination in various countries and found that in the case of the general public, Ecuador, Malaysia, Indonesia, and China were the countries...
with the highest COVID-19 acceptance rate while acceptance rates were lowest in countries like France (58.9%), USA (56.9%), Poland (56.3%), Russia (54.9%), Italy (53.7%), Jordan (28.4%) and Kuwait (23.6%). Various surveys of doctors and nurses revealed that vaccine acceptance was lowest in Congo (27.7%) and highest in Israel (78.1%). The lowest rates for accepting COVID-19 vaccination were found in Africa, Russia, the Middle East, and most of the European countries that showed that in order to build the trust of the general public as well as medical workers, it is necessary to address the hesitation of COVID-19 vaccination.

3. Conclusion
Although it was not an easy task, some pharmaceutical companies have developed vaccines that are more than 90% effective against SARS-CoV-2. Vaccines against COVID-19 cause some common side effects, but misinformation and lack of confidence are the main reasons why people feel hesitant about being vaccinated. In the end, still approved vaccines by the FDA are facing many challenges, including manufacturing on a large scale and distribution of vaccines across different countries of the world.

Compliance with ethical standards

Disclosure of conflict of interest
All the authors (Muhammad Shoaib, Ahmad Waheed, Muhammad Wajid, Hafiza Urwa, Tehmina Khan, Muhammad Saleem Khan, Muhammad Waseem Aslam, Shabbir Ahmad, Kamran Jafar, Hasnain Akmal, Muhammad Iqbal Mahmood, and Samrina Shamim) declare that they have no conflict of interest.

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