Developing Covid-19

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Developing COVID-19's Vaccines: Short Review

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Abstract

Background. Since humanity is attempting to challenge the COVID-19 pandemic by accelerating the production of vaccines against SARS-CoV-2, there could be opposite health side-effects on the participants and researchers. **Materials and Methods:** Institutions, governments, companies, and organizations around the world work relentlessly to produce drugs and/or vaccines for this disease; yet none were approved. In this work, we are presenting the technologies platforms, developed vaccines, development challenges, and the under-process vaccines. **Results:** The recent developments in the diagnosis and types of vaccines were also discussed. **Conclusion:** Many vaccines were invented to stop COVID-19's spreading using different techniques.

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1. Introduction

Every year, millions of people receive vaccines to prevent the transmission of different infectious diseases. The influenza "flu" vaccine is among the well-known and commonly used vaccines. Jonas Salk and Thomas Francis' firstly invented an influenza vaccine in 1938 that represented a milestone for an era of fighting against global dominating pandemics [1]. In large-scale clinical studies, the flu vaccine was widely studied in 1942 to understand the obstacles and overcome the challenges. Despite the efficacy of annual flu vaccines, however, severe flu pandemics tend to occur (e.g., 2009 H1N1 pandemic), and the potential for a worldwide epidemic remained as an ever-present risk. This does not occur only for influenza but for other viruses as well [2], and death cases in children and youngsters are less than other age categories. However, older people had the highest severity and death cases, particularly those with chronic diseases [2].

2. COVID-19

Coronavirus 2019 is an infectious disease that caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) virus and results a pneumonia. It is a positive-sense single-stranded RNA virus of class IV according to Baltimore classification with a high infection rate in humans [3]. The disease was first identified in Wuhan, Hubei, China in late 2019 and has developed to a continuing pandemic [4]. By the beginning of September 2020, around 26 million cases were reported across 188 countries and territories, resulting in more than 860,000 deaths, and over 18 million recovered [5].

3. Developing a Vaccine Against SARS-CoV-2

In response to the pandemic of COVID-19, starting vaccines production is exceptional in terms of size, safety, and pace [6]. Importantly, as the virus duplicated itself within humans, vaccination against SARS-CoV-2 became an urgent necessity to minimize morbidity and mortality. Now, the race is on to discover a safe and effective SARS-CoV-2 vaccine [7].

Through August 2020, 231 under-developing vaccines were within the production process; including a minimum of 25 that are going through advanced steps of clinical studies, six are in Phase III and 19 still in Phase I - II [8]. Vaccines were developed against many coronavirus caused animal diseases, such as the respiratory syncytial virus in birds, canine coronavirus, and feline coronavirus [9]. Big drug manufacturers with long knowledge in the synthesizing of vaccines, such as Johnson & Johnson, GSK, and AstraZeneca, are cooperating with the biotechnology companies, national governments, and universities to accelerate the progress towards finding an effective vaccine

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[10]. Specifically, in the case of COVID-19, a vaccine efficacy of 70 % could be sufficient to stop the pandemic, while if it is 60 % and lower, the epidemics could continue. Efficacy of 60 % and under does not provide a strong immune system to avoid the virus spreading [11].

4. Technology Platforms

Researchers from the Center for Evidence and Practice Improvement (CEPI) announced in April that in early 2020, ten separate platforms of technology were under research and development to create an efficient vaccine against COVID-19. Different molecular platforms, which are focusing on DNA or messenger RNA, were used and the featured ones are illustrated below [12]:

- **Viral vector:** In this approach, only injection of the pathogen materials, or antigens, that greatly stimulate the immune system is used. To introduce genetic material into cells, this method uses a harmless virus or bacterium as a vector or carrier. This technique could be safe and easy to apply using different methods. No infectious viruses, good preclinical data, and applicable clinical results were obtained by this technology for several new viruses, including MERS-CoV [13].
- **Protein subunit:** This is done by incorporating materials of both the pathogens and antigens that best stimulate the immune system, these were produced by cells in vitro and the viral protein genetic code was inserted. Also, it is easy and appropriate to be manufactured, using different techniques [13]. Here, there is no need to treat any infectious virus, and adjuvants1 can be used to improve the immunogenicity. On the other hand, the global export may be restricted; and other kinds of such vaccines seem to be difficult to develop [14].
- **RNA-based:** Injecting the RNA encodes the antigen(s) to generate a stimulated immune response. Hence, the body cells make use of this genetic material to produce the antigens. This technique provides a strong potential, long-term immunity responses, high stability, and relatively easy large-scale development. There is no need to treat an infectious virus, vaccines are usually immunogenic and possible for rapid development. Unfortunately, it is still unproven in humans [8].
- **DNA-based:** This injects the DNA, which encodes the antigen(s), to obtain the desired immune response. Similarly, to RNA-based, the cells of the body make use of this genetic material and generate antigens. This technique is very powerful with long-term immune responses, has a high stability, and relatively easy to scale up. Furthermore, it has the advantages of no infectious virus needs to be treated, low cost of production, high stability against heat, and possibility for quick production. DNA-based was tested for SARS-CoV-1 vaccine in early-stage clinical trials; nevertheless, it is still unproven for humans [15].
- **Inactivated virus:** This is a mechanism that depends on the injection of a dead or inactive type of the germ that carries the disease. The advantages of this technique are its easy synthesizing procedure, where it was used for many approved human vaccines. Also, large capacity could be prepared, a possibility to improve the immunogenicity, and was tested in humans against SARS-CoV-1 adjuvants1 [13]. However, this technique, typically, does not result high immunity because this is caused by live vaccines, multiple doses are required throughout times (booster shots). Besides, significant quantities of the infectious virus must be controlled (could be mitigated by the use of an attenuated virus seed) [16].
- **Live attenuated virus:** This is done by injecting a weakened version of the germ that induces the sickness in conditions close to the normal infection. This technique shows a greater and sustained immune response [15]. An existing network can be used to straight forward the used procedure by many approved human vaccines. Because of the large genome-scale, it takes time to create infectious clones for the attenuated coronavirus vaccine seeds. There has to be thorough monitoring to achieve full safety [3].

5. Vaccine Development

The production of a vaccine includes several steps, from the initial scientific work to the final delivery in the hospitals and clinics. Table 1 shows a rough estimation for the needed time for a vaccine to be synthesized [17,18].

Table 1. The vaccine production process.

Vaccine's process	Normal take	Acceleration
Research	2-4 years	6 months
Preclinical preparation	2 years	6 months
Clinical trails	5 years	1.5 years
Approval	1 year	6 months
Manufacturing	2 years	3-6 months
Distribution	3-6 months	1 month

The examination of previous vaccines' production indicates error rates of 84-90%. Since COVID-19 is a new virus with properties yet to be identified and needs novel vaccine technology and development techniques, the hazards associated with developing a successful vaccine in the preclinical and clinical research stages are significant. The overall regional distribution of COVID-19 vaccine production includes organizations in the United States and Canada with around 46% of the active global vaccine research, compared to 36% in Asian countries, namely China, and 18% in Europe [16].

6. SARS-CoV-2 Vaccine Challenges

Techniques for quick approval for a COVID-19 vaccine are being discussed; in particular, by compressing (few months) the normal approval period that typically takes several years [9]. Previously, challenging studies were performed for less lethal diseases than COVID-19, such as severe influenza, cholera, and malaria [15]. Currently, the studies are ethically questionable due to the unclear risks to volunteers

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of potential COVID-19 disease or the long-term safety of the obtained vaccine [19].

Studies may consider 3 stages to finally approve a vaccine. First, clinical development, where volunteers are tested by specified doses of viruses. Hence, answers to some important questions will be tracked. The questions are: what is the ratio of the developed symptoms, how much it requires the virus to spread the disease, how long it took the infected patients to show symptoms, how long patients are being infectious, and what risk factors are correlated with the serious illness or the efficient immune responses [20]. Second is related to the positive vaccines production; and third is the candidate therapy testing Phase I and Phase IIa with fulfilled dose tests that given to volunteers. Finally, the volunteers examine the Phase IIb trial to see how well the vaccine protects them against the virus [21].

7. The Current SARS-CoV-2 Vaccines

The techniques of inactive and/or live attenuated virus vaccines have been used for decades because of their high immunogenicity and toll-like receptors (TLRs) activation, such as TLR3, TLR7/8, and TLR9 [18]. Nevertheless, long-term surveillance is needed to validate the vaccine's safety because it is alive. The mechanism of host cell invasion is done by interacting the spike (S) protein that presents in SARS-COV-1 and SARS-COV-2 and angiotensinogen conversion enzyme 2 (ACE2) which locates on the host cells' membrane. Thereby, this could be the primary cause of the hosts immune response [22]. The serine protease inhibitor TMPRSS211, that is produced by the host cells, increases this process by priming with the (S) protein [18]. S1 and S2 are the two identified spike (S) protein subunits, which are responsible for generating the immune responses [23]. The virus connection to the ACE2 receptor of the host cell membrane occurs via the subunit S1. In comparison, a fusion between the virus and cell membrane occurs via the S2 subunit. This eventually contributes to the entry of a viral genome into the host cell's cytoplasm [24].

Recombinant proteins and vectors containing the S1 receptor-binding domain (RBD) of spike (S) protein can be used productively in the synthesis of COVID-19's vaccines because of their important ability to neutralize antibodies [28]. The probable vaccines for COVID-19 are in clinical trials as illustrated in Table 2 [25,26], where one candidate is in Phase 1 trial and seven are in Phase 1 and Phase 2 combined trials.

Table 2. SARS-CoV-2 vaccine candidates currently.

Candidate name	Vaccine platform characteristic	Trial phase	Same platform for other disease candidates	Expected completion date	Country (Sponsor)
BNT162 [27]	mRNA	Phases 1 and 2	–	Mid 2021	China, Germany, United States (Pfizer)
mRNA-1273 [28]	mRNA	Phases 1 and 2	Multiple candidates	Mid 2021	United States (Moderna /NIAID)
ChAdOx1 [29]	Viral vector	Phases 1 and 2	MERS, influenza, Chikungunya, Zika, TB, plague	Mid 2021	University of Oxford
Ad5-nCOv [30]	Viral vector	Phases 1 and 2	Ebola	Early 2021	China (CanSino Biological Inc./Beijing Institute of Biotechnology)
INO-4800 [31]	DNA	Phase 1	Lassa, Nipah, filovirus, HPV, HIV, Zika, cancer indications, hepatitis B	Late 2020	United States (Inovio Pharmaceuticals)
NVX-CoV2373 [32]	Protein	Phases 1 and 2	HPV, CCHF, RSV, VZV, EBOV	Mid 2021	United States (Novavax)
Unknown	Inactivated	Phases 1 and 2	SARS	Mid 2021	China (Sinovac)
Unknown	Inactivated	Phases 1 and 2	–	Late 2021	China (Beijing and Wuhan Institutes of Biological Products and Sinopharm)

8. Conclusion

Different techniques could be used to develop a vaccine for COVID-19, where some of them were already used. Currently, there is a race among governments, companies, and academic researchers to find an approved vaccine. Considering the fact that the disease is spreading very fast and finding a vaccine became urgent, several vaccines were passed many trail phases. It is expected to have vaccines for COVID-19 in 2021 because of the considered acceleration in the developing process.

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The authors fulfilled the ethics protocols when they conducted this study.

Authors' Contribution
All authors contributed equally in writing, revising, and editing this work.

Competing Interest
The authors declare that they have no conflict of interests

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