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Review article

DEVELOPMENT OF VACCINE AGAINST SARS-CoV-2: AN UPDATED REVIEW

Rubina Chowdhury, Rofiqul Islam*, Hemanta Kumar Sharma

Department of Pharmaceutical Sciences, Faculty of Science and Engineering, Dibrugarh University, Dibrugarh 786 004, Assam, India

Abstract

Background: *A deadly virus named SARS-CoV was identified as the causative agent in the 2002 outbreak in China. In late 2019, the virus caused a pandemic with a history of two epidemics in the past years, thus earned a new name SARS-CoV-2. The development of a vaccine, therefore, has become the most important requirement.* ***Objective:*** *The objective of the review is to understand and explore the advancements and the probable obstacles in the development of an effective vaccine in a pandemic situation.* ***Methods:*** *An extensive search for appropriate literature were carried out from March 2020 to May 2020 using keywords 'COVID-19', in combination with 'vaccine' and/or 'pandemic' and/or 'coronavirus' on search engines viz., Scopus, Web of Science, PubMed, Science Direct and Google Scholar.* ***Discussions:*** *The discussion and analysis revealed that the work on vaccine development is growing as fast as possible. But due to the obstacle like mutation, it is difficult to produce the specific one with potential effectiveness.* ***Conclusion:*** *Although the vaccine is not successfully produced yet, constant efforts are going on based on the antigenicity of proteins present on the surface of the virus. Since many aspects are yet to be revealed, it is very difficult to precisely say the exact time by which we will have a safe and effective vaccine in our hands. However, with promising results in the initial phases of vaccine development, we can hope for a successful product within a few months.*

Keywords: Coronavirus; SARS-CoV; Vaccine; Pandemic; 2019-nCoV.

* E-mail: rofiqul52940@gmail.com

Introduction

Who can now use the term “gone viral, ” without quivering a little? Who had ever imagined that even an ultramicroscopic imperceptible organism can menace the entire pre-eminent human race? The spread of an infectious disease in late 2019, initially considered to be cases of pneumonia or Influenza-like Illness (ILI), of unknown etiology were reported in Wuhan City of China [1]. Pneumonia brought a terrible blow when the symptoms advanced to more severe and acute in infected patients. The organism responsible for the outburst was briskly identified as beta coronavirus, which is having a closely related sequence of genes to that of the Severe Acute Respiratory Syndrome (SARS) coronavirus, identified in 2003 and accordingly earned a new name as SARS-CoV-2 [2,3].

World Health Organization on February 20, 2020, reported a cumulative total of 74,675 confirmed COVID-19 (Coronavirus Disease-2019) cases with 2121 death cases in many parts of China [4]. With easy human-to-human transmission, the speedily emerging SARS-CoV-2 (SARS-2) has been spreading all over China from ‘ground zero’ Wuhan and entering almost every part of the world [5]. The outbreak was declared to be an International Public Health Emergency by the World Health Organization (WHO) on January 30, 2020, and recognized it as a pandemic on March 11, 2020 [6,7]. As of May 30, 2020, more than 6.04 million cases of COVID-19 have been reported in 185 countries and territories, resulting in more than 367,227 deaths [8]. Even though more than 2,672,712 people have recovered, scientists and researchers believe that there may be a possibility of relapse or reinfection. The United States of America currently has the highest number of confirmed coronavirus cases compared to all other countries and also has the highest number of deaths followed by Italy and Spain [9].

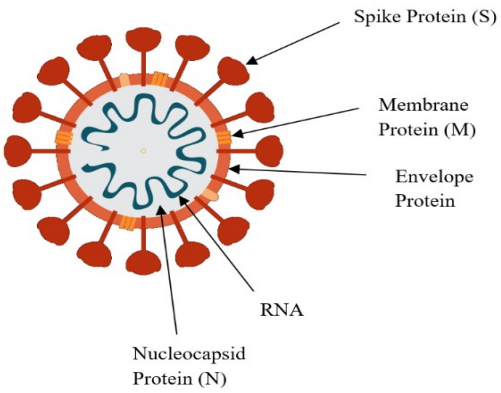
Although people are recovering, thousands of fresh cases are still emerging daily. The entire world is clutched in fear and suffering from the lack of planning and basic health infrastructures. Governments around the world are scrambling and looking for ways to limit and control the virus even at their peak effectiveness. But containment strategies have only slowed down the rapid community transmission of COVID-19. So many existing drugs viz. remdesivir, hydroxychloroquine, chloroquine, a combination of lopinavir and ritonavir have been experimented with but none of them has made any significant difference and now all eyes have turned for the prospect of a vaccine [10,11]. The only way left to confirm the safety of the people is to vaccinate them and to make them immune to the virus itself. Many

steps are being explored in that direction, including its toxicity (safety) level, targeting high-risk populations, need for vaccination success, special route of administration (such as oral or nasal delivery, rather than by injection), drug regimen, its stability and storage, emergency use authorization before licensing, formal production of up to billions of doses, and distribution of licensed vaccine [12,13]. In rushing to provide the vaccine for the COVID-19 pandemic, scientists and governments are adopting the high risk of the "short circuit" vaccine development process [14]. Geopolitical problems, concerns about the safety of at-risk populations, and the challenges of producing billions of doses build the pressure on reducing vaccine development time, in some cases complicating clinical trial protocols for only months, a process that is usually done chronologically [15].

The Virus

The novel Coronavirus, i.e., SARS-CoV-2 belongs to the family Coronaviridae. The members of this family are named after their crown-shaped appearance by surface glycoproteins. The family includes Letovirinae and Orthocoronavirinae as two subfamilies and the latter includes the genera Alphacoronvirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Mammals are typically infected by Alphacoronaviruses and Betacoronaviruses [16,17]. Two types of Alphacoronaviruses viz. 229E and NL63 and two types of Betacoronaviruses viz. OC43 and HKU1 are responsible for causing common cold in humans [16]. Among the Betacoronaviruses, SARS-CoV-1, the Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV), and novel SARS-CoV-2 are the most pathogenic Betacoronaviruses [16,18].

The coronaviruses have a large single-stranded positive-sense RNA genome, which comprises of ~30000 nucleotides. Four structural proteins which are Nucleocapsid (N) protein, Membrane (M) protein, Spike (S) protein and Envelop (E) protein and several non-structural proteins (nsp) are encoded by it as presented in figure 1 [19]. The spike protein (S protein), which is a class I fusion protein conciliates viral adherence to cell surface receptors followed by uptake into endosomes. The S protein in many coronaviruses is often cleaved by furin-like proteases into S1 and S2 subunits. The capsid of the virus is a protein shell enclosing the nuclear capsid or N-protein, which after binding to the single-stranded positive-sense viral RNA allows the virus to confiscate the cells of humans to turn them into virus factories [20].



STRUCTURAL PROTEIN	FUNCTION OF PROTEIN
Nucleocapsid Protein (N)	• Bound to RNA genome to make up nucleocapsid
Spike Protein (S)	• Critical for binding of host cell receptors to facilitate entry to host cell
Envelope protein (E)	• Interacts with M to form viral envelope
Membrane Protein (M)	• Central organiser of CoV assembly • Determines shape of viral envelope

Fig.1: Structure, important components, and functions of coronaviruses

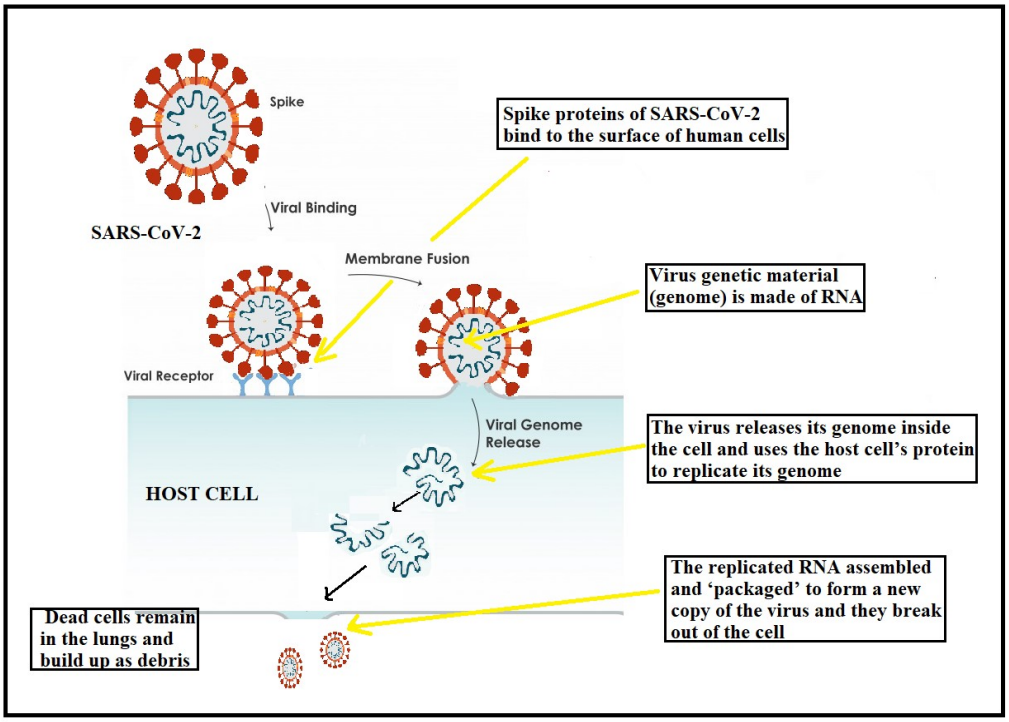


Fig. 2: An overview of the sequences of the coronavirus attack on the host cell

As shown above in figure 2 [21], the virus comes in contact with the human cell and after binding, releases the genetic material which is made up of RNA. This process in SARS-CoV-2 (COVID-19) is primed by a protease called TMPRSS2 [22]. Then it uses the protein of the host cell and replicates its genome. The replicated RNA assembles and produces a new copy of the virus [23,24].

As per WHO guidelines, the virus takes on an average of 5–6 days to show the symptoms in an infected person, but in some, it can take up to 14 days or more [25]. Some of the infected patients develop mild to moderate illness and do not require hospitalization. But most of them show symptoms as mentioned below [25,26].

I. Most common symptoms of COVID-19
   i. Fever
   ii. Dry cough
   iii. Fatigue

II. Less common symptoms of COVID-19
   i. Aches and pains
   ii. Sore throat
   iii. Diarrhea
   iv. Conjunctivitis
   v. Headache
   vi. Loss of taste or smell
   vii. Skin rashes
   viii. Discoloration of fingers or toes

III. Severe symptoms of COVID-19
   i. Difficulty breathing
   ii. Chest pain or pressure
   iii. Loss of speech or movement

People showing mild symptoms who are healthy otherwise must take the basic treatments at home. However, people with severe symptoms should immediately visit a doctor or health facility. The time from the onset of COVID-19 symptoms to death is from 6 to 41 days [27, 28]. This period depends on the patient's age and the immune system. Assessing the risk of COVID-19 symptoms, an increased number of patients and the mortality rate were found associated with the cohort over age 57 [29].

As per WHO guidelines, the basic control and precautionary measures to be practiced has been listed below [30, 31]:

i. Frequently cleanse your hands using soap and water for not less than 20 seconds. When soap and running water are unavailable, use an alcohol-based hand rub with at least 60% alcohol.
ii. Maintain a safe distance from anyone who is coughing or sneezing.
iii. Avoid touching your eyes, nose, or mouth with unwashed hands.
iv. Practice good respiratory etiquette, including covering coughs and sneezes.
v. Stay home if sick.
vi. Immediate medical help should be sought if one has fever, cough, or breathing problems.
vii. Follow the directions of your local health authority.

Scientists are yet to come up with a potential vaccine and till then what best can be done is to follow the guidelines and precautionary measures. This way the pressure on the health infrastructure will be under control and the scientists will get a little more time to develop an effective remedy.

Working principle of a vaccine

The vaccines work as per the same basic principle wherein the pathogen as a part or all of it is presented as a vaccine to the immune system of humans generally in low dose [32]. The immune system identifies it and produces distinctive antibodies to destroy the pathogens. An antibody, as a kind of memory of the immune system, having been induced once, can be quickly mobilized again if the person, infected before encounters the same virus in its natural form. This is known as the immune response which can be generated by various means- traditionally a small dose of the weak form of the virus or the inactivated (by heat or chemicals) form has been injected into the body, and the immune system responds by producing antibodies against the pathogen. This used to be a rudimentary form of immunization. Recent methods of immunization are more selective and specific. These are recombinant vaccines. The word itself means taking the genes and combining them for a specific use. In this method of vaccination, the information within the genes of the virus is studied which makes a virus so lethal at the genetic level. The information studied is used to generate similar effects without actually exposing the human to the virus itself. Based on existing literature, it has been found that the S-protein of SARS-CoV-2 is highly antigenic [22]. The particular genomic sequence of the S-protein, therefore, can be combined with a specific vector. This way an effective vaccine can be produced at a comparatively low cost within a short period. Also, the rDNA-based vaccine will contribute highly to the rapid immunization.

Possibilities and Challenges in Vaccine Development of COVID-19

The Coalition for Epidemic Preparedness Innovation (CEPI, an international nongovernmental organization funded by the Wellcome Trust, the Bill and Melinda Gates Foundation, the European Commission, and eight countries) classifies vaccine development phases as "observable/exploratory" (planning and designing a candidate, which cannot be tested *in vivo*), "preclinical" (*in vivo* testing with preparation for producing a human test), or establishing safety phase I studies in healthy people [33,34]. Phase I trials primarily test the safety and early dosing of a few healthy subjects, while phase II trials, following the success in Phase I, examine immunogenicity;dose differences (efficacy based on biomarkers); and side effects of a vaccine, in usually hundreds of humans. The Phase II trial enables initial protection and immunogenicity testing, is often indiscriminately administered, placebo-controlled, and at multiple sites, while establishing precise, effective doses [35]. Phase III trials usually involve multiple participants, including the control group, and the performance of a vaccine trial to prevent the disease, while keeping a close observation on the adverse effects at the appropriate dose [35,36]. As of mid-May, around 171 COVID-19 vaccine candidates are already in the “exploratory” or “preclinical stages” of development [37,38]. However, in rare cases such as the present one, this strategy can be suppressed and a quicker regulatory approval mechanism can be created and if efficacy and safety are demonstrated, vaccines may be approved by regulatory agencies.

The rapid outburst of SARS-CoV-2 has led to the obligation to expeditiously develop a vaccine against basic scientific understanding using areas such as genomics and structural biology, that is supporting a new era in vaccine development. Coronavirus has caused two recent epidemics- Epidemic of Severe Acute Respiratory Syndrome (SARS) which took place in China in 2002-2004 and the Middle East Respiratory Syndrome (MERS) that started in Saudi Arabia in 2012 [32,39].

Consequently, after the announcement of China on the identification of a novel coronavirus as the cause of the Wuhan outbreak, CEPI contacted its researchers that were developing MERS vaccines or researching for the same cause. Within no time after the identification of first gene sequences, CEPI and others began vaccine development that is proceeding quickly [40].

The novel coronavirus COVID-19 shares around 80-90% genomic similarity to that of the SARS virus of 2003 and binds to the same ACE2 receptor of the host cell [41]. Past research efforts to develop a SARS-CoV vaccine have opened the door for present investigators to design vaccine concepts and approaches for the COVID-19 pandemic. Since existing infrastructures can be used, vaccine development by practicing existing vaccine platforms can be readily accomplished [32]. With the vision to help and support rapid research progress, the gene sequence successfully obtained was released for use and references by the Chinese scientific community. Research has led to the establishment of numerous types of vaccines like the development of inactivated vaccines, live-attenuated vaccines, polysaccharide vaccines, toxoid vaccines, virus-like particles (VLPs), DNA plasmid vaccines, mRNA vaccines to overcome the existing COVID-19 situation.

With so many in the race, Moderna's mRNA based SARS-CoV-2 vaccine candidate mRNA-1273 is the first vaccine candidate to enter into the clinical trials. mRNA-1273 utilizes a portion of the genetic code of coronavirus's spike protein rooted in specialized nanoparticles. The USA based Moderna has the experience of working and developing the SARS-CoV and MERS-CoV vaccines and the understanding of which helped them to progress in a very short span of 45 days. After demonstrating positive results in animal testing, phase I clinical trial of the vaccine started on March 16, 2020, in partnership with the NIH for 45 healthy people of 18–55 years [42]. Several other vaccines based on mRNA targets (e.g., by CureVac (Germany), BNT162 by BioNTech (Mainz, Germany), and Pfizer (New York, USA) are at various stages of development. For example, the BioNTech mRNA vaccine (Mainz, Germany) incorporates nucleic acid at 80 nm special ionizable, glycol-lipid nanoparticles [33]. Another vaccine to enter the clinical trials in China has been produced by CanSino Biologics (China), a company that has also developed an Ebola vaccine [33].

Besides these, there has been a prompt in developing other novel vaccines as well as therapeutic mediations to counter viral infections [33,41,42]. For example, Inovio Pharmaceuticals' INO-4800 (USA) is a DNA-based vaccine using the gene of the spikes of coronavirus. This is sponsored by the Bill and Melinda Gates Foundation which has entered the phase I clinical trials [43,44,47]. With these COVID-19 vaccine candidates and a few others showing promising results in the early trials are giving the hope to have a vaccine by the end of this year [45].

Table 1: Details of COVID-19 candidate vaccines

Platform	Types of Vaccine Candidate	Developer	Stages of Clinical Evaluation
Non-replicating Viral Vector	ChAdOx1-S	University of Oxford/AstraZeneca	Phase2b/3
Non-Replicating Viral Vector	Adenovirus Type 5 Vector	Beijing Institute of Biotechnology/ CanSino Biological Inc.	Phase 2
RNA	LNPencapsulated mRNA	Moderna/NIAID	Phase 2
Inactivated	Inactivated	Sinopharm /Wuhan Institute of Biological Products	Phase 1/2
Inactivated	Inactivated	Sinopharm /Beijing Institute of Biological Products	Phase 1/2
Inactivated	Inactivated + alum	Sinovac	Phase 1/2
Protein Subunit	recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine	Novavax	Phase 1/2
RNA	3 LNP-mRNAs	BioNTech/Pfizer /Fosun Pharma	Phase 1/2
Inactivated	Inactivated	Institute of Medical Biology, Chinese Academy of Medical Sciences	Phase 1
DNA	DNA plasmid vaccine with electroporation	Inovio Pharmaceuticals	Phase 1

As reflected in the draft landscape of COVID-19 candidate vaccines prepared by WHO (Table 1; Updated on May 27, 2020) 115 candidate vaccines are in the phase of pre-clinical evaluation and 10 have entered the various phases of clinical evaluation [46,47].

For once, the entire health community was looking at plasma or antibody therapy to battle COVID-19. China's National Health Commission has added convalescent plasma as a therapeutic method. However, there is no approved remedy for Covid-19 in the state including the therapy using the plasma of the recovered patients. Plasma therapy is being experimented with and there is no evidence to support it as a treatment [45]. To date, ICMR does not recommend it as a treatment option other than clinical trials [40,48,49]. Plasma therapy is only in the testing phase, if not

used properly, it can cause life-threatening complications. Looking at the alarming increase in the number of infected patients, it is more crucial to emphasize the development of a vaccine at this point of time.

Researchers worldwide are working overtime to develop experimentally but potentially life-saving vaccines. Screening out at each step is very essential, that is the reason why clinical trials can't be skipped or hurried. Conducting clinical trials during the pandemic is again a kind of challenge, as it is not predictable when and where the outbreaks will occur and also to prepare trial sites to coincide with the vaccine readiness for testing.

What most people need to accept is that in addition to all the coronavirus-related urgency, there is a specific step procedure that must be followed to create the vaccine. It is not as easy as mixing certain medicinal ingredients and preparing a mixture that will cure people. Before it can be mass-produced and presented to the public, vaccines need to be designed, tested, and regulated just like every other drug. After investigating the disease and the causes of the infection, the short-listed vaccine needs to be tested. In fact, they are being tested rigorously by comparing a non-invasive drug such as a tablet or tablets. Usually, tests are performed on a much larger number of human subjects than the standard drug. Apart from that, for licensing to export, the operation of the vaccine is closely monitored by authorities such as the Central Drugs Standard Control Organization (CDSCO) in India and the Food and Drug Administration (FDA) in the US [48].

As the current situation demands, vaccinologists may choose a shortcut path to get a potentially lifesaving vaccine, which will deviate from the main objective of the immunization; either the vaccine candidates will be unsafe or they'll be ineffective or both. Although SARS and MERS vaccines are being correlated to establish one for COVID-19, yet not confirmed. The potential duration of immunity is unknown for the infections that are naturally acquired. Similarly, whether the single-dose vaccines of COVID–19 will confer the optimal immunity is uncertain.

The RNA based coronavirus, upon infection, can translate the entire RNA with 33,000 bases to a long tape of amino acid sequences. The long chain of amino acid contains several proteins within it, hence known as the polyprotein sequence. Drugs like Remdesivir are found to have an inhibitory action on the various enzymes responsible for the synthesis of such antigenic proteins in the virus [50]. The current efforts in developing a COVID-19 vaccine are mostly targeted on the distinctive sites of the virus. The idea behind this is to make the human body recognize a unique genomic sequence of the site which will help it to fight off the whole virus [51]. But the main problem of concern is the appearance of inactivation of vaccines and resistance to therapeutic agents of the new strain of coronavirus aided by the

change in environment and climatic condition. The already infected patients have enhanced the possibility of successful "escape mutations" in the antigenic protein of the virus [52]. A research study, led by scientists, including an Indian researcher Dr. Tanmoy Bhattacharya at Los Alamos National Laboratory, warned about a mutation called D614G in the spike protein which is becoming dominant globally and that could make the virus more infectious [53]. India-born Prof S Vasan and his associates from Commonwealth Scientific and Industrial Research Organization (CSIRO) in Australia investigated 82 strains of coronavirus and analyzed that nearly 50 percent of these strains have the new mutation in India [53,54]. In this matter of probability, the development of a vaccine and a specific therapeutic agent might lead to a huge waste of resources. However, no specific conclusion has been made on whether the mutations of the virus will impact the severity of the disease or interfere with the effectiveness of the COVID-19 vaccine, as the mutation is not occurring as fast as that of the flu virus [55,56].

Even after the approval of a potentially safe vaccine, another set of challenges may arise- the approved vaccine candidate must be manufactured in large quantities. The problem will be making sure that the approved vaccine gets to all those who need it, including children and pregnant women, who are considered to be at the highest risk. Although some of the high-income countries may pay for the development and manufacture, pandemic tends to hit hard those countries having the most fragile and unfunded healthcare systems, and an inherent imbalance comes between demand and purchasing especially in case of vaccines. We can imagine a scenario where, say, in India, which is a major supplier of vaccine to the developing world, has to immunize its own 1.3 billion strong population first, before exporting. Meanwhile, the million-dollar questions are- Will a qualified manufacturing process be sufficient to improve the vaccine development, or should it be restructured? Will the political and commercial conditions become an obstacle to the global effort to respond to the urgent need for the SARS-CoV-2 vaccine?

Conclusion

Novel coronavirus pandemic will generate simultaneous demand for vaccines around the world. The development and proper distribution of the vaccine will require strong collaboration between pharmaceutical companies, governments, regulatory agencies, and the World Health Organization as well as divergent approaches to cGMP production, release processes, clinical trial design, and regulatory science. A vaccine can save many lives. As recent studies and researches suggest, the SARS-CoV-2 vaccine will probably be developed by overcoming the challenges. Otherwise, we may get it too late to affect the first ripple of this pandemic. By that time, the best hope we can have is to contain the spread of the

disease as far possible; by following the government's guidelines, by repeating the sage advice: stay home, wash your hands.

However, the late coming vaccine might be useful if subsequent waves occur or in a post-pandemic scenario of continuation of the circulation of SARS-CoV-2 as a seasonal virus. We will be better prepared for sure, by learning the lessons while handling the outbreak. The viruses will keep coming as nature is still beyond complete understanding.

This review is based on the existing hypothesis proposed so far. Since SARS-CoV-2 is a novel virus, many aspects are yet to be revealed. At this stage, it is very difficult to precisely say the exact time by which we will have a safe and effective vaccine in our hands.

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