Vaccines for Severe Acute Respiratory Syndrome-related Coronavirus-2

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Abstract

The novel coronavirus infection emerged in Wuhan in the late 2019 which later spread across the globe and was declared as a pandemic in March 2020. The virus was named by World Health Organization as severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) and the disease caused by it as coronavirus disease-2019 (COVID-19) on February 11, 2020. The disease leads to respiratory distress syndrome and mortality, especially in elderly and people with comorbidities. The treatment remains supportive, in the absence of specific treatment, prevention is the only answer. Apart from physical distancing, hand washing, and masks, vaccination is a futuristic option. Although work has started in full swing, the vaccine may not be available before 12–18 months. Here, the vaccine scenario changes by the day, but I have tried to evaluate the types of vaccines possible and the ones where trials have started.

Keywords: Coronavirus vaccination, COVID-19, SARS-CoV-2.

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A novel coronavirus infection emerged in Wuhan, China in the later part of 2019. Initially, it was transmitted to humans by animals on the local wet markets and this was followed by human-to-human transmission. The virus then spread across China and 200 other nations across the globe. Severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19) were the names given by the World Health Organization for the virus and the disease caused by this virus, respectively, on February 11, 2020.[1] Coronavirus disease-2019 has an incubation period of 2–11 days and clinically present with severe respiratory illness. The mortality is significantly seen among the elderly and individuals with underlying comorbid conditions, such as cardiac and respiratory diseases, diabetes, and hypertension.[2] The case fatality rate (CFR) is 2–3%, less than its predecessors, severe acute respiratory syndrome (SARS) (10%), and middle east respiratory syndrome (MERS) (30%).[3] Controlling this viral infection would be challenging without a prospect vaccine as this SARS-CoV-2 virus can transmit from infected individuals who are asymptomatic and also it has the ability to cause a pandemic. This study provides a brief overview of the major candidate vaccines, along with their merits. Information has been derived from publicly available websites as much of this information has not entered the peer-reviewed literature. At the time of writing, there are 110 vaccine candidates across the world but mostly they are at the preclinical stage.[4] All methods are being thought of injectable live and killed, nasal spray and tablets. If introduced before the pandemic ends, it will be the first given to frontline health care professional's (HCP), paramedics, elderly population then the general population.

Severe acute respiratory syndrome-related coronavirus-2 probably mutated from bats before infecting one or more mammal species like pangolin and finally infected humans. Severe acute respiratory syndrome virus and SARS-CoV-2 both belong to genus beta coronavirus and exhibit approximately 79.5% nucleotide similar to each other. Similarly, both bind to angiotensin converting enzyme (ACE-2) receptors found in the human lung.[5] This gives a little head start to the SARS-CoV-2 vaccine strategies as they are built on the vaccines already tested for SARS.

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Immunizations with whole virus vaccines and complete spike protein vaccines have resulted in undesired immunopotentiation by eosinophilic infiltration or causes increased infectivity thus causing hurdles in the development of SARS coronavirus vaccines.[3] These findings are under investigation as the basis of these is unclear. Therefore, the vaccine should not cause immunopotentiation to be completely safe. Another key element of testing a SARS-CoV-2 vaccine is the selection of intended target population. The population under high risk for the COVID-19 diseases like the frontline healthcare workers, individuals with underlying comorbid illness, and those above 60 years of age have to be prioritized for vaccine clinical trials and licensure.[6]

The vaccine candidates can be the traditional whole cell vaccines, subunit vaccines, or the DNA and RNA nucleic acid vaccines. Their merits and demerits are discussed below:

Whole virus vaccines: The classic traditional strategy for viral vaccinations include inactivated whole virus and live-attenuated vaccines. The whole virus vaccines are advantageous because of their inherent immunogenicity and also the ability to stimulate toll-like receptors. However, these vaccines usually take 10–15 years from concept to production. However, some of the precursor vaccines have been tested on animals during the SARS outbreak. Extensive testing is required for the live virus vaccines to confirm their safety as compared to the inactivated vaccines. The findings of increased immunopotentiation like eosinophil infiltrates and increased infectivity after a challenge dose are an issue for live coronavirus vaccines.[5]

Among the whole cell vaccine candidates, Johnson & Johnson is planning to test a COVID-19 vaccine based on their Ebola vaccine platform.[7] A live influenza vaccine that expresses SARS-CoV-2 proteins has been developed by the researchers at the Honk Kong University.[8] Codagenix has also developed a technology called "codon deoptimization" to make versions of viruses and viral therapies relatively harmless. Using this technology, the virulent pathogens are replaced by the milder strains.[9] Serum Institute of India has tied up with Codagenix to conduct further clinical trials in India. Animal trials are about to begin in June. The development and testing of a unique vaccine built on the backbone of M2SR, a flu vaccine candidate against COVID-19 called CoroFlu, has begun by the University of Wisconsin-Madison a FluGen vaccine companies. They plan to induce immunity against coronavirus by inserting the gene sequences from SARS-CoV-2 into M2SR.[10]

Subunit Vaccines

Since there is an 80% similarity among the amino acids of both the viruses SARS-CoV and SARS-CoV-2 and also they bind to the ACE2 receptor, either of these proteins can be used to produce a subunit vaccine. Eliciting an immune response against the S-spike protein by the subunit vaccines is required to prevent both the SARS coronavirus to dock onto the host ACE2 receptor.[11] The University of Queensland under funding from the Coalition for Epidemic Preparedness (CEPI) is synthesizing viral surface proteins, to present them more easily to the immune system. Another company, Novavax has developed and produced adjuvanted full-length spike nanoparticles and have shown better immunogenic response in mice.[12] Using patented Trimer-Tag® technology, a subunit vaccine consisting of trimerized SARS-CoV-2 S-protein is being developed by the Clover Biopharmaceuticals.[13] They have already used this technology to develop vaccines for HIV, RSV, and flu which have proved effective in various animal models. A subunit vaccine comprising the receptor-binding domain (RBD) of the SARS-CoV S-protein has been developed and tested by the Consortium led by the Texas Children's Hospital Centre for Vaccine Development.[5,14] With homologous virus challenge, the SARS-CoV RBD vaccine has elicited high levels of protective immunity when the vaccine was formulated with alum. Also, this vaccine has an advantage of minimizing the host immunopotentiation.[5]

Nucleic Acid Vaccines

Several major biotech companies have advanced nucleic acid vaccine platforms for COVID-19. These could be DNA, RNA, or mRNA based. There have been promising results in mice, where the mice had shown a protective immunity against influenza in 1993 when they were immunized with DNA. But, the same have not been translated in humans for decades. There are expectations on production of the first licensed human nucleic acid vaccine with the recently available new modifications and formulations which have enhanced the performance of the nucleic acid vaccine in humans. Inovio Pharmaceuticals is developing a DNA vaccine. Zydus Vaccines India has also two vaccine candidates based on plasmid DNA and a measles-based virus replicating factor vaccine.[4] The mRNA sequence which codes for a disease-specific antigen is introduced by the RNA vaccines. The immune system recognizes the disease-specific antigen when proceed by this mRNA sequence and produces antibodies to fight the real virus. RNA vaccines do not use infectious elements and hence are safer for the patient and can be produced faster at a cheaper price than the traditional vaccines. Production of RNA vaccines is laboratory based, and the process could be standardized and scaled, allowing rapid responses to large outbreaks and epidemics. There are several early stage clinical trials for RNA vaccines for infectious diseases and cancer. Hence, further understanding on the side effects and better evidence for their long-term efficacy are required before mRNA vaccines become a standard treatment, and this requires more research work.[15]

The mRNA vaccines can be: (a) non-replicating mRNA: This is the simplest RNA vaccine where the antigen is made by the body cells when the mRNA strand is packaged and introduced into the body. (b) *In vivo* self-replicating mRNA: this produces more robust immune response as small amount of vaccine helps in the production of greater quantities of antigen. This is ensured by packaging additional RNA strands with the pathogen-mRNA strand, thus it will be copied once the vaccine is inside the cell and increased quantity of antigens are produced. (c) *In vitro* dendritic cell non-replicating mRNA vaccine. Dendritic cells are immune cells which help in stimulating the immune response by presenting the antigens on their cell surface to other types of immune cells. Here, the patient's immune response is stimulated by giving the dendritic cells transfected with the RNA vaccine. These dendritic cells are extracted from the same individual and they are transfected with the RNA vaccine.

The benefits of mRNA vaccines over conventional approaches are (a) safety: RNA vaccines are not infectious as they do not contain pathogen particles or inactivated pathogen. Once the protein antigen is made the introduced RNA strand gets degraded and thus does not integrate into the host genome. (b) Efficacy: early clinical trial results indicate that they are tolerated well by the healthy individuals, with few side effects and they also produce a reliable immune response. (c) Production: these vaccines can fasten the response in the emerging outbreaks as they can be produced rapidly in the laboratory in a process that can be standardized. There are many challenges also. Being nuclear material, they may elicit an unintended immune reaction. Body breaks down the free RNA rapidly which makes the delivery of these RNA vaccines difficult. These vaccines have to be frozen or refrigerated like the conventional vaccines. Work is ongoing to reliably produce vaccines that can be stored outside the cold chain.[15]

Vaccines Which Have Started Human Trials

National Institute of Allergy and Infectious Diseases (NIAID) along with Moderna has already started a phase I open-label trial and has enrolled 45 healthy adult volunteers' aged 18–55 years. The vaccine is called mRNA-1273 and has shown promise in animal models. This vaccine is given as two doses, 28 days apart to the study participants in the upper arm via intramuscular route. These participants are assigned into 3 groups with 15 people in each group. Each participant will receive a 25, 100, or 250 µg dose at both vaccinations based on the group in which the individual is assigned with 15 people in each group.[16] Phase I safety trial of a recombinant adenovirus vaccine candidate Ad5-nCoV has been started by CanSino Biologics Inc., China. The recruitment of 108 healthy adults in Wuhan began in March. It has simultaneously started phase II trials with 500 patients.[17]

Geno-Immune Medical Institute, Shenzhen has started trials with a vaccine based on dendritic cells modified with lentiviral vector code named LV-SMENP-DC. Phase I trials have started in

March 2020 with 100 volunteers in Shenzhen, China and they plan to continue trials till the end of 2023.[17] ChAdOx1 nCoV-19, a vaccine candidate based on an adenovirus vector, has been developed by Jenner Institute of the University of Oxford. They have signed a manufacturing contract with Advent and SII. The animal studies were initiated in March 2020, and simultaneously recruitment of 510 human participants for a phase I/II trial began on 27 March. These participants will be randomized into 2 groups, of which 260 participants would receive the experimental vaccine and 250 would receive a saline injection, with 6 months of follow-up.[18] The phase I trial of a DNA-based vaccine candidate called INO-4800 has been initiated on April 6, 2020 by the Inovio Pharmaceuticals in collaboration with a Chinese firm and support from CEPI and the Gates Foundation. Forty healthy volunteers are included in this trial with 6 months of follow-up at sites in Philadelphia and Kansas City.[17]

The coronavirus epidemics keep occurring at regular frequency—SARS in 2002, MERS in 2012, and now COVID-19. The ultimate aim is to produce a universal coronavirus vaccine to guard against future epidemics and endemics also. The development of the most promising candidate vaccine has to be continued even if the pandemic ends abruptly. They have to be stockpiled for emergency use if there is recurrence of an outbreak. A global financing system that supports end-to-end development and large-scale manufacturing and deployment and protects private-sector partners from significant financial losses will be a critical component of future pandemic preparedness.[17]

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