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Challenges in the synthesis of n-CoV vaccine - A review

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Abstract:

This review highlights the challenges and difficulties faced by the researchers towards the synthesis of the n-CoV vaccine.The articles were collected from search engines like PubMed, Google scholar, Biorxiv, MedRxiv, Cochrane, and also two primary Chinese databases were used for biomedical research namely CNK1 and WanFang. The relevant articles were collected from the period from 2000 to 2020 to date. This review reveals that the COVID vaccine will be soon discovered in spite of potential obstacles. Phase I of the nCoV vaccine was successfully done. Scientists and Physicians are drilling down to establish an effective vaccine to eradicate this pandemic threat CORONAVIRUS by inculcating different guidelines for the synthesis of vaccines.In the current background of the SARS CoV-2 pandemic, population immunization by vaccination is recognized as a priority for public health. The clinical safety and effectiveness proof is considered as the most important scientific obstacles. This review thus highlights the various challenges in the design, evaluation, and synthesis of n-CoV vaccines.

Keywords:

Coronavirus, vaccine, challenges, clinical trials, epitopes, mortality, genetic sequence

Introduction:

Coronavirus disease (COVID-19) was discovered in China in December 2019. A cluster of patients was admitted with fever, cough, shortness of breath, and other symptoms. Then the patients were scanned by computed tomography, which revealed varied opacities (denser, more profuse, and confluent) in initial diagnosis, which led the doctors to conclude that it was pneumonia. Additional analysis of the diseases revealed that it was pneumonia but the origin was unknown. Then they came to a conclusion by identifying the pathogen as coronavirus caused by a novel strain of CoV (n-CoV-19) (Zhu *et al.*, 2020)**.** It is a virus that is a member of the family of beta coronavirus. It induces illness in birds, mammals. A common cold had been the most common symptom. The common cold then was lethal to life as it was combined with SARS, MERS, and COVID-19. The coronavirus with its large form is a single-stranded, positive RNA structure. The virus' most pathogenic structure was the spikes of glycoproteins that were presented in that virus capsule. It was transmitted via contact with someone infected (Shereen *et al.*, 2020)**.** It caused multiple high organ failure including pneumonia, fever, cough, and also found the heart, kidney, and GIT to be affected. The coronavirus was more infectious because it could live on any surface for at least 2 hours. It later becomes a pandemic threat to global health and to the public at large. As morbidity and mortality rates rise, the scientist drills down to find

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the mechanism for this virus, to find a vaccine to eliminate this bio-war (Wang *et al.*, 2020)**.** The intermediate source of origin and transmission to humans is not known but the rapid human to humans transmission has been widely reported. No clinically approved antiviral medication or vaccine is available for use against COVID-19. However, few broad-spectrum antiviral drugs have been evaluated against COVID-19 in clinical trials, resulting in clinical recovery(Tian *et al.*, 2020)**.**

The vaccine is the substance that is used to stimulate an individual's immune response by evoking antibody activity. Various techniques are employed for the nCoV vaccine synthesis. The vaccine's mechanism is for it to artificially evoke the antibodies. Our immune system first evokes the antibodies by introducing new viruses, generating a memory for that specific virus (Prompetchara, Ketloy and Palaga, 2020)**.** The conventional way of creating a virus is to grow/cultivate the virus in a medium and inject it in an inactivated form into an object of examination. Now, there is an urge to take a cutting-edge vaccine in this pandemic situation. Scientists are working hard to develop an efficient vaccine that is undergoing clinical trials. This disease has spread rapidly across the globe since the outbreak of the novel coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus(Ahmed, Quadeer and McKay, no date)**.**

Given the imminent challenge posed by a pandemic, scientists and physicians have rushed to understand this new virus and the pathophysiology of this disease in order to identify possible treatment regimens and to discover effective vaccines (SohaibShahzan, SmilineGirija and VijayashreePriyadharsini, 2019). The vaccines aim primarily at antiviral strategies involving small molecules and biological targeting of the complex molecular interaction involved in infection and replication of coronavirus. Many articles provide information on the strong intellectual groundwork for ongoing therapeutic agents and vaccine development (Pang *et al.*, 2020)**.** The need to produce a SARS-Cov2 vaccine quickly comes at a time of acceleration in basic scientific understanding, especially in areas such as genomics and structural biology, which is promoting a new age in the production of vaccines. The research community and the vaccine industry have been asking in the past decade to find vaccines for HINI Influenza, Ebola, Lima, and now SARS-CoV2 (Pratha, AshwathaPratha and Geetha, 2017). In this way, an H1N1 influenza vaccine was created and key regulators have previously agreed that vaccines made using technologies based on eggs and cells should be approved under the rule used for a strain update. But here comes the difficulties of the COVID-19 vaccine synthesis (Ashwin and Muralidharan, 2015). The vaccine synthesis employs many techniques, including attenuated virus vaccine, protein-based, gene-based, DNA-based, mRNA-based, subunit vaccine, and non-specific vaccines. Some reports also suggest there are genetic similarities between SARS and COVID. It's really uncertain what the truth is. Even though there are many types of vaccine preparation, it is only when it is effective that the success lies. In addition, the research reveals that the SARS-CoV cannot be grown in a chicken embryo medium. This vaccine clinical trial requires a high level of biosafety, and more candidates (Liu *et al.*, 2020)**.**

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The main drawback is that the synthesis of vaccines requires a minimum of 1 year for trial since phase III of vaccine preparation is the longest (Udugama*et al.*, 2020)**.** So, this study analyses the challenges faced by scientists in the synthesis of a vaccine against the dreadful n-CoV strains. Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Ariga*et al.*, 2018; Basha, Ganapathy and Venugopalan, 2018; Hannah *et al.*, 2018; Hussainy*et al.*, 2018; Jeevanandan and Govindaraju, 2018; Kannan and Venugopalan, 2018; Kumar and Antony, 2018; Manohar and Sharma, 2018; Menon *et al.*, 2018; Nandakumar and Nasim, 2018; Nandhini, Babu and Mohanraj, 2018; Ravinthar and Jayalakshmi, 2018; Seppan*et al.*, 2018; Teja, Ramesh and Priya, 2018; Duraisamy*et al.*, 2019; Gheena and Ezhilarasan, 2019; Hema Shree *et al.*, 2019; Rajakeerthi and Ms, 2019; Rajendran *et al.*, 2019; Sekar*et al.*, 2019; Sharma *et al.*, 2019; Siddique *et al.*, 2019; Janani, Palanivelu and Sandhya, 2020; Johnson *et al.*, 2020; Jose, Ajitha and Subbaiyan, 2020).

Retrieval of data:

The articles were collected from search engines like PubMed, Google scholar, Biorxiv, MedRxiv, Cochrane, and also two primary Chinese databases were used for biomedical research namely CNK1 and WanFang. The relevant articles were collected from the period from 2000 to 2020 to date. It is a five-step process in the selection of articles- identification of clear objectives - identification of relevant articles - selection - data extraction - analysis and report. Articles related to challenges in the synthesis of vaccines for coronavirus, about the vaccine types, techniques, challenges, limitations, and about the clinical trials of various coronaviruses vaccines were included and articles that had general information about viruses, articles related to MERS, SARS were excluded.Our institution is passionate about high quality evidence based research and has excelled in various fields ((Pc, Marimuthu and Devadoss, 2018; Ramesh *et al.*, 2018; VijayashreePriyadharsini, SmilineGirija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai*et al.*, 2019; Sridharan *et al.*, 2019; VijayashreePriyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

Vaccines and coronavirus - an overview:

A vaccine is a biological preparation that provides the active immunity acquired for specific infectious diseases. Vaccine administration is called vaccination. Vaccine development is a complex and time-consuming process that differs from conventional process development. Normally a vaccine development time is 12-15 years. Vaccines are the most cost-effective healthcare interventions known to prevent death and disease (Ong *et al.*, 2020)**.** Vaccines typically contain medical products identical to the responsible microorganisms. For the disease and often consisting of one of the killed or attenuated microorganisms, their toxins or surface proteins, introduced by mouth, injection, or nasal spray to stimulate the immune system in us and to recognize and destroy foreign agents. Clinical trials show the effectiveness of the vaccines by proving their potential to avoid the short-term (Girija As and Priyadharsini J, 2019). Then

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virulent microorganisms such as bacteria and viruses are very crucial factors in the production of the vaccines. Antigens are administered into the body in classical vaccines, resulting from inactivated or partially activated attenuated viruses (Caddy, 2020)**.** These antigens can activate the immune system, and they are cells for the production of antibodies. If a person comes into contact with native pathogens, the immune system will already have the necessary antibodies ready and multiply them much more quickly (Girija, SmilineGirija, Shoba, *et al.,* 2020)**.**

A coronavirus is a group of related RNA viruses that cause disease in mammals as well as birds. Among humans, the virus causes infections in the respiratory tract that can range from mild to lethal (Ksiazek*et al.,* 2003)**.** Some cases of the common cold include mild illness, while lethal varieties can cause SARS, MERS, and COVID-19. There are no vaccines or antivirals for this human infection of coronavirus whatsoever. Coronavirus structure is mainly, roughly a spherical particle with bulbous surface projection. Be well informed about the COVID-19 virus, the disease it causes, and how it spreads, is the best way to prevent and slow down transmission. There are no unique COVID-19 vaccines or therapies available at this time. There are also several current clinical trials testing new therapies (Hall and Tucker, 2020)**.** The virus particle has an average diameter of about 125 nm. It is an enveloped glycoprotein virus. Infected carriers can plunge viruses into the atmosphere. The coronavirus spike protein interaction with its complementary cell receptor is crucial in deciding the tissue tropism, infectivity, and different species distribution of the virus released (Wrapp*et al.,* 2020)**.** Coronavirus is transmitted by an aerosol or fecal-oral route from one host to another, depending on the coronavirus species (Xu *et al.,* 2020)**.**

Guidelines to synthesize n-cov vaccines:

A vaccine produced by the tinkering of synbio- not only looks scalable to a level of billions but it also looks like it will function without the need for cooling. Develop and create protein-based nanoparticles and add viral molecules in them that are peptide-free so that when the whole thing is bundled into a vaccine, it can avoid the new coronavirus to the general population (Wang *et al.,* 2007)**.** The vaccines are based on proteins also known as the recombinant vaccine used to vaccinate against viral infections such as HIV. These are easier to produce but require more time to grow. The gene-based vaccination is the best way to get the vaccination to produce minute amounts of the viral protein that activates the immune response (Zhang *et al.,* 2020)**.** RNA vaccines are easy to make since they don't take much longer. In a test tube, the RNA vaccines are manufactured using a biochemical reaction that takes just hours. Friendly virus vaccines are made by inserting into an adenovirus the coronavirus gene which codes for the spike protein (Du *et al.,* 2009)**.** Virus-like particle vaccine, in which a mimic virus particle can concentrate the target for easy penetration. Like vector vaccines with a heterologous antigen that induces immunity from cells (Marohn and Barry, 2013). The process is still being used in clinical trials. The approach used in epitope vaccines is where the synthetic peptide associated with reverse vaccinology. The fragments are attached herewith chemical synthesis techniques provided by

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intact antigens that robust the immune system (Enayatkhani*et al.*, 2020)**.** There is no COVID-19 vaccine available while previous vaccines or methods used to develop a SARS-CoV vaccine can be successful. Recombinant protein from the SARS-CoV strain Urbani (AY278741) was administered to mice and hamsters, developed neutralizing antibodies, and protected against SARS-CoV(Begum *et al.*, no date)**.**

The DNA fragment, entire virus inactivated, or SARS-CoV live-vectored strain (AY278741), greatly decreased the viral infection in different animal models. In addition, numerous other SARS-CoV strains were used to develop inactivated or live-vectored vaccines that effectively reduced the viral load in animal models. The mRNA-based vaccine developed by the United States National Institute for Allergy and Infectious Diseases against SARS-CoV-2 is being evaluated in phase 1 (Chen and Joyce, 2020)**.** INO-4800- DNA dependent vaccine for human research will be available soon. Centre for Disease Control and Prevention Center (CDC) working on inactivated virus vaccine production. The sample of the mRNA dependent vaccine will be available soon. Biopharmaceuticals are developing a recombinant vaccine based on the 2019-nCoV S subunit trimer protein(*Website*, no date)**.**

Vaccines based on cross-reacting antigens among the SARS group of viruses:

The SARS-CoV-2 genome was confirmed to be more than 80 percent similar to the previous human coronavirus. The four structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N), encode the structural Proteins. The orf1ab is the largest gene encoding the pp1ab protein and 15 nsps in SARS-CoV-2. The orf1a gene encodes 10 nsps for the pp1a protein. SARS-CoV-2 is similar to the SARS-coronavirus community, as per the evolutionary tree (Phan *et al.*, 2020)**.** Recent studies have shown major differences in SARS-CoV and SARS-CoV-2 such as the absence of 8a protein and the number of amino acids in SARS-CoV-2 in 8b and 3c protein. It is also reported that the Wuhan coronavirus spike glycoprotein is altered through homologous recombination (Girija*et al.*, 2019). In a fluorescent test, it was reported that the SARS-CoV-2 also uses the same cell receptor ACE2 (angiotensin-converting enzyme 2) and the host cell entry mechanism used by the SARS-CoV before. The single N501 T mutation in the Spike protein from SARS-CoV-2 may have significantly enhanced its binding affinity to ACE2(Hoffmann *et al.*, 2020).

Synthesis of non-specific vaccines:

There is some evidence that the Bacillus Calmette-Guerin tuberculosis vaccine has received clear beneficial effects against infections not linked to it. Some reports say a link exists between the COVID-19 mortality rates and the BCG vaccine (Shahana and Muralidharan, 2016). The number of cases and deaths clarified by the BCG vaccination program varies from 12.5% to 38%. By dividing the countries into three groups with a high, medium or low growth rate of cases, there is a highly significant difference between the groups in the BCG category, BCG has been found to increase the life expectancy in many people, especially the elderly (Vaishali and Geetha, 2018).

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We need to look at these possibilities for further purposes. BCG, which can stay alive in the human skin for many months, not only activates particular B and T memory cells but also stimulates the innate blood cells for a prolonged time (Sala and Miyakawa, 2020)**.**

Challenges and limitations in cov vaccine design, synthesis, and evaluation:

The pandemic coronavirus tends to be a highly sophisticated pathogen evasion due to the novel vaccine failure. Alternate methods were used to resolve this failure, but the virus' spike proteins showed structural variation in the receptor domain was not apparent (Girija, Jayaseelan and Arumugam, 2018). The scientist, therefore, confronted a challenge in defining the receptor-binding domain. The whole-cell antigen test was then used to characterize the vaccine, but there was not enough pathogenicity in the viral strains of SARS-COV2. Then the N-terminal domain that has the protein was selected as RBD, but it showed high variability with different epitopes and the tendency of the virus to escape the immune response (Pallesen*et al.*, 2017)**.** Scientists are working on discovering the SARS-CoV sequence for vaccine synthesis but the sequence is still uncertain. The prediction of epitopes was carried in the silico process, this shows a spike glycoprotein sequence of MHC. But then later it was found that it was discovered later, indicating the various mutations. Many bioinformatics methods were used to classify the epitopes, including IEDB analysis to find the mapping of the epitope (Saif, 2020)**.**

Glycoprotein spike protein sequence was analyzed including a sequence of KRSFIEDLCFNKV which showed a notable relationship between SARS and COVID-19. The scientist experiences so many difficulties in determining the correct target (Smiline, Vijayashree and Paramasivam, 2018). Another problem is that it takes more time to better evaluate its impact and use in order for a vaccine to develop. Selections of antigen also play a significant role in the efficacy of the vaccines. n-COV vaccine antigen collection list comprises whole-cell antigen, spike protein, ALE receptor, S1 subunit, fusion protein, nucleocapsid protein (N protein), membrane protein, protein envelope (E protein) (Phelan, 2020)**.**

Global immune deficiency is a risk factor for the efficacy of anti-COVID 19 vaccines, particularly in elderly people who have been exposed to a multitude of factors that lead to the weakening of the immune system, as mentioned above. Such factors also contribute to diseases linked to obesity: e.g., type II diabetes, metabolic syndrome, and immune-mediated cancers. Mechanical causes for these diseases include poor antigen detection, decreased immune cell quantity and functionality, increased part level/length and timing of humoral immune alterations, diminished cellular response initiation, and memory cell disorders (Peeples, 2020). The creation and manufacture of a COVID 19 vaccine is an urgent issue, but the resolution is likely to take several months. Although several organizations have announced that the COVID 19 vaccine will soon be available, in fact, this will be very difficult to achieve (Paramasivam, VijayashreePriyadharsini and Raghunandhakumar, 2020). The key explanation is that the vaccine should be effective, both in the short term and in the long term, before it is placed on the

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market. It is very relevant because situations of contact with other viruses have occurred in the history of vaccine development, luckily with no significant consequences (Lurie *et al.*, 2020).

Anything to be tested on humans should be reviewed for purity first, and then sterile manufacturing lines should be given to prevent these situations. Everything takes time. In rare cases, some immunization-generated antibodies can promote an aggravated form of the disease (a situation called ADE, enhancement dependent on an antibody (Marickar, Geetha and Neelakantan, 2014). When these antibodies restore contact with the virus, they will, in turn, help it get into the cells and cause infection(Thorpe-Vargas and Vaccinations, no date). Most viral infections (influenza, Dengue, Zika, etc.) have identified ADE, but also in coronaviruses. Several animal studies have shown that some types of anti-SARS and anti-MERS vaccines, although effective in generating antibodies, can lead to more severe forms of disease when the virus is subsequently inoculated. The second explanation is that not only must the vaccine be safe but also effective. It must be able to establish the synthesis, at a certain concentration, of antibodies of a certain form and provide defense for a reasonable time. Nevertheless, vaccinations never produce immunity for all individuals vaccinated (Renuka and Muralidharan, 2017). The causes are complex and range from genetic and immunological influences to the vaccine content itself to how it is administered. Given the vaccine would produce an efficient immune response to a sufficient number of individuals among those vaccinated, there is an uncertain timeline for vaccine safety (Calina*et al.*, 2020). Last but not least, both protection and efficacy depend greatly on the type of vaccine, i.e. the device or method being used. Many technologies are very new, and therefore more thorough testing is required (M, Geetha and Thangavelu, 2019). Others are old but COVID 19 needs to be modified. Another thing is not only a company's ability to develop the technology but alsoit's large-scale manufacturing capability to make it available internationally rapidly (VijayashreePriyadharsini, SmilineGirija and Paramasivam, 2018). Because there is no precedent for the proposed platforms for anti-SARS COV-2 vaccine commercially available, entirely new production lines, capable of generating billions of doses in a few months, must be considered. And this must be achieved without stopping existing vaccines, which are already included in the official protocols and guidelines (Cohen, 2020).

Currently, this ability will be difficult to achieve and will represent an unparalleled effort. DNA and RNA vaccines are based on the idea that certain nucleic acids are injected into some vaccinated cells, causing them to produce immunogenic viral proteins(PD) (Priyadharsini*et al.*, 2018). Though some recent data seem promising, these principles have questionable human performance. In reality, non-replicative vectors are many viruses (e.g., adenovirus) that are genetically engineered to show SARS CoV proteins on the outside surface (Lee and McGeer, 2020). Yet they are so common that many of us have dealt with them in our lives and as a result, before they do their job, we already have immunity and neutralize them. The viruses should be variants of SARS CoV-2 produced by genetic modification less to no pathogenic at all. They are by far the most immunogenic but there is a possibility that after mutations they will become

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pathogenic. Inactivated viruses, viral fragments, and synthetic peptides all have relatively low immunogenicity(Basu, Sarkar and Maulik, no date)**.**

Phase trials on n-CoV vaccine:

While research teams around the world are working to explore key characteristics, pathogenesis, and treatment methods, focusing on competitive therapeutic approaches and cross-resistance to other vaccines is deemed appropriate. For example, vaccines for other illnesses such as rubella or measles can establish cross-resistance for SARS-CoV-2 (Girija, SmilineGirija, Shankar, *et al.*, 2020)**.** During synthesis, the vaccine gets obsolete and ineffective. A biosafety level 3 should be in effect for the synthesis of the nCOV vaccine. The vaccine, including human trials, is designed only for a short time. Viruses vaccine is commonly used in chicken eggs. But the coronavirus is found to be inactive on its medium and could not develop (Al-Hazmi, 2016)**.**

Phase I, Phase II, Phase III vaccine trials typically undergo 3 stages (Figure 1). Phase I of the nCoV vaccine was successfully used, but only up to 16.2 percent of the vaccine was completed in Phase III, a congested process. In addition, live viruses injected can be dangerous experiments, because they were more stable than any other virus. Security is the most important thing that should be taken into account during the production of drugs and vaccines and some scientists advise us not to rush to produce the COVID-19 vaccine and drugs without sufficient safety guarantees (Checcucci*et al.*, 2020)**.**

Conclusion:

From the literature reviewed, it is evident that the COVID-19 vaccine trials are so promising and scientists across the world are heading towards a promising end. However, a reasonable understanding on the pathogenesis of the immuno-biology of CoV is also essential in the discovery of proper drugs and vaccines against n-CoV. This review had thus highlighted the various protocols that are currently available in the design, evaluation, and synthesis of novel vaccines with the challenges and limitations, in achieving the same, to curb the menace of COVID disease.

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Author contribution:

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1. Execution of the work
2. Data collection

3. Drafting of manuscript

SmilineGirija AS

1. Concept and design of the study
2. Validation of the data collection
3. Revision and proof-reading of the review

Brundha MP

1. Validation of the data collection
2. Revision and proof-reading of the review

Conflict of interest:

None to declare

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Title of the figure

Vaccine preparation differences between the classical vaccine and the corona vaccine.

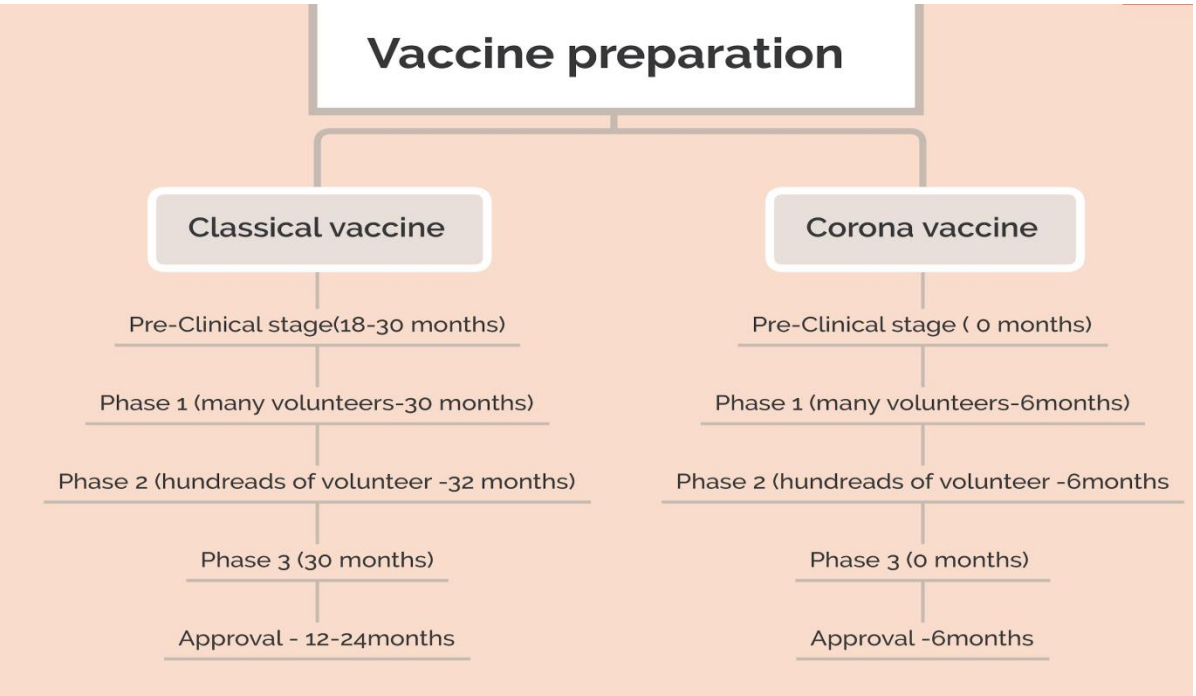

Figure 1: Representation of clinical phase trials difference between classical and corona vaccine.