

Review Article

Stages in COVID-19 vaccine development: The Nemesis, the Hubris and the Elpis

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Abstract

The nemesis: SARS-CoV-2 pandemic: Leaving in its wake millions of infections, accompanied by an immense magnitude of morbidity and multitude of mortality, and an unfathomable economic toll, the COVID-19 pandemic has led to a global calamity. An effective and safe COVID-19 vaccine is urgently needed to prevent the disease, thwart the complications and avert deaths resulting from unrestrained transmission of the infection.

The hubris: Vaccine development: While most of the platforms of vaccine candidates have focused on the spike (S) protein and its variants as the primary antigen of COVID-19 infection, various techniques involved include nucleic acid technologies (RNA and DNA), non-replicating viral vectors, peptides, recombinant proteins, live attenuated and inactivated viruses. There are novel vaccine technologies being developed using next-generation strategies for precision and flexibility for antigen manipulation relating to SARS-CoV-2 infection mechanisms.

The elpis: Updates and prospects: There were nine different technology platforms under research and development to create an effective vaccine against COVID 19. Although there are no licensed vaccines against COVID-19 yet, there are various potential vaccine candidates under development and advanced clinical trials. Out of them, one having undergone phase III clinical trials, has become available in some countries for use among the high-risk groups following emergency use authorization. Other COVID-19 vaccines may soon follow the suit.

Conclusion: Hopes and concerns: The hope of benefiting from the vaccine to the extent that it may be the only way to tide over and control the COVID-19 pandemic, is accompanied by the likely fear of adverse effects and opposition in public for COVID-19 vaccination, including the vaccine hesitancy. Further, there is concern among scientific circles that vaccine may have opposite of the desired effect by causing antibody-dependent disease enhancement.

More Information

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Keywords: COVID-19 vaccines; Genomic sequencing; Coronavac; Covaxin; EpiVacCorona; Moderna's vaccine; Oxford-AstraZeneca COVID-19 vaccine; Pfizer-BioNTech COVID-19 vaccine; Sputnik V; Vaccine technology platforms; Vaccine hesitancy



Introduction

Curbing the infection

Leaving in its wake millions of infections, accompanied by an immense magnitude of mortality and multitude of morbidity and an unfathomable economic toll, the COVID-19 pandemic has led to a global calamity [1]. The disease has seriously affected the vulnerable groups in the society including those 65 years of age or older, persons with underlying conditions, and the economically deprived populations. It is feared that more of devastation is likely to be witnessed in form of serious post-COVID-19 complications especially in the survivors of the serious illness. An effective and safe vaccine is thus urgently needed to prevent the disease, thwart the complications and avert deaths resulting from unrestrained transmission of the infection [2].

Although there are no licensed vaccines against COVID-19 yet, there are various potential vaccine candidates based on a variety of platforms including lipid nanoparticle mRNA, DNA, adjuvanted protein, inactivated virus particles, and non-replicating viral vectors are in various phases of clinical trials, including 11 vaccine candidates in phase 3 trials, followed by over a hundred vaccine candidates in preclinical testing [3].

The safety and immunogenicity data relating the vaccines in this context are important. The clinical significance of SARS-CoV-2 binding and neutralizing antibody titres and their ability to predict efficacy is needed to be evaluated and confirmed. Though the immune correlates of protection against SARS-CoV-2 are yet to be determined, the neutralising antibodies are thought to be associated with protection



based on results from studies in COVID-19 non-human primate challenge models inferring that neutralising antibody response is correlated with protection [4]. These findings have led to the use of neutralisation assays to assess immune responses in recent human COVID-19 vaccine trials [5].

The Nemesis: SARS-CoV-2 virus: Invasion and the pandemic

The virus and the disease: During December 2019, an outbreak of apparently viral pneumonia was reported from the city of Wuhan, in Hubei province, China. Soon the disease spread to other parts of China and several countries to become a pandemic. By 9 January 2020, it was established that the disease was caused by a novel coronavirus, 2019-nCoV or SARS-CoV-2 and was named COVID-19 [6]. Later, during the first half of January 2020, the Chinese researchers shared the genome sequence of the virus, followed by identification of the same by the Mutualized Platform for Microbiology (P2M), Pasteur Institute, Paris on 29 January 2020 from the samples taken from the initial suspected patients in France [7].

Following the sequencing of SARS-CoV-2 genome, an international response was triggered to develop a prophylactic vaccine to provide acquired immunity against COVID-19. By April 2020, over hundred institutes and companies in 19 countries were working on the vaccine for COVID-19. Initially it was said, including by WHO in February 2020, that a vaccine for the disease was not expected to become available in less than 18 months. Later, it has been claimed by researchers that with the help of genetic Engineering, the COVID-19 Vaccine can possibly be made in months rather than years [8].

Various vaccines under development to combat the COVID-19 have been modelled on the original strain, common among hCoV-19 genetic sequences published during the initial months of the course of the disease pandemic. Understanding the evolution and mutations of SARS-CoV-2 during the COVID-19 pandemic is imperative for disease control and prevention through the vaccine programme. A spike protein mutation D614G has emerged through supplanting aspartic acid (D) in the 614th position of the amino acid with glycine (G), hence the change known as D614G.

The D614G mutation has supposedly enhanced viral replication in human airway tissues, enhanced viral survival in the upper airway of infected hamsters, and increased susceptibility to neutralization. It appears that the mutation may have increased the infectivity of the virus [9]. The work by Plante, et al underlines the importance of this mutation in viral spread, vaccine efficacy, and antibody therapy [10]. It has been pointed out, the vaccines against COVID-19 are hoped to work against new G-strain, as well [11]. Further, the study involving Hamsters concluded that the D614G mutation may not reduce the ability of vaccines in clinical settings to protect against COVID-19 and the neutralising antibodies are to be assessed against the circulating variant of the virus before clinical development.

SARS-CoV-2 genomic sequencing: The genome of SARS-CoV-2 is comprised of a single-stranded positive-sense RNA. It is composed of 13–15 (12 functional) open reading frames (ORFs) containing ~30,000 nucleotides and contains 38% of the guanine-cytosine (GC) content and 11 protein-coding genes, with 12 expressed proteins [12]. The ORFs are arranged as replicase and protease (1a–1b) and major S, E, M, and N proteins. These gene products play important roles in viral entry, fusion, and survival in host cells.

Basically, the genomic sequencing is a technique to interpret genetic information found within the virus. So far, there are over 1,000 COVID-19 genomes published worldwide [13]. The genomic sequencing helps in understanding when and where the version of the virus originated and how the virus is evolving. Sequencing the genome of SARS-CoV-2 virus also helps in understanding the disease transmission kinetics, its spread in population groups and planning and evaluating the containment efforts. In addition, it helps to track the viral mutations as the disease spreads.

In general, the viruses circulating locally have small genetic changes compared to the ones that are circulating elsewhere. Thus, the genomic sequence can be used to estimate the infected population size and how the virus is spreading. Further, understanding of the genomic structure of the virus helps in developing drugs and vaccines for therapy as well as prophylaxis of COVID-19.

The Hubris: COVID-19 vaccine: Development programmes

The basis for vaccine development: It has been documented that the immunological memory after infection with seasonal human coronaviruses (hCoVs) may potentially contribute to cross-protection against SARS-CoV-2. In a cohort of 350 SARS-CoV-2–uninfected individuals, a small proportion had circulating immunoglobulin G (IgG) antibodies that could cross-react with the S2 subunit of the SARS-CoV-2 spike protein [14]. The anti-S2 antibodies from SARS-CoV-2–uninfected patients show specific neutralizing activity against both SARS-CoV-2 and SARS-CoV-2 S pseudo-types. These antibodies are present in a higher proportion of SARS-CoV-2–uninfected children and adolescents compared with other age groups. By contrast and notably, convalescent COVID-19 patients generate IgA, IgG, and IgM antibodies that recognize both the S1 and S2 subunits.

The fact that viral S protein elicits an antibody response is the cornerstone for development of a vaccine to protect against SARS-CoV-2 infection through generating a strong neutralizing antibody response [15]. In fact, the COVID-19 pandemic has dramatically expedited global vaccine development efforts, most targeting the viral spike (S) glycoprotein. The S protein, which is localized on the virus surface and engages through the host cell angiotensin-converting enzyme 2 (ACE2) receptors. Eliciting neutralizing antibodies that block S-ACE2 interaction or indirectly prevent membrane fusion, constitute

an attractive modality for vaccine-elicited protection. Further, the S protein is crucial in inducing neutralizing antibodies to protect from re-infection. The neutralizing antibodies not only bind to the viral spike protein, but also prevent it from being able to attach to and enter human cells.

The immune response to SARS-CoV-2 spike protein especially in relation to B and T cells has been investigated. Yu, et al. designed a series of prototype DNA vaccines against the SARS-CoV-2 spike protein, which is used by the virus to bind and invade human cells [16]. Analysis of the vaccine candidates in rhesus macaques showed that animals developed protective humoral and cellular immune responses when challenged with the virus. There were observed neutralizing antibody titres at levels similar to those seen in patients recovered from SARS-CoV-2 infection [17]. Most antibodies isolated from the COVID-19 patients are specific to SARS-CoV-2 virus. However, COVA1-16 is a relatively rare antibody that also cross-neutralizes SARS-CoV [18]. Further, Yuan, et al. have documented the structure of CR3022, a neutralizing antibody obtained from convalescent COVID-19 patients in complex with the receptor-binding domain of SARS-CoV-2 spike [19].

The B cells are responsible for producing the antibodies that recognize SARS-CoV-2, while T cells play an important role in supporting the development of the B cell response. The subjects showing a strong neutralizing antibody activity have a robust B cell response. Further, a particular subset of T cells, called T-follicular helper cells, has been found to be a predictor of an effective immune response. The T-follicular helper cells are involved in helping B cells to make antibodies. The humoral and circulating follicular helper T cell (cTFH) immunity against spike in recovered COVID-19 patients, S-specific antibodies, memory B cells and cTFH are consistently elicited after SARS-CoV-2 infection, indicating robust humoral immunity and positively associated with plasma neutralizing activity, whereas there is comparatively lower frequency of B cells or cTFH specific for the receptor binding domain of S protein [20]. These findings are, thus, consistent with the immune response in patients recovered from COVID-19.

The COVID-19 vaccine platforms: While most of the platforms of vaccine candidates have focused on the spike (S) protein and its variants as the primary antigen of COVID-19 infection, various techniques involved include nucleic acid technologies (RNA and DNA), non-replicating viral vectors, peptides, recombinant proteins, live attenuated viruses, and inactivated viruses [21]. The main protein, S protein to boost the immune system can be given as a vaccine in many different forms such as inactivated (dead) virus, as expressed protein, in a DNA or RNA vector that will lead the cells to make this protein and stimulate to make antibodies and activate T cells to control the viral infection or eliminate the infected cells to reduce disease severity and complications (Figure 1).

As reported during September 2020, there were nine

different technology platforms (Table 1) under research and development to create an effective vaccine against COVID-19 [22].

There are novel vaccine technologies being developed for COVID-19 using next-generation strategies for precision and flexibility for antigen manipulation on COVID-19 infection mechanisms [23].

Vaccine development stages and clinical trials: Vaccine development stages include -

- Exploratory or Preclinical Phase - Planning and designing a candidate vaccine.
- Phase I trials test primarily for safety and preliminary dosing in a few dozen healthy subjects.
- Phase II trials – following success in Phase I – evaluate immunogenicity, dose levels and adverse effects of the candidate vaccine, typically in hundreds of people. The phase I and II consist of randomized and placebo-controlled trials.
- Phase III trials typically involve several participants at multiple sites including a control group. It aims to establish the effectiveness of the vaccine to prevent the disease as well as monitoring for the adverse effects at the optimal dose.

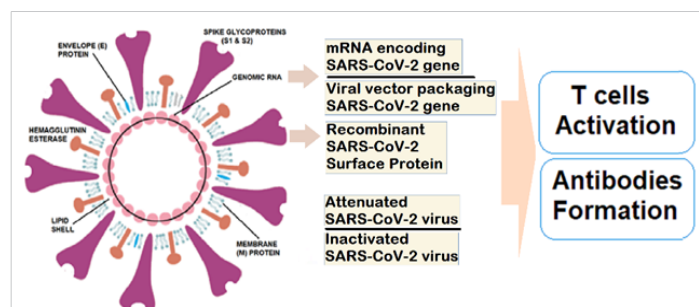


Figure 1: The potential candidates for development of COVID-19 vaccines.

COVID-19 Vaccine platforms	Antigen product and Immunological response
Protein subunits	Antigen fragments - Spike (S) protein or RBD, Weak immunological response Requires repeated vaccination Strong induction
Virus-like particle	Multiple viral antigens, Weak response but greater than protein subunits Requires repeated vaccination Strong induction
Inactivated virus	Multiple viral antigens Weak immunological response Requires repeated vaccination Strong induction
Live attenuated virus	Multiple viral antigens Sustained immunological response Requires only a single delivery Strong induction
DNA-based	Codes for S protein Weaker response than mRNA- based vaccine Requires repeated Vaccination
mRNA-based	Codes for S protein or RBD May be delivered encapsulated with nanoparticle Response depends on adjuvants and formulation May require repeated vaccination
Chimpanzee adenovirus Non-replicating viral vector	Spike protein Unaffected by lack of pre-existing anti-vector immunity Strong with single delivery
Human serotype 26 adenovirus Non-replicating viral vector	Spike protein Response affected by pre-existing anti-vector immunity Requires repeated or heterologous boost vaccination
Human serotype 5 adenovirus Non-replicating viral vector	Spike protein Response affected by pre-existing anti-vector immunity Strong with single delivery

Table 1: COVID-19 Vaccine development technology platforms.



Currently, there are more than a hundred COVID-19 vaccine candidates under development, with several of them already in the human trial phase [24]. The WHO is working in collaboration with scientists, business groups, and various health organizations through the *Access to COVID-19 Tools (ACT) Accelerator* to streamline and speed up the effort. The WHO through the COVAX, which is one of three pillars of the ACT Accelerator, is bringing together governments, global health organisations, manufacturers, scientists, private sector, civil society and philanthropy, to provide equitable access to COVID-19 diagnostics, treatments and vaccines to protect people in all countries.

In a statement issued by the International Coalition of Medicines Regulatory Authorities (ICMRA) and the WHO on 6 November 2020, it was endorsed that ICMRA and WHO are committed to ensure that people in various countries have access to safe and effective health products against COVID-19 as early as possible, while the scientific standards for the evaluation and safety monitoring of treatments and vaccines are rigorously maintained [25]. Simultaneously, they are working to ensure to reduce the risks associated with unproven treatments, and potentially fraudulent and false claims.

Enrolment and plan of clinical trials: The human challenge studies or controlled human infection trials relating to vaccine development, involve an intentional exposure of the participants or test subjects to the vaccine products following preliminary proof of its safety and efficacy in laboratory animals and healthy humans. In this context, the fast-tracking for clinical trials for a COVID-19 vaccine involves compressing the clinical trial period of Phase II and Phase III trials from years to few months. Such challenge studies have been done earlier involving diseases like common flue, typhoid fever, cholera, and malaria which were less deadly than COVID-19.

There is fear that fast-tracking for clinical trials and bypassing typical Phase III research, providing for the accelerated path to license a COVID-19 vaccine may be disastrous and may expose the participants to dangers beyond those considered the anticipated potential side effects. The young adult volunteers are deliberately infected with COVID-19 in a challenge trial conducted and once an infection dose of COVID-19 is identified, the candidate COVID-19 vaccine is tested for effectiveness in preventing infection. Following the challenge, the participants are closely monitored.

Although challenge studies are potentially hazardous for the participants, they are the only way to rapidly produce a vaccine that can be able to prevent the disease in estimated millions of human-beings worldwide and avert significant morbidity and mortality from COVID-19 infection [26]. The clinical COVID-19 challenge studies in healthy

people are conducted as per the WHO Guidance Document including scientific and ethical evaluation, public consultation and coordination, selection and informed consent of the participants, and monitoring by independent experts.

The Efficacy of the COVID-19 vaccines: The effectiveness of a new vaccine is defined by its efficacy [27]. The minimal efficacy limit set by WHO is 50%. Whereas an efficacy of less than 60% may fail to achieve herd immunity. There are other determinants for the efficacy and factors like genetics, health status (underlying disease, nutrition, pregnancy, and sensitivities or allergies), immune competence, age, obesity, and environmental factors, which may affect the susceptibility to infection and severity of the disease, and response to a vaccine. Further, the viral mutations altering its structure may have impact on the vaccine efficacy [28].

The Elpis: Vaccine updates and future scenario for COVID-19

The vaccines in advanced stages of clinical trials –

Out of various COVID-19 vaccine candidates in preclinical and clinical trials, only some are in advanced stages of clinical trials including 11 in phase 3 trials and few vaccine candidates are due for emergency use authorisation (Table 2).

A. Moderna mRNA-1273 vaccine

The mRNA-1273, the Moderna's mRNA vaccine candidate against the SARS-CoV-2 virus, encodes for a prefusion stabilized form of the Spike (S) protein. Based on data from the results of the Phase 1 study, the dose of 100 mcg is generally well-tolerated across various age groups. Further in the older adults, it has been shown to produce the virus-neutralising antibodies at levels similar to that in the younger subjects [29]. Moderna has revealed no serious safety concerns. An independent board that conducted the interim analysis of the

Vaccine	Technology platform	Current phase – Clinical studies	Timeline
mRNA-1273 SARS-CoV-2 Vaccine Moderna, Inc.	mRNA-1273 (a mRNA compound) encoding prefusion stabilized S protein	Submitted preliminary data from its Phase III clinical trial on 16 Nov 2020.	Mar 2020 – Late 2022
AZD1222 – University of Oxford, AstraZeneca	Modified chimp adenovirus vector (ChAdOx1)	Phase III (30,000) Completed Phase I-II in the UK, Sao Paulo	May 2020 – Aug 2021
Ad5-nCoV, CanSinoBIO, Beijing Institute of Biotechnology	Recombinant adenovirus type 5 vector	Phase III (40,000) Completed Phase II China and Pakistan	Mar 2020 – Dec 2020
BNT162 - b2 Pfizer, BioNTech, And Fosun	modified mRNA encapsulated in lipid nanoparticles encoding a mutated form of S protein	Phase III (30,000) Completed phase I-II in the US, Germany	Apr 2020 – May 2021
Gam-COVID-Vac – Sputnik V Gamaleya Research Institute of Epidemiology and Microbiology	Non-replicating viral vector	Phase III (40,000) Randomized double-blind, placebo-controlled to evaluate efficacy and safety in Moscow	Aug 2020 – May 2021
CoronaVac Sinovac Biotech Ltd.	Inactivated SARS-CoV-2	Phase III (23,490) Double-blind, randomized, placebo-controlled to evaluate efficacy and safety in Brazil, Chile, Indonesia, and Turkey	Jul 2020 – Aug & Oct 2021

Table 2: The Vaccines in Advanced Stages of Clinical trials.



vaccine trials found side effects such as fatigue in 9.7% of participants, muscle pain in 8.9%, joint pain in 5.2%, and headache in 4.5%.

More than 30,000 participants at 100 clinical research sites in the United States are participating in the study, which launched on July 27, 2020, after results from earlier stage clinical testing indicated that the vaccine candidate is well-tolerated and immunogenic. Recognizing the disproportionate impact of the epidemic on minority populations, the study has included 37% of the trial volunteers from racial and ethnic minorities.

The vaccine has been co-developed by the Cambridge, Massachusetts-based biotechnology company Moderna, Inc., and the National Institute of Allergy and Infectious Diseases, a part of the National Institutes of Health. It combines Moderna's mRNA (messenger RNA) delivery platform with the stabilized SARS-CoV-2 spike immunogen (S-2P) developed by NIAID scientists. The vaccine will be manufactured at Visp, Switzerland by its partner Lonza Group, to produce the first doses in December of 2020. Another Lonza's site at Portsmouth, New Hampshire, aims to produce it exclusively for the U.S.A.

Recently, on 16 November 2020, Moderna, Inc. announced that the independent, NIH-appointed Data Safety Monitoring Board for the Phase 3 study of mRNA-1273, has confirmed that Moderna vaccine trial has met the statistical criteria pre-specified in the study protocol for efficacy, with the vaccine having efficacy of 94.5%. Later, on the following day, it announced that the European Medicines Agency human medicines committee has started a review of the vaccine, following the confirmation of eligibility of mRNA-1273 for submission on October 14, 2020.

B. Pfizer-BioNTech COVID-19 vaccine

The mRNA-based COVID-19 vaccine candidate, BNT162-b2, developed by Pfizer and its German partner, BioNTech SE, has shown 95% effectivity. According to Pfizer data, of the 170 volunteers who contracted COVID-19 during Phase III trials involving over 43,000 people, 162 had received a placebo and only eight received the two-dose vaccine, indicating 95% efficacy of the vaccine.

It is a two-dose vaccine, and the second dose is given 3 weeks later. It takes about 2 weeks for the immune system to make sufficient antibody protection after vaccination. After the first dose, efficacy was 52% and after second dose (3 weeks later), efficacy is 95% (90% - 98%). Further, Pfizer has claimed that the vaccine has consistent efficacy across different ages and ethnicities, and its efficacy in adults over 65 years, who are at particular risk from the virus, is over 94%. Presently, it is not recommended for those under 16 and in pregnant women.

As per the data, the vaccine is well-tolerated and has mild to moderate side effects. About 2% volunteers in the study complained of headache, whereas 2% and 3.7% suffered with fatigue following the first dose and second dose, respectively. Further, there is safety data on about 100 children of 12-15 years of age and about 45% of US trial participants enrolled were 56-85 years old.

On 2 December 2020, Medicines and Healthcare products Regulatory Agency (MHRA) has approved the Pfizer/BioNTech COVID-19 vaccine for widespread use in the UK. This is followed by EUA by health regulatory agencies in Bahrain, Canada, Saudi Arabia, and very recently by USA on 12th December.

Both the Moderna's and Pfizer's COVID-19 vaccines, rely on a technology called messenger RNA, which is being used for the first time to develop a vaccine. The technology is designed to tweak the host cells to make certain proteins for immunological response. These vaccines have specific cold chain and handling requirements. Minus 70 °C (-94°F) is required by the Pfizer vaccine, whereas for Moderna's vaccine it is Minus 20 °C. The cold chain requirement, specially for the Pfizer's vaccine can be an obstacle for most Asian countries where high environmental temperature is compounded by poor infrastructure. After reaching a vaccination center, the vaccine is to be thawed and used within five days.

C. AstraZeneca-Oxford COVID-19 vaccine

The AstraZeneca-Oxford AZD1222 or ChAdOx1 vaccine uses an adenovirus to deliver the gene for the spike protein of SARS-CoV-2 to trigger a robust immune response in adults aged 56-69 and over 70, as per the results of Phase II clinical trials. As per an interim analysis blending two trials of the vaccine in which people received different doses, the efficacy ranges from 62% to 90%, depending on the dosing strategy. Further, it appears to be well tolerated across all age groups. The AstraZeneca/Oxford vaccine candidate initial efficacy trials were conducted in the United Kingdom and Brazil.

As per the data, the immunogenicity was similar across age groups after a boost vaccination. The immunisation with ChAdOx1 nCoV-19 has shown to result in development of neutralising antibodies against SARS-CoV-2 in almost 100% of participants including older adults without severe comorbidities, with higher levels in boosted compared with non-boosted groups [30]. The adverse reactions to the vaccine are mild, with the most common effects being injection-site pain and tenderness, feverishness, fatigue, headache, and myalgias.

In India, the Phase III trials of the Oxford vaccine (named 'Covishield' in India) are being conducted by the Serum Institute of India. Recently on 20 Nov 2020, it was announced that the vaccine is planned to be tested on a limited basis by



administering it to the frontline workers and the elderly. The vaccine is likely to be available for healthcare workers and elderly people by around February 2021 and by April for the general public. The Serum Institute of India has claimed that its vaccine has 90% efficacy.

The AstraZeneca/Oxford vaccine will be relatively cheap, about \$3 per dose, and only needs refrigeration temperatures for storage, whereas the mRNA vaccines will be costlier at least \$20 per dose and must be kept at sub-zero temperatures.

D. Chinese COVID-19 vaccine

The 'Coronavac', the Sinovac Biotech Ltd.'s COVID-19 vaccine, is a two-dose vaccine. It is under clinical trial involving 9,000 volunteers at Butantan Institute, São Paulo, Brazil. The vaccine is also in the final Phase III trials at University Research Hospital in Kocaeli, Turkey. It was recently declared that Sinovac is likely to publish the efficacy results from its vaccine trials by 15 December, this year.

The vaccine has been offered to Chinese population for emergency use since 17 Oct 2020 onwards, and reportedly, CoronaVac is one of three experimental COVID-19 vaccines China has been using to inoculate around 1 million people under an emergency use programme.

Another Chinese COVID-19 vaccine, with Ad5-nCoV (Recombinant adenovirus type 5 vector) technology platform, named 'CanSinoBIO' is developed by the Beijing Institute of Biotechnology and under Phase III trials involving 40,000 volunteers in China and Pakistan.

E. Russian COVID-19 vaccine

The Russian COVID-19 vaccine, named 'EpiVacCorona' is being developed by Vector State Research Center of Virology and Biotechnology. On 16 Oct 2020, Russia has announced completion of successful clinical trials of EpiVacCorona.

Another Russian COVID-19 vaccine named 'Gam-COVID-Vac', also known as 'Sputnik V', is based on the non-replicating viral vector technology platform to deliver the S protein gene and being developed by the Gamaleya National Research Center for Epidemiology and Microbiology and the Russian Direct Investment Fund (RDIF). Sputnik V vaccine is claimed to be 92% effective at protecting people from COVID-19 according to the interim trial results. The vaccine is to be kept at a temperature of -20 °C to -70 °C.

A combined approach is also being tested in Russia by AstraZeneca, by using a mix of its vaccine with the locally made Sputnik V vaccine in clinical trials. In India, the Russian vaccine, Sputnik V, is under mid- to late-stage clinical trials by Hyderabad-based Dr Reddy's Laboratories in India.

F. Other COVID-19 vaccines

In India, trials are underway for 'Covaxin', an

indigenous COVID-19 vaccine being developed by the Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR) and National Institute of Virology (NIV), Pune. Covaxin uses a part of inactivated SARS-CoV-2 virus to provoke the immune response. The vaccination schedule consists of two doses of Covaxin for each study participant, administered via intramuscular injection 28 days apart. The Phase III of the human clinical trial of Covaxin is currently underway at All India Institute of Medical Sciences, New Delhi. As stated in a latest communique by Bharat Biotech on 23 Nov 2020, Covaxin is expected to be 60% efficacious, the vaccine can be stored at temperatures between 2 °C and 8 °C, economical at a projected cost ₹ 500-600 (About 8 USD) per dose for the general public and could be ready for rollout by next year, in June 2021.

Another COVID-19 vaccine, 'ZyCoV-D', developed by the Indian pharma giant, Zydus Cadila, using the DNA based platform using non-replicating and non-integrating plasmid carrying the gene of interest, is currently under phase II of human trials. According to the data from the preclinical stage, the vaccine was found to be immunogenic in multiple animal species and the antibodies produced were able to completely neutralize the wild type virus. In the Phase I clinical trials, the vaccine candidate was found to be safe and well tolerated. The vaccine is expected to be available by March 2021.

Two other vaccine candidates by Sanofi and GSK are not expected to be ready until the end of 2021. The development and trials of the COVID-19 vaccine by CSL and University of Queensland in Australia was abandoned recently due to technical issues about false positive HIV results among subjects involved in early testing.

The British researchers are also studying inhaled versions of COVID-19 vaccine candidates to see if they can deliver a localised immune response in the respiratory tract. An alternative to the common injection in the arm, the spray vaccine is supposed to trigger specific immune responses in airways by mimicking the natural infection of a respiratory virus. China is also set to start trial of nasal spray COVID-19 vaccine. The researchers working on inhaled vaccine plan to utilize some of the unique cellular features of the lungs, nose, and throat.

COVID-19 vaccination - other issues:

The Fast Tracks for COVID-19 vaccines: Because of the urgency created by the COVID-19 pandemic, the development of various vaccines is on a fast track. Classically, for a vaccine the preclinical stage is about 18 to 30 months, followed by the phase I, II and III, each of them lasting for about two and half years, and the approval followed by production of the vaccine taking a period of another one to two years. For the COVID-19 vaccines being developed urgently, the preclinical stage is short one, followed by phase I and II each compressed to duration as short as 6 months and the phase III shortened to zero month,



and the COVID-19 vaccine is foreseen to get an approval for emergency use and start its production simultaneously. The urgency and the haste are likely to involve errors at multiple stages and carry a potential scope for disaster.

Timeline for the COVID-19 vaccination: It is being envisaged that following the emergency authorization for use by US Food and Drug Administration, European Medicines Agency (EMA) or other governing body in a country concerned, the vaccine will initially be offered to people at high risk for the disease and healthcare workers (Dec 2020 -March 2021), followed by those at risk (March 2021 or later), before being available to the general population (July 2021 or later). It is thought that a target to vaccinate 75 percent population is likely to attain localised herd immunity.

Opposition to the COVID-19 vaccines: The hope of benefiting from the vaccine to the extent that the vaccine may be the only way to tide over and control the COVID-19 pandemic, is accompanied by the likely opposition in public for COVID-19 vaccination, including the vaccine hesitancy. As apparent from various surveys, some people are understandably concerned that the speed of both scientific review and vaccine regulation could compromise safety, despite vaccine developers' and regulators' assurances to the contrary. Vaccine distribution poses another formidable challenge. It is also accompanied by issues such as its cost and who will be paying for it.

In a Medscape reader poll involving 308 UK physicians, it was found that 4 in 10 doctors would not have a COVID-19 vaccine as soon as one is approved by the Medicines and Healthcare products Regulatory Agency in the country. About 56% cited safety concerns, 27% would rather wait, 7% mentioned personal health reasons, and 14% had other reasons. Overall, 59% said vaccination for healthcare staff should not be compulsory [31]. With the growing number of people who oppose the vaccination, their attitudes have also changed over last few months. The polling by Kantar of 1000 people carried out recently on 10-11 November, found that 76% of people in Britain would like to take a vaccine for COVID-19, but the score has fallen since June 2020.

In another European survey, 73.9% participants were willing to get vaccinated against COVID-19 if a vaccine would be available; 18.9% of respondents stated that they were not sure, and 7.2% stated that they do not want to get vaccinated [32]. The common reasons for opposing COVID-19 vaccination, are based on the belief that the vaccine may not be safe (24%), the concern about the side effects (21%), considering the COVID-19 infection not dangerous (14%), rejecting vaccinations as a general principle (11%), and some (8%) not willing to meddle with the course of the Nature [33].

The COVID-19 vaccine nationalism: The COVID-19 pandemic has triggered a global race for development of its vaccine. Further, there has evolved a competition among

various countries to ensure the COVID-19 vaccine availability to their citizens. The wealthy governments have invested in vaccine candidates and have made bilateral agreements with developers, resulting in the vaccine doses being reserved.

With over 1.5 billion potential dose purchases and 1 billion confirmed dose purchases, the US alone has signed up for more than 2.6 billion doses. This is followed by the European Union's 1.2 billion doses and another 750 million potential purchase. India has confirmed dose purchases exceeding 1.5 billion, ranking third in terms of the number of COVID-19 vaccine doses committed to procure. Thus, there are already more than 8 billion doses of COVID-19 vaccine currently reserved due to advance market commitments before a clearly confirmed outcome of the effectiveness of a COVID-19 vaccine is released. These factors may hinder the delivery of health innovations to several lower-income countries and potentially leave their populations vulnerable to COVID-19.

The advanced deals made by high-income countries as well as middle-income countries have led to a fear that this may create a challenge for equitable global distribution of coronavirus vaccines [34]. In response to the vaccine nationalism, there has been the creation of the COVAX Facility led by the WHO, which is an international partnership aiming to financially support leading vaccine candidates and ensure access to vaccines for lower-income countries. Seventy-nine higher-income countries are COVAX members. Their governments will help support 92 lower-income countries for affording COVID-19 vaccines.

The populations at greatest risk of serious COVID-19 include people with coexisting health conditions and older adults. A safe and effective vaccine will be an important tool in controlling the global COVID-19 pandemic and the success rate of a vaccine to be introduced for use, as per the WHO recommendations, should show the disease risk reduction by at least 50%. It is estimated about 70% of people must be inoculated to end the pandemic, and Asia alone is home to more than 4.6 billion - or three-fifths of the global population. Further, the Director General of WHO has cautioned that the COVID-19 vaccines alone will not be enough to stop pandemic and that the vaccines should complement the other tools such as universal masking and social distance, not replace them.

Vaccine related risks and competition: Whereas most of the leading Western vaccines are based on advanced technology platforms such as genetically engineered viral vectors, designer proteins, and snippets of RNA, the China's vaccine candidates and an Indian vaccine candidate make use of the inactivated virus. The inactivated virus, containing a full set of viral proteins, along with an adjuvant effectively alerts the immune system to produce antibody and T cell responses. Unlike the mRNA vaccines, which require to be stored at sub-zero temperatures, the inactivated virus vaccines require ordinary refrigeration.



There are risks related to the COVID-19 vaccines. Many scientists find the inactivated virus vaccines as outmoded, difficult to make in high volume, and potentially dangerous. Further, inactivated COVID-19 vaccines are more likely to trigger antibody enhanced disease in immunized people, in whom ineffective antibodies form immune complexes that clog the lungs and vasculature. This occurred with a vaccine against respiratory syncytial virus given to children in the 1960s, and in animal experiments with vaccines against SARS and MERS. In case of the Adenovirus-based vaccines, pre-existing immunity to Ad5 can attack the vector, leading to a weaker-than-expected antibody response. Further, historically, in 2007, it was feared that the efficacy trials of an Ad5-based AIDS vaccine might have actually raised the risk of HIV infection. Further, the prospect of producing large batches of virus before being inactivated poses certain challenges, as instances of the live poliovirus having escaped from European plants involved in making inactivated polio virus vaccines.

China's vaccine effort is supplemented by the country's dramatic success with aggressive public health measures and testing of entire cities. Further, China is not waiting for the phase III results before widely using its vaccines at home to vaccinate large populations outside of clinical trials. The Coronavac, inactivated virus vaccine and CanSino based adenovirus 5 (Ad5) incorporated with the S protein have been offered to Chinese population for emergency use since 17th Oct 2020 onwards and as against the doubting attitudes and mistrust toward COVID-19 vaccines in the United States and European countries, people in China have already lined up to receive the experimental vaccines even before their value and safety have been proved.

China is doing the clinical trials and brokering vaccine deals in various countries including the Arab and South American countries. The China's COVID-19 vaccines manufacturers claim to produce billions of doses by next year for the countries not having access vaccine because of vaccine nationalism and the countries, like Brazil, Mexico, Chile, Argentina, Turkey, Indonesia, and Pakistan, that have hosted China's efficacy trials in procuring a secure vaccine supply.

With the pandemic controlled at home, China looks forward to supplying its COVID-19 vaccines to various countries around the world. During October, China joined the COVID-19 Vaccines Global Access (COVAX) Facility, led by WHO, CEPI, and Gavi, the Vaccine Alliance, to make sure that the products are safe and effective and available to higher income as well as low-income countries. The COVAX has not, so far, received support from the United States or Russia [35].

Vaccine related injury and compensation: As early as 2005, the International Federation of Pharmaceutical Manufacturers and Associations demanded that manufacturers be granted protection from lawsuits associated with vaccine-related adverse events if they were going to participate in

pandemic responses. Following which, in the United States, the Public Readiness and Emergency Preparedness Act was passed in the background of clinical trials of avian influenza vaccine, providing manufacturers immunity from lawsuits related to injuries caused by vaccines, with narrow exceptions, in the event of a declared public health emergency. In the current situation the same kind of immunity is being claimed by the vaccine manufacturers [36].

About 25 countries have no-fault vaccine-injury compensation systems for routine immunizations and required changes could be made to policies related to funding, proving injury, and distributing compensation. Other countries need to agree to appropriately provide legal immunity and indemnify the WHO, donors, manufacturers, and health care workers who vaccinate people. Simultaneously, there is required a mechanism for efficiently handling a high volume of claims from throughout the world.

To meet this, it is being explored that the COVAX Facility may establish a procedure for compensating people who may suffer from severe adverse events related to the vaccination. Further, the international body for compensation based at the COVAX Facility may be practicable solution to facilitate the procurement of COVID-19 vaccines while ensuring that vulnerable people are able to seek compensation for injuries, and it could as well set a precedent for future vaccination campaigns.

Conclusion

The Limitations, the concerns and hesitancy

Immunological response to the vaccines: Understanding immune memory to SARS-CoV-2 is critical for improving diagnostics and vaccines, and for assessing the likely future course of the pandemic. The various components of immune memory of SARS-CoV-2 tend to persist for about 6 months [37]. The S-specific memory B cells are more abundant at 6 months than at 1 month. Whereas the SARS-CoV-2-specific CD4⁺ T cells and CD8⁺ T cells decline with a half-life of 3-5 months.

The neutralising antibodies appear to be the only component of immune response that can provide protection from the infection. The spike IgG titres show a modest decline in 6 to 8 months. But the magnitude of the antibody response against SARS-CoV-2 is highly heterogenous between individuals. Immunization studies in non-human primates have indicated that circulating neutralization titres of 200 or more may provide sterilizing immunity. Further, the presence of sub-sterilizing neutralizing antibody titres at the time of exposure to infection may blunt the size of the initial infection and may contribute to limit the disease severity.

Efficacy vs. exaggerated immune reactions: The confirmation of the correlation between antibody titres and



protection against COVID-19 can only be possible through a large clinical efficacy study. In the meantime, the assays for measuring antibody may fill the gap but their validity needs to be ascertained. There is an uncertainty relating to the expected efficacy. It is being projected, depending on the profiles observed for other viral vaccines, that the vaccine's efficacy against severe COVID-19 may be higher than efficacy against mild disease.

But there is another aspect of the immunological response to the vaccine. Although the antibody production by a potential vaccine is intended to neutralize the COVID-19 infection, it is feared that the vaccine may have an opposite effect by causing antibody-dependent disease enhancement (ADE), which might trigger the cytokine storm in case the person is infected by the virus in future, after the vaccination [38]. Following inoculation of inactivated whole-virion coronavirus vaccine, the antibodies targeting S protein, may involve the Fc receptor (FcR)-expressing cells, a phenomenon well documented with flaviviruses, leading to ADE. The technology used for vaccine, its dose, timing of repeat vaccinations for the possible recurrence of COVID-19 infection, and elderly age are factors related to the risk and extent of ADE.

The vaccine hesitancy and concerns: The rapid development and urgency of producing a vaccine for the COVID-19 in view of the raging pandemic may increase the risks and failure rate of delivering a safe and effective vaccine. There are indications that the potential success rate may be only 10% for various COVID-19 vaccine candidates under development [39]. It is, thus, important to continue the developmental research for an effective and safe SARS-CoV-2 vaccine.

On the other hand, at least 10% of the people in different surveys perceive the COVID-19 vaccines as unsafe or unnecessary and consider refusing the vaccination. This public perception has been called vaccine hesitancy [40]. Such behaviour can increase the risk of further viral spread that could lead to future COVID-19 outbreaks. As per a survey in the United States about 67% or 80% of people would accept a new vaccination against COVID-19, with wide disparity relating to education level, employment status, and racial and geographical background [41]. Similar and comparable findings have been documented in a study from the United Kingdom [42].

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