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Review Article

CHALLENGES AND PROGRESS IN DEVELOPMENT OF VACCINE FOR COVID-19: A REVIEW

Mudit Kumar*

Department of Pharmacy, GSVM Medical College Kanpur, Uttar Pradesh, India

Address for Correspondence: *Mudit Kumar, Department of Pharmacy, GSVM Medical College Kanpur, Uttar Pradesh, India*

E-mail: *muditkumar1421978@gmail.com*

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Abstract:

The world has experienced several epidemics posing serious threat to global public health, including the 2002 severe acute respiratory syndrome (SARS) epidemic that caused 800 deaths out of about 8 000 cases, the 2009 H1N1 pandemic with 18 500 deaths, the 2012 Middle East respiratory syndrome (MERS) epidemic that caused 800 deaths out of 2 500 cases, the 2014 Ebola outbreak with 28616 cases and 11310 deaths, and the current coronavirus disease (COVID-19) pandemic with more than 2,321,772 deaths out of over 106,404,698 confirmed cases till now.and is affecting 213 countries all over the world. Coronavirus (CoV) disease-2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome-CoV-2. The disease started in 2019 in Wuhan, China, and has spread globally, resulting in a pandemic. Common symptoms include fever, cough, and shortness of breath. Muscle pain, sputum production, and sore throat are less common symptoms. While the majority of cases result in mild symptoms, some progress to pneumonia and multiorgan failure. The deaths per number of diagnosed cases is estimated at between 1% and 5%, on an average but varies by age and other health conditions. The infection is spread from one person to others via respiratory droplets, often produced during coughing and sneezing. It takes 2–14 days to develop symptoms from the day of exposure. Reverse transcription-polymerase chain reaction from a nasopharyngeal swab or oropharyngeal swab is the standard method of diagnosis. The infection can also be diagnosed from a combination of symptoms, risk factors, and a chest computed tomography scan showing features of viral pneumonia. Measures recommended to prevent the disease include frequent hand washing, maintaining distance from other people, and not touching one's face. The use of masks is recommended for those who are suspected to have the virus and to their caregivers, besides the general public. The importance of a collaborative international effort, the ethical implications of vaccine development, the efficacy needed for an immunogenic vaccine, vaccine coverage, the potential limitations and challenges of vaccine development. Although the demand for a vaccine far surpasses the production capacity, it will be beneficial to have a limited number of vaccines available for the more vulnerable population by the end of 2020 and for the rest of the global population by the end of 2021.

Keywords: Coronavirus; COVID-19; SARS-CoV-2; vaccine development, DNA vaccine, RNA vaccine, non-replication viral vector vaccine, inactivated virus particle vaccine, neutralizing antibodies

Introduction:

Coronaviruses (CoVs) are enveloped,single-stranded RNA viruses ranging from 60 to 140 nm in diameter with spike-like projections on its surface, giving it a crown-like appearance under the electron microscope, hence the name CoV. Four CoVs namely HKU1, NL63, 229E, and OC43 have been in circulation in humans, and generally cause mild respiratory disease.[1] On December 31, 2019, a cluster of cases of "pneumonia of unknown origin" in people associated with the Wuhan's Huanan Seafood Wholesale Market has been reported in Hubei province, China. Only a few days later, Chinese health authorities confirmed that this cluster was associated with a novel CoV and was named CoV disease-19 (COVID-19) by the World Health Organization (WHO).[2] COVID-19 is closely associated with bat-derived severe acute respiratory syndrome (SARS-CoV)-like CoV (bat-SL-covzc45 and bat-SL-covzxc21) (with 88% identity), but is far away from SARS-CoV (about 79%) and MERS-CoV (about 50%), by 7th February 2021 number of reported cases are 106,404,698 worldwide with 2,321,772 deaths reported. India has reported around 10,827,314 cases with 155,032 mortality till 7th February 2021.[3]

Aetiology and origin of SARS-CoV-2

Coronaviruses (CoVs) are positively sensed single-stranded RNA viruses that belong to the order Nidovirales, family Coronaviridae, subfamily Orthocoronavirinae with 4 genera: alpha, beta, delta, and gamma coronaviruses[4]. Alpha CoVs and beta CoVs originated from bats and rodents while delta CoVs and gamma CoVs have their origins from avian species[5]. The beta CoVs including SARS- CoV-1 was isolated from bats in 1992 with civet cats being the intermediary host; MERS-CoV was isolated from dometry camels in 2003; and of course, the currently circulating SARS-CoV-2 formally referred to as 2019 novel coronavirus (2019-nCoV) causing COVID-19. SARS-CoV-2 has a pleomorphic and circular structure with a diameter of about 60-140 nm. It can be transmitted from human-to-human by respiratory droplets from sneezing, coughing, and aerosols, with symptomatic people being the major source of transmission. It has a dynamic incubation period of about 2 to 14 days[6].

Epidemiology of Coronavirus Disease-19

A cluster of pneumonia cases of unknown origin in Hubei province, China, caused concern among health officials in late December 2019. On December 31, an alert was issued by the Wuhan Municipal Health Commission, a rapid response team was sent to Wuhan by the Chinese Center for Disease Control and Prevention (China CDC), and a notification was made to the WHO. Likely potential causes including influenza, avian influenza, adenovirus, SARS-CoV, and MERS-CoV were ruled out. Epidemiological investigation implicated Wuhan's Huanan Seafood Wholesale Market, which was shut down and disinfected, and active case finding was initiated and vigorously pursued. On January 7, 2020, the causative pathogen was identified as a novel CoV, and genomic characterization and test method development ensued. Now named 2019-nCoV, the virus is distinct from both SARS-CoV and MERS-CoV, yet closely related. Early cases suggested that COVID-19 (i.e., the new name for disease caused by the novel CoV) may be less severe than SARS and MERS. However, illness onset among rapidly increasing numbers of people and mounting evidence of human-to-human transmission suggests that 2019-nCoV is more contagious than both SARS-CoV and MERS-CoV[7,8]. The first fatal case was reported on January 11, 2020. The massive migration of Chinese during the Chinese New Year fueled the epidemic. Cases in other provinces of China and those in other countries (Thailand, Japan, and South Korea in quick succession) were reported in people who were returning from Wuhan. Transmission to health-care workers caring for patients was described on January 20, 2020.

Diagnosis of COVID-19

Coronaviruses have been reported to cause 5% to 10% of acute respiratory infections with more than 2% of the population as healthy carriers of HCoV [9] . The clinical diagnoses are similar to those of other human coronaviruses. The WHO gave a case definition as a patient with fever and at least a symptom of cough or shortness of breath, and with no other cause that explains the symptom and history of journey to or residence of any location reporting local transmission of COVID-19 during the 14 days prior to symptom onset, or a patient with acute respiratory illness and having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to the onset of symptoms, or a patient with severe acute respiratory infection [fever and at least one sign/ symptom of respiratory disease (e.g., cough, shortness of breath)] and requiring hospitalization and with no other aetiology that fully explains the clinical presentation. A probable case is a suspect case with an inconclusive testing for COVID-19 while a confirmed case is a person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms [10]

Laboratory diagnoses require the collection of respiratory specimens including oropharyngeal or nasopharyngeal aspirates or washes, oropharyngeal or nasopharyngeal swabs, sputum, bronchoalveolar lavage and tracheal aspirates [11] usually examined and tested with the cultural method of viral isolation in tissue culture or cell lines, the serological technique of antibody titre measurement, electron microscopy for examination of viral particles, conventional and real-time reverse transcriptase polymerase chain reaction.

Common symptoms of COVID-19 include

Cold- or flu-like symptoms usually set in from 2–14 days after a coronavirus infection and are typically mild. However, symptoms vary from person-to-person, and some forms of the virus can be fatal.

1. Fever
2. Breathlessness
3. Sore Throat
4. Cough
5. Exacerbated asthma
6. Watery Diarrhoea
7. Runny nose

Treatment of COVID-19

There is no cure, so treatments include self-care and over-the-counter (OTC) medication. People can take several steps, including:

1. Resting and avoiding overexertion and contamination
2. Using 70% alcohol based sanitizer
3. Avoiding touching mouth or nose with unclean hands
4. Washing the hands with soap for over 2 minutes or using alcohol based sanitizer
5. Maintaining social distance of 1-2 meter
6. Drinking enough water
7. Avoiding smoking and smoky areas
8. Taking acetaminophen, ibuprofen, or naproxen for pain and fever
9. Using a clean humidifier or mist vaporizer
10. A doctor can diagnose the virus by taking a sample of respiratory fluids, such as mucus from the nose, or blood.
11. Standard recommendations to prevent infection spread Its include covering mouth and nose when coughing and sneezing.
12. Avoid close contact with anyone showing symptoms of respiratory illness such as coughing and sneezing.
13. Avoiding going in crowded places and postpone unnecessary travel in public transport
14. Oxygen and Respiratory support wherever required
15. Low molecular weight heparin to stop prothrombin formation
16. Dexamethasone to combat cytokine storm

Various Platforms for COVID-19 Vaccine Development

There are various platforms being looked for the development of COVID-19 vaccines. These include RNA, DNA, nonreplicating viral vectors and inactivated vaccines.

Challenges Associated With Vaccine Production For Covid-19

The empirical-based vaccine companies have achieved important improvements to human health in the past decade [12]. Nevertheless, in terms of current immunology and molecular microbiology, vaccine research is still immature, leading to the requirement of a more extended period to produce a new vaccine [12]. Increased health issues, highly sophisticated production procedures, and related research criteria have to be considered scrupulously and meticulously when developing new vaccines. In order to address overlapping medical, technological, regulatory, and public safety requirements, a new collection of rules and guidelines would be required if a SARS-CoV-2 vaccine is developed on a fast-track basis for possible clinical use [12]. A correlation between immune responses and protective effects has been gradually questioned for nominee vaccines in recent years [13]. The preparation of structure-guided antigens is very popular. At the same time, advances in vaccine development are very far from being an established research field. After nearly four decades of studies, the cessation of HVTN702 announced recently informed us again of a significant discrepancy between research and the development of human immunodeficiency virus (HIV) vaccines [12]. Can the protective function of antibodies be the main immune responses to SARS-CoV-2 for specific vaccine programs? The obstacle-free animal models would be highly useful for choosing the candidates for clinical trials, despite an inherent difficulty in coordinating feasibility trials efficiently. Current vaccine development requires a spectrum of requisite skill sets. Over the last two decades, a broad range of innovations has arisen [14]. Considering complex vaccine specifications against quickly spreading new viral infections, vaccine technologies with prior human research experience would have considerable benefits, especially health concerns. Additionally, it is worthy of note that the inventor could rapidly push his/her vaccine development into a scale-up Good Manufacturing Practice (GMP) output with theoretically 10-million doses. Those with an existing facility and manufacturing expertise would be in a far more favorable position [12]. The challenge confronting regulatory agencies for the rapid development of SARS-CoV-2 vaccines is close to that of vaccine producers. High-level considerations would be paid to the health assessment of candidate vaccines against SARS-CoV-2. Immunopathogenesis of the virus plays a crucial role in the SARS-CoV-2 infection, ensuring that vaccination against such a virus would not induce the same forms of adverse immune reactions. This would affect the form of vaccines and the expected immunogens to be chosen. Would a competent manufacturing cycle be adequate for nominee vaccines to proceed, or will it be validated? Will the production and regulatory expertise acquired in other countries be used to evaluate an application for a vaccine in the current country? Is it necessary to consider cell banks or other intermediate goods through national borders? Can the political or economic concerns become obstacles for

worldwide efforts to resolve the immediate need for SARS-CoV-2 vaccines? Eventually, the preparation will now begin to allow the globe to have equitable access to effective SARS-CoV-2 vaccines, if the worldwide needs occur. The following concerns have to be resolved: vaccine ownership, unparalleled development financing, the pricing and supply network, and the coordinated delivery of such vaccines to achieve complete pandemic control. Vaccination strategies based on the pathogenesis of coronavirus in the host A better understanding of SARS-CoV-2 pathogenesis, protective immunity, and natural immunity duration will assist in the development of SARS-CoV-2 vaccines [15]. An overview of SARS-CoV-2 pathogenesis, including the infected target organs and the transmission route to certain organs, can help develop vaccines to interfere with viral propagation and avoid target organ infections [15]. Whether SARS-CoV-2 targets the lungs to induce pneumonia through viremia or after upper respiratory infections are a significant consideration. Live replicating vector vaccines and attenuated virus vaccines for influenza infections efficiently trigger local mucosal immunity, resulting in the shield of the upper and lower respiratory tracts and the limitation of nasal shedding [15]. Even though live attenuated influenza virus vaccines primarily induce local immunoglobulin A (IgA) antibodies but less systemic IgG antibodies, they protect influenza infections [16]. Conversely, if the lungs are not the primary sites of SARS-CoV-2 infections, intramuscular parenteral (IM) vaccinations that mostly induce serum virusneutralizing (VN) antibodies to prevent viremia and are also transuded into the lungs would prevent SARS-CoV-2 infections [15]. It might be similar to the mechanism underlying eliminating human respiratory infections by inactivated influenza vaccines via IM. Alternatively, a parenteral vaccine itself, including an S subunit or the receptor-binding domain (RBD) of the S subunit, could be useful as an annual booster vaccination in people who have convalesced from SARS-CoV-2 infections, again, like seasonal influenza [15]. This would improve memory B- and T-cell responses and tolerance, and prevent them from being re-infected with the viruses. For certain SARS-CoV-2 cases, diarrhea and fecal shedding have been recorded, and thus oronasal vaccinations could be more appropriate in this scenario [17]. Three populations should, therefore, be considered in SARS-CoV-2 vaccinations: vulnerable individuals with no immunity; convalescent individuals with varying degrees of immunity like subclinically affected people; and those with pre-existing immunity to SARS and MERS [15]. Consequently, the immunogenicity, protective ability, or negative impacts of nominee vaccines can differ across such categories. Evaluating pre-existing immunity levels would be critical to confirm the vaccines' effectiveness and protection in each community and the various age categories within each community, particularly in the elderly with the highest mortality rates

Major strategies for developing SARS-CoV-2 vaccines

Whole Virus Vaccines

Live-attenuated virus vaccines and inactivated virus vaccines are prepared based on conventional production procedures. According to company reports, Johnson & Johnson is one of the multinational pharmaceuticals that set out to develop SARS-CoV-2 vaccines [18]; Based on their Ebola vaccine design, they employed Janssen's AdVac® adenoviral vector and its PER.C6® cell line technologies for manufacturing a vaccine [18,19]. Additionally, researchers at Hong Kong University have produced a live influenza vaccine co-expressing SARS-CoV-2 proteins [20]. Codagenix has developed a technique for "codon deoptimization" to attenuate viruses and develop vaccination methods for SARS-CoV-2 [21]. A critical benefit of whole virus vaccines is their immunogenicity to activate toll-like receptors (TLRs), like TLR3, TLR7/8, and TLR9, which are expressed on innate immune cells. Nonetheless, it is indispensable for live viruses to be examined for safety profiles and protective effects. It is, especially, a prerequisite to determine whether or not antibody-dependent enhancement occurs after vaccination with live or killed SARS-CoV-2 virus vaccines [22].

Subunit Vaccines

In SARS-CoV vaccines and SARS-CoV-2 vaccines, the most palpable targets are S proteins in the development of subunit vaccines, which would lead to inhibition of the binding of the viruses to the host angiotensin-converting enzyme 2 (ACE2) [22]. The University of Queensland is now synthesizing viral surface proteins under support from the Coalition for Epidemic Preparedness Innovations (CEPI), which activates the host immune system more effectively. In addition, Novavax created and manufactured immunogenic, virus-like nanoparticles encompassing recombinant S-proteins [23]. However, Clover Biopharmaceuticals is developing a subunit vaccine composed of a trimerized SARS-CoV-2 S-proteins utilizing its proprietary Trimer-Tag® technology [24]. In contrast, full-length S-proteins might induce enhanced infectiveness and eosinophilic infiltration following the challenge by SARS-CoV-2. Consequently, a group headed by the Texas Children's Hospital Center for Vaccine Production at Baylor College of Medicine (such as the University of Texas Medical Branch and the New

York Blood Center) produced and validated a subunit vaccine consisting of the receptor-binding domain (RBD) of SARS-CoV S-protein [22,25,26]. The SARS-CoV RBD vaccine adsorbed on alum induces elevated protective immunity levels to the threat of homologous viruses. The RBD-based vaccine has an advantage in its potential to reduce host immunopotentiation [22]. SARS-CoV and SARS-CoV-2 RBDs have an amino acid identity of more than 80% and bind to the same ACE2 receptor, indicating that the strategy for developing vaccines for SARS-CoV-2 could be utilized for the development of SARS-CoV vaccines [27].

Nucleic Acid Vaccines

Several pharmaceutical companies have developed SARS-CoV-2 nucleic acid vaccines. For example, Inovio Pharmaceuticals designed a DNA vaccine, although other companies have been pursuing RNA vaccine strategies, including Moderna Therapeutics and Curevac [27]. In 1993, it was demonstrated that DNA vaccines induced protective immunity against influenza in mice models. However, these nonclinical studies have not yet been translated into clinical studies in humans for decades [27]. More recently, much improvement has been made in nucleic acid vaccines' formulations, increasing safety. Whereas nucleic acid vaccines are currently used for only animals, it is getting more likely that nucleic acid vaccines could be applied to humans.

Selection of antigens

Whole-cell antigen (WCA)

Includes all the virus elements, including proteins, lipids, polysaccharides, nucleic acids, and other structural and non-structural components. Killed and live-attenuated virus vaccines are typical WCA vaccines [28,29]. Considering WCA's diverse formulations, it is important to carefully monitor the quality assurance and the performance evaluation. To date, many institutions have effectively identified SARS-CoV-2 virus strains and have begun creating killed or live-attenuated WCA vaccines. It is essential to select strains with low pathogenicity or no pathogenicity, in which stringent screening of vaccine candidates is pivotal [30].

Spike protein (S protein)

S protein is probably the most promising source of antigens for developing SARS-CoV-2 vaccines. Firstly, it is a virus surface protein and is explicitly identified by the host immune system [31]. Secondly, it mediates the interaction between the host cells and viruses via ACE2 as an entry receptor, thereby inducing pathogenicity [31,32]. In addition, homologue proteins have also been used for the development of SARS-CoV and MERS-CoV vaccines, which are effective in nonclinical studies [16, 33-36]. The SARS-CoV-2 S protein monomer comprises 1273 amino acids, with a molecular weight of about 140 kDa. Self-association assembles the S protein spontaneously into a homo-trimer, similar to other first-generation membrane fusion proteins (viral fusion protein Class I). The S protein is comprised of two subunits (S1 and S2). The subunit S1 is further divided into two domains, the N-terminal domain (NTD) and the C-terminal domain (CTD), in which the RBD is encoded within CTD. The S2 subunit comprises the essential elements necessary for membrane fusion, including an internal membrane fusion peptide (FP), two 7-peptide repeats (HR), a membrane-proximal external region (MPER), and a transmembrane domain (TM) [37]. The structure of the SARS-CoV-2 S trimer in pre-fusion confirmation and that of the RBD domain bound to ACE2 have recently been solved, offering useful information on S protein-based development vaccines [31, 32]. To date, the full-length S-protein, the RBD domain, the subunit S1, NTD, and FP have been developed as possible vaccines.

Nucleocapsid protein (N protein)

N protein is highly conserved among CoVs, with a molecular weight of around 50 kDa. This protein is involved in nucleocapsid production, budding virus signal transduction, RNA replication, and mRNA transcription [62,38]. N protein has been documented to be strongly antigenic, inducing antibodies to this antigen in 89% of patients who suffered from SARS [39]. In vaccinated C57BL/6 mice, DNA vaccine encoding SARS-CoV N protein induced a high level of N protein-specific humoral and cellular immune responses and reduced viruses' titer markedly [40]. In addition, N protein vaccines of avian contagious bronchitis virus induced the activation of cytotoxic T lymphocytes (CTLs) and resulted in a decrease in clinical signs and lung clearing, indicating that N protein-mediated cellular responses are important in the defense against virus infections [41,42]. On the other hand, other studies revealed that the N protein immunization did not lead substantially to the production of neutralizing antibodies and did not offer protection against infections in hamsters [43]. These findings indicate that the efficacy of N protein-based SARS-CoV-2 vaccines is not guaranteed. However, owing to its strong immunogenicity, N protein itself can be used as a marker in diagnostic assays. **Membrane protein (M protein)**

M protein is a transmembrane glycoprotein with a molecular weight of approximately 25 kDa and is involved in viral replication. This protein exists abundantly on the surface of SARS-CoV [44].

Immunization of the full-length M protein-induced neutralizing antibodies in patients with SARS [45]. Immunogenic and structural analyses demonstrated that a T-cell epitope cluster capable of triggering a robust cellular immune response exists in the M protein [46]. M protein is also highly conserved in many virus species to be used as a target antigen for SARS-CoV-2 vaccine development [44].

Envelope protein (E protein)

E protein consists of 76–109 amino acids and has ion-conduction properties. It has been shown that E protein could be an inducer of inflammasomes, leading to the production of IL-1β and, ultimately, strong inflammatory responses. It is suspected that E protein is responsible for cytokine storm in patients with SARS-CoV [47]. It might be, therefore, difficult to control immune responses after immunization with E protein-based vaccines. In this context, E protein is not ideal as an immunogen in vaccines' development, in contrast to S, N, and M proteins.

Prospects

Little is understood about SARS-CoV-2 etiology, epidemiology, functional origin, pathogenic process, pathological immune responses, and so on. In addition, the host cellular and humoral immune responses to SARS-CoV-2, which are important for the development of vaccines, remain unknown. These issues are to be tackled in the immediate future through fundamental studies for vaccines' effective development. Many countries and R&D institutions have declared their plans for SARS-CoV-2 vaccine development. The preparation of vaccine candidates per se is not a formidable task, because the procedure for producing vaccine candidates for SARS-CoV-2 is essentially the same as that for SARS-CoV. On the contrary, it is extremely difficult to examine many issues, including safety, protective effects, and a consistent vaccine administration level. In general, the safety, immunogenicity, and effectiveness of the vaccine will be tested across three phases of clinical trials. Usually, it requires more than 10 years to launch new vaccines, and more than 90% of the candidates fail to be filed by the regulatory authority. Over the last three decades, a record of about 3,000 vaccine formulations have been applied to the review of the U.S. Food and Drug Administration (USFDA), and less than 20 vaccines have been authorized for sale. For public safety, we have to produce vaccines in compliance with science legislation for development and manufacturing, and stringent laws governing vaccines' selling. There were 149 mutation sites in 103 sequenced SARS-CoV-2 genomes, and the virus has developed into two different variants, called L and S, in the early stage of COVID-19 in Wuhan. The research also revealed that the two variants displayed significant regional spread and dissemination variations, leading to vaccine design challenges [48]. Clinical trials evaluating different medicines are currently underway, hopefully leading to discovering a new medication to combat SARS-CoV-2-related diseases. In addition, the accelerated production and delivery of vaccines are an effective means for terminating the global SARS-CoV-2 pandemic. While vaccines' development is slower than the spread of the pandemic, it would still be essential and required. Firstly, the pandemic continues to expand worldwide, and more and more reported cases are being found, and the inflection point has not been achieved. Secondly, infections with SARS-CoV-2 will become a flu-like seasonal illness, and long coexist with humans [49]. It must be remembered that SARS-CoV-2 has been reported in no more than 6 months, and subsequent studies on pathogenic characteristics and mechanisms of SARS-CoV-2 have only started. Therefore, since evidence and knowledge so far gathered are quite limited and inconclusive, they must be compiled continuously and recorded.

Covid-19 Vaccination in India

On 16 January 2021, India started its national vaccination programme against the SARS-CoV-2 which is responsible for the COVID-19 pandemic. The drive prioritises healthcare and frontline workers, and then those over the age of 50 or suffering from certain medical conditions. According to health officials, India has administered 54,16,849 vaccine doses across the country as of 05 February 2021[50].

Development

Pune-based Serum Institute of India announced that it would apply for clinical trials of certain strains from Drug Controller General of India (DCGI) in April 2020. As per company president Adar Poonawalla, a vaccine for COVID-19 will be delivered within a year. However, it may not be effective on 20 to 30% people.[51] Two other companies are also trying to develop a vaccine: Zydus Cadila, which is replicating viral vector and developing a DNA plasmid vaccine,[52] and Hyderabad-based Bharat Biotech, in collaboration with US based FluGen, which is expecting the first clinical trials of a nasal vaccine by late 2020.[53] As of late February, the Serum Institute of India had begun animal trials of vaccine candidates,[54] followed by Zydus Cadila in March.[55] ICMR partnered with Bharat Biotech in May to develop COVID vaccine completely in India.[56] Till May, there were over 30

candidates of COVID-19 vaccine in development in India, many of which were already in pre-clinical tests.[57] Per reports emerged in July, ICMR was preparing to launch BBV152 COVID vaccine or Covaxin, India's first COVID-19 vaccine on 15 August following its ongoing human trials in July.[58] Although, later deadline was cited as only meant to cut "red tape" and expected timeline of any Indian vaccine not to be before 2021.[59] COVAXIN has been reported to have positive results on animals in building immunity against COVID-19 in pre-clinical trials.[60] In mid-July, Zydus Cadila too had followed with human trials of its vaccine named ZyCoV-D.[12] In early August, SII's got approval from DCGI for trial phases II & III.[61] SII has also joined GAVI in a partnership with Bill & Melinda Gates Foundation to produce 100 million doses of vaccine for developing countries.[62] In September, India's science minister Dr. Harsh Vardhan announced that the first vaccine for use will be available by first quarter of 2021.[63] 30 million health workers directly dealing with COVID patients, especially doctors and other medical personnel are supposed to be first to receive the vaccine.[64,65]

COVID-19 Vaccines with Approval for Emergency or Conditional Usage

Covishield

On 1 January 2021, the Drug Controller General of India, approved the emergency or conditional use of AstraZeneca's COVID-19 vaccine AZD1222 (marketed as Covishield).[66] Covishield is developed by the University of Oxford and its spin-out company, Vaccitech.[67] It's a viral vector vaccine based on replication-deficient Adenovirus that causes cold in Chimpanzees. It can be stored, transported and handled at normal refrigerated conditions (two-eight degrees Celsius/ 36-46 degrees Fahrenheit). It has a shelf-life of at least six months.

Covaxin

On 2 January 2021, BBV152 (marketed as Covaxin), first indigenous vaccine, developed by Bharat Biotech in association with the Indian Council of Medical Research and National Institute of Virology received approval from the Drug Controller General of India for its emergency or conditional usage.[68] However, this approval was met with some concern as the vaccine had not then completed phase-3 trials.[69].

Table 1:

Vaccine	Progress	Doses ordered	Approval	Deployment
Oxford-AstraZeneca	Phase III clinical trials	500 million[70]	01 January 2021[71]	16 January 2021[29]
Covaxin	*Phase III clinical trials in progress	10 million	01 January 2021(restricted)[72]	16 January 2021[29]
Novavax	Phase III clinical trials	1 billion[70]	Pending	Pending
Pfizer–BioNTech	Phase III clinical trials	Pending	Pending [a]	Pending
Moderna	Phase III clinical trials	Pending	Pending	Pending
Sputnik V	Phase III clinical trials	100 million[73]	Pending	Pending

Conclusion

Conclusion Experience in vaccine development for CoV strains such as SARS-CoV and MERS-CoV guides the development of SARS-CoV-2 vaccines. ADE and other harmful effects commonly identified with SARS and MERS vaccine candidates should be carefully examined for the safety validation of SARS-CoV-2 vaccine candidates. Although such characteristics were only seen in certain animal models and vaccine regimens, SARS-CoV-2 vaccine candidates' potential remains to be regarded. Furthermore, as previously recognized in the SARS-CoV and MERS-CoV vaccine development, the

risk of the short-term immunogenicity resulting from neutralizing antibodies following natural infection should be cautiously considered in the development of SARS-CoV-2 vaccines. It is a good sign that India has started its national vaccination programme against the SARS-CoV-2 which is responsible for the COVID-19 pandemic. The drive prioritises healthcare and frontline workers, and then those over the age of 50 or suffering from certain medical conditions.

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