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COVID 19: RECENT VACCINE AND VACCINE UNDER TRAIL

AMISHA PATEL[1#*], B. RAY[2†], ASHMAUL HUSSAIN[1#] AND P. K. BEHERA[3‡]

[1]GCP,SBP, Odisha, India.
[2]CPS, Puri(Under BPUT) Odisha, India.
[3]School of Chemistry, SambalpurUniversity, Odisha, India.

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Review Article

ABSTRACT

Since 2002, there has been a record ofCoronavirus disease outbreak caused by SARS-CoV,MERS-CoV, as well as the novel SARS-CoV-2, the causalagent of the Coronavirus Disease 2019 that broke outin Wuhan, China in December the same year and hassince become widespread across several countries andcontinents leading to thousands of deaths More than 180 vaccine candidates, based on several different platforms(Fig. vaccine platform used for SARS-CoV-2 vaccine developement), are currently in development against SARS-CoV-2(57) (Fig. overview of the SARS-CoV-2 vaccine development landscape). TheWorld Health Organization (WHO) maintains a working document(57)that includes most of the vaccines in development and is available at https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Clinical trials are evaluating COVID-19 vaccines in tens of thousands of study participants to Generate the scientific data and other information needed to determine safety and effectiveness These clinical trials are being conducted by manufacturers according to rigorous standards.

Keywords: MERS-CoV; SARS-CoV-2; human par influenza; influenza virus.

1. INTRODUCTION

Since 2002, there has been a record ofCoronavirus disease outbreak caused by SARS-CoV,MERS-CoV, as well as the novel SARS-CoV-2, the causalagent of the Coronavirus Disease 2019 that broke outin Wuhan, China in December the same year and hassince become widespread across several countries andcontinents leading to thousands of deaths [1]. As atAugust 9, 2020, COVID-19 has spread to 213 countriesand territories, with 19, 847,800 cases recordedglobally and 730, 372 deaths. The global race for thedevelopment of vaccine for the novel Coronavirusdisease became intensive upon the release of thegenetic sequence of SARS-CoV-2 on the 11th of January2020. Early efforts have been intensified into theclinical course of COVID-19, counting severe cases andtreating those who are already infected [2].

[#] *B.Pharm.*
[†] *Associate Prof.*
[‡] *Professor.*
**Corresponding author: Email: amishapatel2829@gmail.com;*

Consultations, the expectation is that effective vaccinefor the Coronavirus disease-2019 (COVID-19) may not come into the market this year. However, certainantiviral drugs are presently under investigation for possible cure of COVID-19. As the cases of infectioncontinues to rise and mortality rate blossom, therecurring question had been; why has there been novaccine developed yet for COVID-19? Researchersfarand wide currently engaged in research for vaccine development for COVID-19 are facing big challenges inthe scientific, economic and logistical perspectives. Thefact remains that the entire human race is still currentlynaive to COVID-19, hence, bringing about repeatedoccurrences of unacceptably high mortality, significant changes to our way of life, and intense economicdisruption.

History of development of vaccine : Coronaviruses belong to the Coronaviridae family in the Nidovirales order. Corona represents crown-like spikes on the outer surface of the virus; thus, it was named coronavirus. Coronaviruses are minute in size (65-125 nm in diameter) and contain a single-stranded RNA as nucleic material, with a size ranging from 26 to 32 kilobases (kb) in length. The subgroups of the coronavirus family are alpha (α), beta (β), gamma (γ), and delta (δ) [3]. The SARS-CoV-2 belongs to the same coronavirus group (Betacoronavirus) as SARS and MERS viruses that caused two of the more severe epidemics in recent years. As with SARS and MERS, this new coronavirus, 2019-nCoV, is believed to be of zoonotic origin, but may also be transmitted through the respiratory tract, by direct contact, and possibly via patients excreta which may contain the living virus [4].

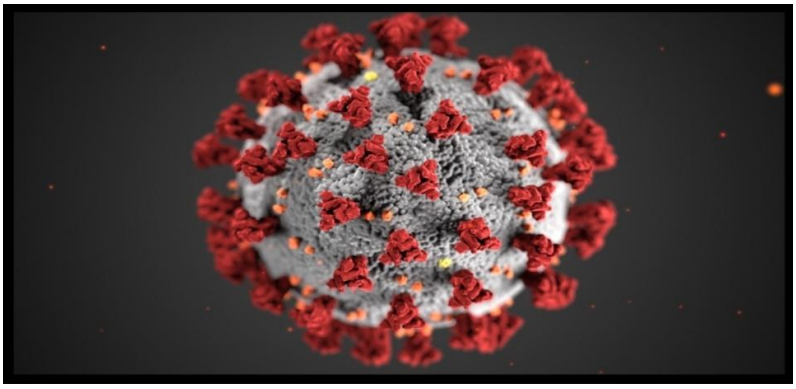

Fig. 1. A graphical representation of the ultrastructural morphology of coronavirus (SARS-CoV-2)

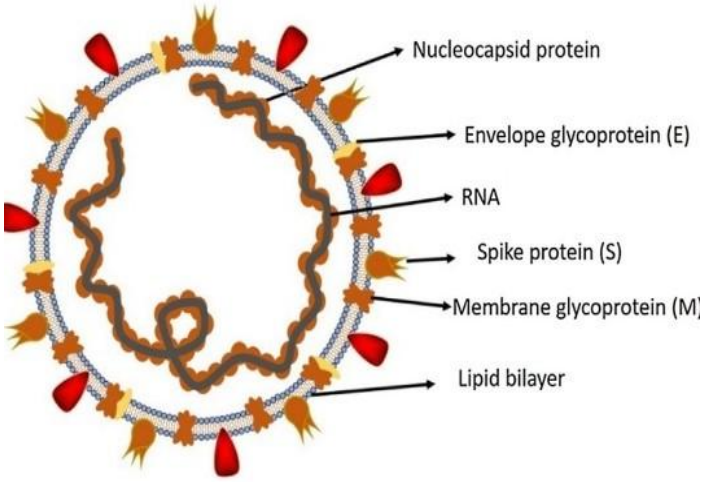

Fig.2. Structure of respiratory syndrome causing human corona viruses

Primary reservoirs and host of coronaviruses: The source of origination and transmission are important to be determined in order to develop preventive strategies to contain the infection. In the case of SARS-CoV, the researchers initially focused on raccon dogs and palm civets as a key reservoir of infection. However, only the samples isolated from the civets at the foodmarket showed positive results for viral RNA detection, suggesting that the civet palm might be secondary hosts [5]. In 2001 the samples were isolated from the healthy persons of Hongkong and the molecular assessment showed 2.5% frequency rate of antibodies against SARS-coronavirus. These indications suggested thatSARS-coronavirus may be circulating in humans before causing the outbreak in 2003 [6]. Later on, Rhinolophus bats were also found to have anti-SARS-CoV antibodies suggesting the bats as a source of viral replication [7]. The Middle East respiratory syndrome(MERS) coronavirus first emerged in 2012 in Saudi Arabia [8]. MERS-coronavirus also pertains to beta-coronavirus and having camels as a zoonotic source or primary host [9]. In a recent study,MERS-coronavirus was also detected in Pipistrellus and Perimyotisbats [8], proffering that bats are the key host and transmitting medium of the virus [10,11]. Initially, a group of researchers suggested snakes be the possible host, however, after genomic similarityfindings of novel coronavirus with SARS-like bat viruses supported the statement that not snakes but only bats could be the key reservoirs (Table 1) [12,13]. Further analysis of homologous recombination revealed that receptor binding spike glycoprotein of novel coronavirus is developed from a SARS-CoV (CoVZXC21. or CoVZC45) and a yet unknown Beta-CoV [14] .

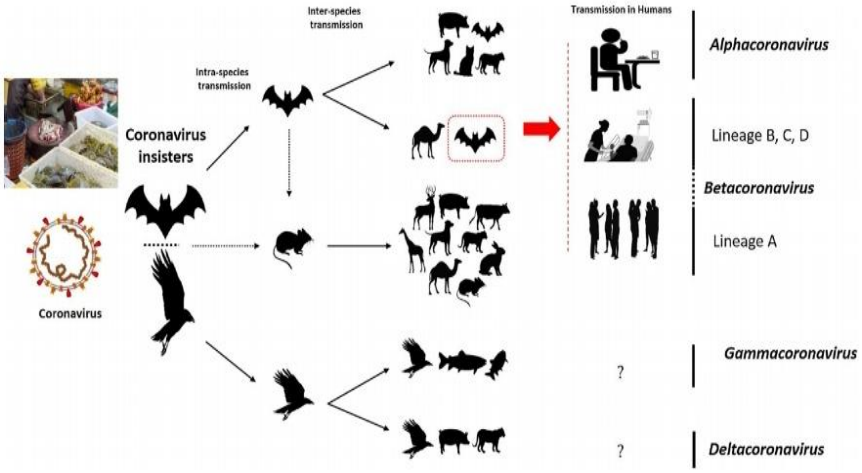

Fig. 3. The key reservoirs and mode of transmission of coronaviruses (suspected reservoirs of SARS-CoV-2 are red encircled); only alpha and beta corona viruses have ability to infect humans ,the consumption of infected animal as a source of food is the major cause of animal to human transmission of the virus and due to close contact with an infected person, the virus is further transmitted to healthy persons .Dotted black arrow shows the possibility of viral transfer from bat whereas the solid black arrow represent the confirmed transfer

Table 1. Comparative analysis of biological featured of SAARS-CoV and SARS- CoV-2

Features	SARS-CoV	SARS-CoV-2
Emergence date	November 2002	December 2019
Area of emergence	Guangdong, China	Wuhan, China
Date of fully controlled	July 2003	Not controlled yet
Key hosts	Bat, palm civets and Raccon dogs	Bat
Number of countries infected	26	109
Entry receptor in humans	ACE2 receptor	ACE2 receptor
Sign and symptoms	fever, malaise, myalgia, headache, diarrhoea, shivering, cough and shortness of breath	Cough, fever and shortness of breath
Disease caused	SARS, ARDS	SARS, COVID-19
Total infected patients	8098	123882
Total recovered patients	7322	67051
Total died patients	776 (9.6% mortality rate)	4473 (3.61% mortality rate)

2. WHY DO WE NEED VACCINES FOR COVID-19?

The whole world is concerned about the vaccine For COVID-19 due to fatality of this condition. On-time Vaccination is highly imperative to contain the SARS-CoV-2 pandemic which has been identified to possess a high Level of infectivity and high rate of human to human Transmission [15,16]. Traditional public health strategies are Currently being employed towards mitigating the virus Spread alongside the use of extensive lockdowns in Communities and observance of physical distancing. Continuous enforcement of the preventive strategies has Been challenging [17-21]. Moreover, for how long shall the Communities remain on lockdown? Experts have stated That the general public will have to live With the pandemic's social and economic disruption for Quite a while. Obviously successful COVID-19 vaccine Development is needed as soon as possible. However, Vaccine trials are currently on course, yet development Of vaccine can take many months to years [22]. A Vaccine is targeted at boosting natural immune response To an invading virus by priming it to recognize antigens And distinct molecules located on the surface of Pathogens. Basically, the response of the immune System is based on the availability of these antigens From the production of special immune cells to directly Attack the pathogen, or by the production of proteins Named antibodies. Antibodies become attached to an Antigen, then become attracted by the immune cells that Engulf and destroy the pathogen. Vaccine possesses the Ability to usurp herd immunity in communities and Territories in a bid to reduce disease incidence, prevent Transmission, and lower economic and social burden of the disease. Increased immunization coverage is a potent approach in fighting the pandemic effectively, block secondary infection waves, and mitigate seasonal endemic infection outbursts [23-27]. Along the way, there could be the eradication of the disease as seen in several past diseases (poliomyelitis, smallpox etc.) with higher potential than COVID-19 to result in pandemic [28,29].Recent efforts by researchers is seen in the continuous monitoring of the genetic sequence of SARS-CoV-2 due to possible rapid mutations so as to acquire crucial data required to assist in providing adequate responses for this current outbreak and that to come in the future. This is very important for the vaccine development studies. Viruses originating from animal species and getting transferred to humans are specifically problematic. They have the capacity to undergo rapid mutations due to their animal origin, for which no preexisting immunity is essentially available in the human population [30-35]. Interestingly, mutations do not practically affect the functioning of the virus regardless of the fact that mutations within the genome of the virus take place during outbreaks. Such mutations are also unlikely to present any significant resistance to a future Vaccine [36].

Application (BLA) is filed, reviewed by regulatory agencies and finally the exploratory work on vaccine design and evaluation in animal models, which can take years. This is then followed by a stage in which more formal preclinical experiments are conducted, a process for vaccine production is designed and formal toxicology studies are performed; this stage can also last for several years [37-42]. Next, an application for an investigational new drug is filed and phase I clinical trials (testing in fewer than 100 individuals; approximately 2 years) are performed to generate an initial safety profile of the vaccine candidate and to obtain preliminary immunogenicity data. If the results are promising and funding is available, a vaccine candidate is then moved into phase II clinical trials (testing in a few hundred individuals, also lasting about 2 years) to further investigate immunogenicity and to determine an appropriate dose and optimal vaccine regimens. If the results of phase II trials are encouraging, the decision might be made to move forward with very costly phase III clinical trials (in thousands of individuals; approximately 2 years) in which efficacy and safety are evaluated [43-47]. If the outcome of phase III trials meets the pre-defined end points, a biologics license application is filed with regulatory agencies (for example, the United States Food and Drug Administration (FDA) or the European Medicines Agency). The licensing process can take another 1–2 years, especially if additional data are requested. Importantly, because it is very expensive, the overall process of vaccine development is slowed by economic risk assessment at every step. Vaccine development pro-gresses through these stages only if the developer is convinced that the data are promising, that the risk of failure is relatively low and that there is (still) a market for the vaccine [48]. The SARS-CoV-2 pandemic has required rapid action and the development of vaccines in an unprecedented timeframe. Data from the preclinical development of vaccine candidates for SARS-CoV vaccine is licensed. After that point, large-scale production begins. Vaccine development for SARS-CoV-2 is following an accelerated timeline. Because of knowledge gained from the initial development of vaccines for SARS-CoV and MERS-CoV, the discovery phase was omitted. Existing processes were adopted, and phase I/II trials were started. Phase III trials were initiated after the interim analysis of phase I/II results, with several clinical trial stages running in parallel. In the meantime, vaccine producers have

started the large-scale production of several vaccine candidates, at risk. The exact pathway by which these vaccine candidates will be licensed—for example, through an initial emergency use authorization—is not yet clear [49].

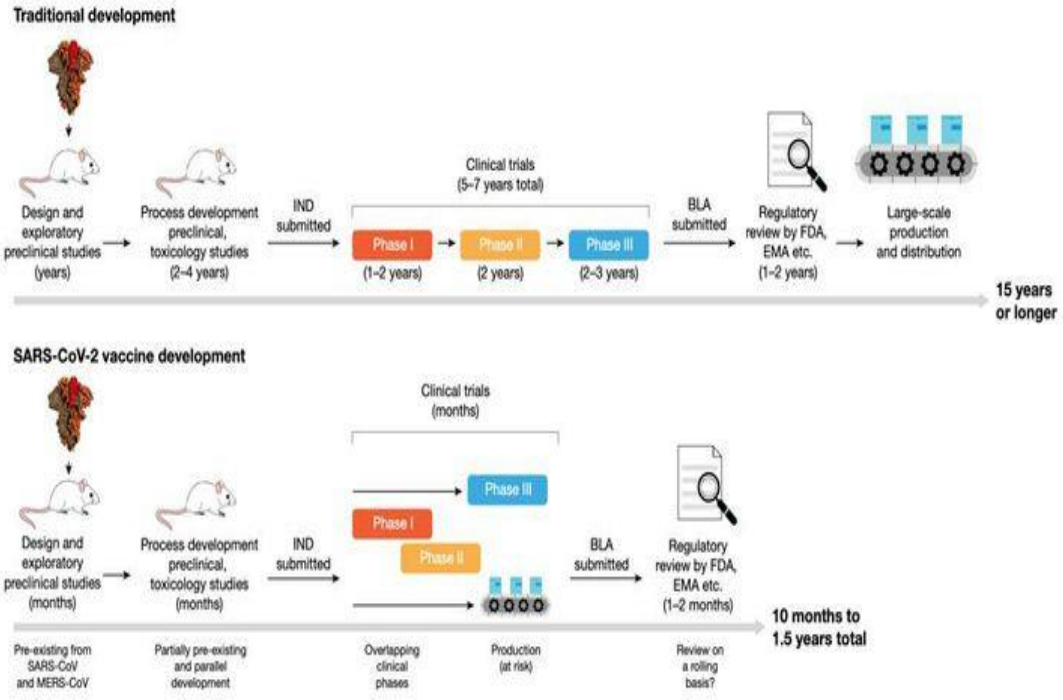

Fig. 4. Traditional and accelerated vaccine-development pipelines.Traditional vaccine development can take 15 years or more, starting with a Lengthy discovery phase in which vaccines are designed and exploratory Preclinical experiments are conducted. This is usually followed by a phase in Which more formal preclinical experiments and toxicology studies are Performed and in which production processes are developed. During this Process an investigational new drug (IND) application is filed and the vaccine Candidate then enters phase I, II and III trials. If, when phase III trials are Completed, the predetermined end points have been met, a biologics licence

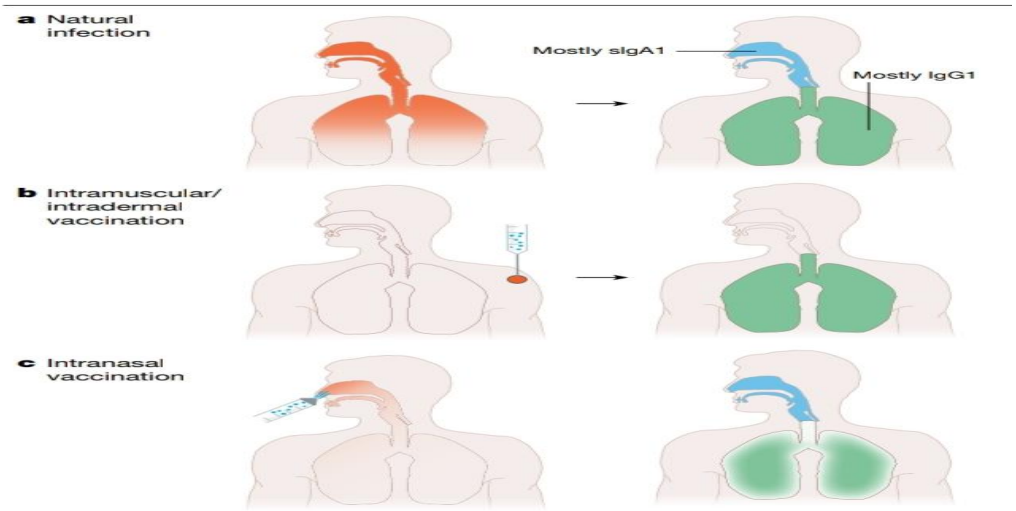

Fig. 5.

Fig. Mucosal and systemic immune responses to natural infection with Respiratory viruses and to vaccination. The lower human respiratory tract Is thought to be mostly protected by IgG (IgG1 is most prevalent), the main type Of antibody in serum, which is transported into the lung. The upper respiratory Tract is thought to be mostly protected by secretory IgA1 (sIgA1). A, Natural Infection with respiratory viruses induces both a systemic immune response, Dominated by IgG1, as well as a mucosal immune response in the upper Respiratory tract that is dominated by sIgA1. This process can lead to sterilizing Immunity for many respiratory viruses. B, Intramuscular or intradermal Vaccination leads in many cases to a strong induction of serum IgG but not to an Induction of mucosal IgA. Although some IgG can also be found on the mucosal Surfaces of the upper respiratory tract, the lack of sIgA often leaves an Individual vulnerable to infection of the upper respiratory tract. C, Intranasal Vaccination can efficiently induce mucosal antibody responses, thereby Potentially providing sterilizing immunity in the upper respiratory tract. However, systemic immune responses are often lower after this type of Vaccination [50-54]. Currently, all SARS-CoV-2 vaccine candidates in clinical Development are administered intramuscularly, and very few of the more than 180 vaccine candidates in development are designed to induce mucosal Immunity. Although mucosal immunity might not be required to protect from Severe or even symptomatic disease, it could be required to achieve optimal Protection from infection and onward transmission of SARS CoV-2 .

3. TYPES OF VACCINE IN DEVELOPMENT

More than 180 vaccine candidates, based on several different platforms (Fig. vaccine platform used for SARS-CoV-2 vaccine developement), are currently in development against SARS-CoV-2(57) (Fig. overview of the SARS-CoV-2 vaccine development landscape). TheWorld Health Organization (WHO) maintains a working document [55] that includes most of the vaccines in development and is available at https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. The platforms can be divided into 'traditional'approaches (inactivated or live-virus vaccines), platforms that have recently resulted in licensed vaccines (recombinant protein vaccines and vectored vaccines), and platforms that have yet to result in a licensed vaccine (RNA and DNA vaccines).

4. INACTIVATED VACCINES

Inactivated vaccines (under the Fig. c) are produced by growing SARS-CoV-2 in cell culture, usually on Vero cells, followed by chemical inactivation of the virus [56-57]. They can be produced relatively easily; however, their yield could be limited by the productivity of the virus in cell culture and the requirement for production facilities at biosafety level 3. Examples ofinactivated vaccine candidates include CoronaVac (initially known asPiCoVacc), which is under development by Sinovac Biotech in China [57-58] and is further discussed below, as well as several other candidates that are being developed in China, by Bharat Biotech in India and by the Research Institute for Biological Safety Problems in Kazakhstan. These vaccines are usually administered intramuscularly and can contain alum (aluminium hydroxide) or other adjuvants. Because the whole virus is presented to the immune system, immune responses are likely to target not only the spike protein of SARS-CoV-2 but also the matrix, envelope and nucleoprotein. Several inactivated vaccine candidates have entered clinical trials, with three candidates from China in phaseIII trials, and one from India, one from Kazakhstan and two from China in phase I or II clinical trials [55].

5. LIVE ATTENUATED VACCINES

Live attenuated vaccines (under the Fig. d) are produced by generating a genetically weakened version of the virus that replicates to a limited extent,causing no disease but inducing immune responses that are similar to that induced by natural infection (Fig. Mucosal and systemic immune response to natural infection with respiratory viruses and to vaccination). Attenuation can be achieved by adapting the virus to unfavourableconditions (for example, growth at lower temperature, growth in non-human cells) or by rational modification of the virus (for example, by codon de-optimization or bydeleting genes that are responsible for counteracting innate immunerecognition [59-60]. An important advantage of these vaccines is that they can be given intranasally, after which they induce mucosal immune responses that can protect the upper respiratory tract (Fig)—the major entry portal of the virus. In addition, because the virus is replicating in the vaccinated individual, the immune response is likely to target both structural and non-structural viral proteins by way of antibodies and cellular immune responses. However, disadvantages to these vaccines include safety concerns and the need to modify the virus, which is time-consuming if carried out by traditional methods and technically challenging when reverse genetics is used. Only three live attenuated vaccines are currently in preclinical development (Fig.), all of which attenuated by codon de-optimization and one that is being developed in collaboration between Codagenix and the Serum Institute of India [55].

6. RECOMBINANT PROTEIN VACCINES

Recombinant protein vaccines can be divided into recombinant spike-protein-based vaccines (under the Fig. e), recombinant RBD-based vaccines(under the Fig. f) and virus-like particle (VLP)-based vaccines (under the Fig. g).These recombinant proteins can be expressed in different expression systems including insect cells, mammalian cells, yeast and plants [61,55,62] ;it is likely that RBD-based vaccines could also be expressed in Escherichia coli [63]. Yields, and the type and extent of post-translational modifications, vary depending on the expression system. For recombinantspikeprotein-based vaccines in particular, modifications such as deletion of the polybasic cleavage site [64-66], inclusion of two (or more) stabilizing mutations [67,64,68,69] and inclusion of trimerization domains—as well as the mode of purification (soluble protein versus membrane extraction)—might influence the elicited immune response. The advantage of these vaccines is that they can be produced without handling live virus. In addition, some recombinant protein vaccines—such as the FluBlokvaccine for influenza—have been licensed, and there is considerable experience in producing them. However, such vaccines also have disadvantages. The spike protein is relatively hard to express, and this is likely to have an effect on production yields and on how many doses can be produced [61]. The RBD is easier to express; however, it is a relatively small protein when expressed alone and, although potent neutralizing antibodies bind to the RBD, it lacks other neutralizing epitopes that are present on the full-length spike. This might render RBD-based vaccines more prone to impact from antigenic drift than vaccines that include the full-length spike protein. Many recombinant protein vaccine candidates against SARS-CoV-2 are currently in preclinical development, and several spike-protein-based and RBD-based vaccines have entered clinical trials [55]. Of those, data from NHPs and from phase I trials have been reported for Novavax42 , which are described in more detail below. VLP-based vaccine candidates, including one produced by Medicago, have also entered clinical trials [55]. Similar to inactivatedvaccines, these candidates are typically injected and are not expectedto result in robust mucosal immunity.

7. REPLICATION-INCOMPETENT VECTORS

Replication-incompetent vectors (under the Fig.h) represent a large group of vaccines in development. Such vaccines are typically based on another virus that has been engineered to express the spike protein and has been disabled from replication in vivo by the deletion of parts of its genome. The majority of these approaches are based on adenovirus (AdV) vectors, although modified vaccinia Ankara (MVA), human parainfluenza virus vectors, influenza virus, adeno-associated virus and Sendai virus are used as well [55,65,70-74]. The majority of these vectors are delivered intramuscularly, enter the cells of the vaccinated individual and then express the spike protein, to which the host immune system responds. These approaches have many advantages. It is notnecessary to handle live SARS-CoV-2 during production, there is considerable experience with producing larger quantities of some of these vectors (an Ad26–MVA-based prime–boost vaccine against the Ebola virus was recently licensed in the European Union), and the vectors show good stimulation of both B cell and T cell responses. A disadvantage is that some of these vectors are affected and are partially neutralized by pre-existing vector immunity [71] This is circumvented by using vector types that are either rare in humans [65] or are derived fromanimal viruses [72] or by using viruses that do not induce much immunityby themselves (for example, adeno-associated viruses). In addition, vector immunity can be problematic when prime–boost regimens are used, although this can be circumvented by priming with one vector and boosting with a different vector. Several replication-incompetent vector vaccine candidates against SARS-CoV-2 have progressed far in clinical development: results from NHP trials and/or clinical trials in humans have been reported for ChAdOx1 nCoV-19 (based on a chimpanzee AdV) [72] by Janssen (using an AdV26-based vector) [71] and by CanSino(AdV5) [70-71] another from Rei Thera (gorilla AdV) is in phase I trials [55].

Replication-competent vectors: Replication-competent vectors (under the Fig.i) are typically derived from attenuated or vaccine strains of viruses that have been engineered to express a transgene, in this case the spike protein. In some cases, animal viruses that do not replicate efficiently and cause no disease in humans are used as well. This approach can result in a more robust induction of immunity, because the vector is propagating to some extent in the vaccinated individual and often also triggers a strong innate immune response. Some of these vectors can also be administered through mucosal surfaces, which might trigger mucosal immune responses . Currently, only two replication-competent vectors are in phaseI clinical trials: an engineered measles vaccine strain developed by InstitutePasteur and Themis (now acquired by Merck), and a vector based on the influenza virus that is under development by Beijing Wantai Biological Pharmacy [55]. However, several others—including vectors

based on vesicular stomatitis virus (VSV) [75] horsepox and Newcastle disease virus (NDV) [76-77]are currently in development [55] Vectors based.

Fig. Vaccine platforms used for SARS-COV-2 vaccine development .a, A schematic of the structural proteins of the SARS-CoV-2 virion, including the lipid membrane, the genomic RNA covered by the nucleoprotein on the inside, the envelope and matrix proteins within the membrane, and the spike protein on the surface of the virus. b, The structure of the spike protein; one monomer is highlighted in dark brown and the RBD is shown in red. c–l, Current SARS-CoV-2 vaccine candidates include inactivated virus vaccines (c), live attenuated vaccines (d), recombinant protein vaccines based on the spike protein (e), the RBD (f) or on virus-like particles (g), replication-incompetent vector vaccines (h), replication-competent vector vaccines (i), inactivated virus vector vaccines that display the spike protein on their surface (j), DNA vaccines (k) and RNA vaccines (l).on NDV are of interest because this virus grows to high titres in eggs, and the vectors could be produced using the global influenza virus vaccine pipeline. In contrast to measles and the VSV vectors, they are likely to be safe enough to administer intranasally, which could result in mucosal immunity .

Inactivated virus vectors: Some SARS-CoV-2 vaccine candidates that are currently under developmentrely on viral vectors that display the spike protein on their surface but are then inactivated before use [55] (above the Fig. j). The advantage of this approach is that the inactivation process renders the vectorssafer because they cannot replicate, even in an immunocompromisedhost. Using standard viral vectors, the amount of antigen that is presented to the immune system cannot easily be controlled; however, in inactivated vectored vaccines it can be readily standardized—as is the case for inactivated or recombinant protein vaccines. Examples of inactivated virus vectors include NDV-based vaccines that display the spike protein on their surface—which can be produced in a similar manner to influenza virus vaccines [78] as well as rabies vectors [55]. These technologies are currently in the preclinical stage.

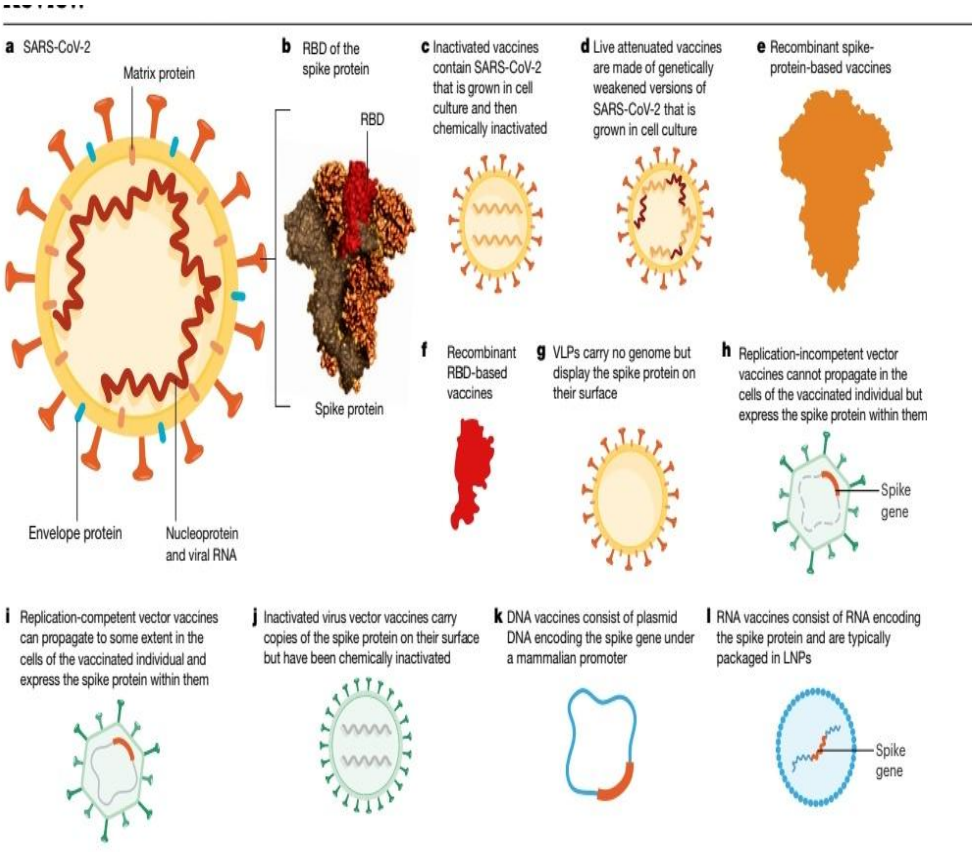

Fig. 6.

DNA vaccines:: DNA vaccines (above the Fig. k) are based on plasmid DNA that can be produced at large scale in bacteria. Typically, these plasmids contain mammalian expression promoters and the gene that encodes the spike protein, which is expressed in the vaccinated individual upon delivery. The great advantage of these technologies is the possibility of large-scale production in E. coli, as well as the high stability of plasmid DNA. However, DNAvaccines often show low immunogenicity, and have to be administered via delivery devices to make them efficient. This requirement for delivery devices, such as electroporators, limits their use. Four different DNA vaccine candidates against SARS-CoV-2 are currently in phase I/II clinical trials [55].

RNA vaccines: Finally, RNA vaccines (above the Fig. l) are a relatively recent development.Similar to DNA vaccines, the genetic information for the antigen isdelivered instead of the antigen itself, and the antigen is then expressed in the cells of the vaccinated individual. Either mRNA (with modifications) or a self-replicating RNA can be used. Higher doses are required for mRNA than for self-replicating RNA, which amplifies itself [79] and the RNA is usually delivered via lipid nanoparticles (LNPs). RNA vaccines have shown great promise in recent years and many of them are in development, for example for Zika virus or cytomegalovirus. As potential vaccines against SARS-CoV-2, promising preclinical results have been published for a number of RNA vaccine candidates [80-82]: Pfizer and Moderna currently have candidates in phase III trials , CureVac and Arcturus have candidates in phase I/II trials, and a vaccine candidate from Imperial College London and the Chinese Liberation Army is in phase I trials [55,83,84]. Advantages of this technology are that the vaccine can be produced completely in vitro. However, the technology is new, and it is unclear what issues will be encountered in terms of large-scale production and long-term storage stability, because frozen storage is required. In addition, these vaccines are administered by injection and are therefore unlikely to induce strong mucosal immunity (fig –Mucosal and systemic immune responses to natural infection with respiratory viruses and vaccination).

Fig – overview of the SAR-CoV-2 vaccine development landscape.The chart shows the distribution of candidates from different vaccine platforms over the different development phases. *The two vaccines that are currently licensed include one produced by CanSino, which is currently in use in the Chinese military, and the vaccine from Gamaleya Research Institute in Russia,which was licensed without a phase 3 trail .

Steps in vaccine development: Actions taken to ensure a new vaccine is safe and works well

Pre-clinical studies: Vaccine is tested in animal studies for efficacy and safety, including challenge studies

Phase I clinical trial: Small groups of healthy adult volunteers receive the vaccine to test for safety

Phase II clinical trial: Vaccine is given to a larger group of people who have characteristics (such as age and physical health) similar to Those for whom the new vaccine is intended

Phase III clinical trial: Vaccine is given to thousands of people and tested for efficacy and safety.

Phase IV post marketing surveillance: Ongoing studies after the vaccine is approved and licensed, to monitor adverse events and to study long-term Effects of the vaccine in the population.

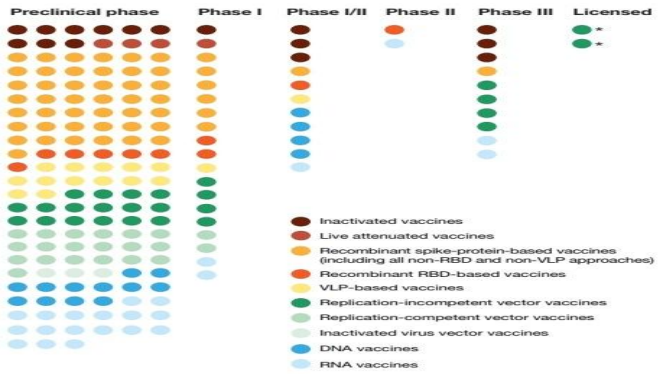

Fig. 7.

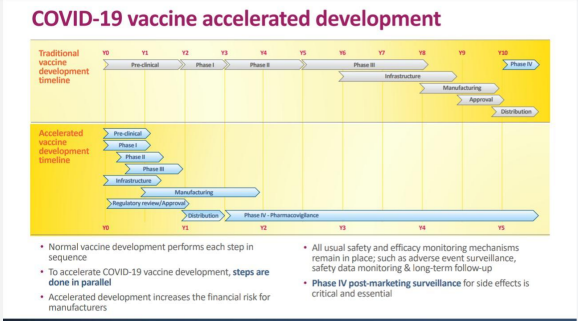

Fig. 8.

Human challenge studies: Studies in which a vaccine is given followed by the pathogen against which the vaccine is designed to protect. Such Trials are uncommon in people as they present considerable ethical challenges.

COVID-19 Authorized /approved vaccines

Name	Vaccine Type	Primary Developers	Country of Origin	Authorization/Approval
Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech; Fosun Pharma	Multinational	Albania, Argentina, Australia, Bahrain, Canada, Chile, Colombia, Costa Rica, Ecuador, EU, Faroe Islands, Greenland, Iceland, Iraq, Israel, Jordan, Kuwait, Malaysia, Mexico, New Zealand, Norway, Oman, Panama, Philippines, Qatar, Saudi Arabia, Serbia, Singapore, Switzerland, UAE, UK, US, Vatican City, WHO
Moderna COVID-19 Vaccine (mRNA-1273)	mRNA-based vaccine	Moderna, BARDA, NIAID	US	Canada, EU, Faroe Islands, Greenland, Iceland, Israel, Norway, Qatar, Saudi Arabia, Singapore, Switzerland, United Kingdom, United States
COVID-19 Vaccine AstraZeneca (AZD1222); also known as Covishield	Adenovirus vaccine	BARDA, OWS	UK	Argentina, Bahrain, Bangladesh, Brazil, Chile, Dominican Republic, Ecuador, El Salvador, EU, Hungary, India, Iraq, Mexico, Morocco, Myanmar, Nepal, Pakistan, Philippines, Saudi Arabia, South Africa, South Korea, Sri Lanka, Thailand, UK, Vietnam
Sputnik V	Non-replicating viral vector	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	Algeria, Argentina, Armenia, Bahrain, Belarus, Bolivia, Guinea, Hungary, Iran, Kazakhstan, Laos, Lebanon, Mexico, Mongolia, Nicaragua, Pakistan, Palestine, Paraguay, RepublikaSrpska, Russia, Serbia, Tunisia, Turkmenistan, United Arab Emirates, Venezuela
CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China	Azerbaijan, Bolivia, Brazil, China, Chile, Colombia, Indonesia, Laos, Turkey, Uruguay
BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	Bahrain, Cambodia, China, Egypt, Hungary, Jordan, Iraq, Laos, Macau, Morocco, Pakistan, Peru, Serbia, Seychelles, UAE

How safe are the COVID-19 vaccines?

The safety requirements for COVID-19 vaccines are the same as for any other vaccine and will Not be lowered in the context of the pandemic

• Safety trials begin in the lab, with tests and research on cells and animals first, before moving on To human studies

• The principle is to start small and only move to the next stage of testing if there are no safety Concerns

• Clinical trials are evaluating COVID-19 vaccines in tens of thousands of study participants to Generate the scientific data and other information needed to determine safety and effectiveness

• These clinical trials are being conducted by manufacturers according to rigorous standards

• The COVID-19 vaccines are tested in a broad population of people – not only young, physically fit Volunteers, but also older people and people with underlying health conditions

• After deployment, the vaccines will continue to be carefully monitored for safety and Effectiveness

Why are there so many COVID-19 vaccines in development?

• There are many different COVID-19 vaccines in development using different technologies because itMost discussed topics online on COVID-19 vaccinesis not yet known which ones will be effective and safe

• Based on experience, roughly 7% of vaccines in preclinical studies succeed. Candidates that reachclinical trials have about a 20% chance of succeeding

• Different vaccine types may be needed for different population groups

• For example, some vaccines may work in older persons and some may not, as the immune systemweakens with older age

• Several vaccines are needed to allow countries with as much vaccine as possible to increase thesupply

• Not everyone will be able to be vaccinated right away because of limited supply. It is important thatthe initial supplies of vaccine are given to people in a fair, ethical, and transparent way

• WHO recommends prioritization based on the WHO SAGE Prioritization Roadmap

COVID-19 Vaccine under trail

Candidate	Mechanism	Sponsor	Trial Phase	Institution
JNJ-78436735 (formerly Ad26.COV2.S)	Non-replicating viral vector	Johnson & Johnson	Phase 3	Johnson & Johnson
NVX-CoV2373	Nanoparticle vaccine	Novavax	Phase 3	Novavax
ZF2001	Recombinant vaccine	Anhui ZhifeiLongcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	Phase 3	Various
CVnCoV	mRNA-based vaccine	CureVac; GSK	Phase 2b/3	CureVac
Bacillus Calmette-Guerin (BCG) vaccine	Live-attenuated vaccine	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital	Phase 2/3	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital
INO-4800	DNA vaccine (plasmid)	Inovio Pharmaceuticals	Phase 2/3	Center for Pharmaceutical Research, Kansas City. Mo.; University of Pennsylvania, Philadelphia
VIR-7831	Plant-based adjuvant vaccine	Medicago; GSK; Dynavax	Phase 2/3	Medicago
No name announced	Adenovirus-based vaccine	ImmunityBio; NantKwest	Phase 2/3	
UB-612	Multitope peptide-based vaccine	COVAXX	Phase 2/3	United Biomedical Inc. (UBI)
ZyCoV-D	DNA vaccine (plasmid)	ZydusCadila	Phase 2	ZydusCadila

Candidate	Mechanism	Sponsor	Trial Phase	Institution
Abdala (CIGB 66)	Protein subunit vaccine	Finlay Institute of Vaccines	Phase 2	Finlay Institute of Vaccines
BNT162	mRNA-based vaccine	Pfizer, BioNTech	Phase 1/2/3	Multiple study sites in Europe, North America and China
AdCLD-CoV19	Adenovirus-based vaccine	Cellid; LG Chem	Phase 1/2a	Korea University Guro Hospital
Nanocovax	Recombinant vaccine (Spike protein)	Nanogen Biopharmaceutical	Phase 1/2	Military Medical Academy (Vietnam)
EuCorVac-19	nanoparticle vaccine	EuBiologics	Phase 1/2	Eunpyeong St. Mary's Hospital
Protein subunit vaccine	Finlay Institute of Vaccines		Phase 1/2	Finlay Institute of Vaccines
IIBR-100	Recombinant vesicular stomatitis virus (rVSV) vaccine	Israel Institute for Biological Research	Phase 1/2	Hadassah Medical Center; Sheba Medical Center Hospital
No name announced	SF9 cell vaccine candidate	West China Hospital, Sichuan University	Phase 1/2	West China Hospital, Sichuan University
Soberana 1 and 2	Monovalent/conjugate vaccine	Finlay Institute of Vaccines	Phase 1/2	Finlay Institute of Vaccines
VLA2001	Inactivated vaccine	Valneva; National Institute for Health Research (NIHR)	Phase 1/2	Multiple NIHR testing sites

Candidate	Mechanism	Sponsor	Trial Phase	Institution
CORVax12	DNA vaccine (plasmid)	OncoSec; Providence Cancer Institute	Phase 1	Providence Portland Medical Center
MVA-SARS-2-S	Modified vaccinia virus ankara (MVA) vector vaccine candidate	Universitätsklinikum Hamburg-Eppendorf; German Center for Infection Research; Philipps University Marburg Medical Center; Ludwig-Maximilians - University of Munich	Phase 1	University Medical Center Hamburg-Eppendorf
COH04S1	Modified vaccinia virus ankara (MVA) vector vaccine candidate	City of Hope Medical Center; National Cancer Institute	Phase 1	City of Hope Medical Center
pVAC	Multi-peptide vaccine candidate	University Hospital Tuebingen	Phase 1	University Hospital Tuebingen
AdimrSC-2f	Protein subunit vaccine	Adimmune	Phase 1	Adimmune
bacTRL-Spike	Monovalent oral vaccine (bifidobacteria)	Symvivo	Phase 1	Symvivo Corporation
COVAX-19	Monovalent recombinant protein vaccine	Vaxine Pty Ltd.	Phase 1	Royal Adelaide Hospital
DelNS1-2019-nCoV-RBD-OPT1	Replicating viral vector	Xiamen University, Beijing Wantai Biological Pharmacy	Phase 1	Jiangsu Provincial Centre For Disease Control and Prevention
GRAd-COV2	Adenovirus-based vaccine	ReiThera; Leukocare; Univercells	Phase 1	LazzaroSpallanzani National Institute for Infectious Diseases
UQ-CSL V451	Protein subunit vaccine	CSL; The University of Queensland	Phase 1	

Candidate	Mechanism	Sponsor	Trial Phase	Institution
SCB-2019	Protein subunit vaccine	GlaxoSmithKline, Sanofi, Clover Biopharmaceuticals, Dynavax and Xiamen Innovax; CEPI	Phase 1	Linear Clinical Research (Australia)
VXA-CoV2-1	Recombinant vaccine (adenovirus type 5 vector)	Vaxart	Phase 1	Vaxart
AAVCOVID	Gene-based vaccine	Massachusetts Eye and Ear; Massachusetts General Hospital; University of Pennsylvania	Pre-clinical	
AdCOVID	Intranasal vaccine	Altimmune	Pre-clinical	University of Alabama at Birmingham
ChAd-SARS-CoV-2-S	Adenovirus-based vaccine	Washington University School of Medicine in St. Louis	Pre-clinical	Washington University School of Medicine in St. Louis
HaloVax	Self-assembling vaccine	Voltron Therapeutics, Inc.; Hoth Therapeutics, Inc.	Pre-clinical	MGH Vaccine and Immunotherapy Center
LineaDNA	DNA vaccine	Takis Biotech	Pre-clinical	Takis Biotech
MRT5500	Recombinant vaccine	Sanofi, Translate Bio	Pre-clinical	
No name announced	Ii-Key peptide COVID-19 vaccine	Generex Biotechnology	Pre-clinical	Generex
No name announced	Protein subunit vaccine	University of Saskatchewan Vaccine and Infectious Disease Organization-International Vaccine Centre	Pre-clinical	University of Saskatchewan Vaccine and Infectious Disease Organization-International Vaccine Centre

Candidate	Mechanism	Sponsor	Trial Phase	Institution
No name announced	mRNA-based vaccine	Chulalongkorn University's Center of Excellence in Vaccine Research and Development	Pre-clinical	
No name announced	gp96-based vaccine	Heat Biologics	Pre-clinical	University of Miami Miller School of Medicine
No name announced	Inactivated vaccine	Shenzhen Kangtai Biological Products	Pre-clinical	
PittCoVacc	Recombinant protein subunit vaccine (delivered through microneedle array)	UPMC/University of Pittsburgh School of Medicine	Pre-clinical	University of Pittsburgh
T-COVIDTM	Intranasal vaccine	Altimmune	Pre-clinical	
LNP-nCoVsaRNA	Self-amplifying RNA vaccine	Imperial College London	No longer being studied	Imperial College London
V590	Recombinant vaccine (vesicular stomatitis virus)	Merck; IAVI	No longer being studied	
V591	Measles vector vaccine	University of Pittsburgh's Center for Vaccine Research	No longer being studied	University of Pittsburgh; Themis Biosciences; Institut Pasteur"

8. CONCLUSION

There are many different COVID-19 vaccines in development using different technologies because it Most discussed topics online on COVID-19 vaccinesis not yet known which ones will be effective and safe Based on experience, roughly 7% of vaccines in preclinical studies succeed. Candidates that reach clinical trials have about a 20% chance of succeeding Different vaccine types may be needed for different population groups For example, some vaccines may work in older persons and some may not, as the immune system weakens with older age. Deep study need to focus on the development of Vaccine as per the different physiological compatibility.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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