Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Immunopharmacology 111 (2022) 109175

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Recent advances in the vaccine development for the prophylaxis of SARS Covid-19

Vipul Kumar [a], Sahil Kumar [a,*], Prabodh Chander Sharma [b]

[a] Department of Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR), Delhi Pharmaceutical Sciences and Research University, New Delhi 110017, India
[b] Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Delhi Pharmaceutical Sciences and Research University, New Delhi 110017, India

ARTICLE INFO

Keywords:
Vaccine
SARS-CoV-2
COVID-19
Vaccine development
Virus

ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-caused Coronavirus Disease 2019 (COVID-19) is currently a global pandemic that has wreaked havoc on public health, lives, and the global economy. The present COVID-19 outbreak has put pressure on the scientific community to develop medications and vaccinations to combat COVID-19. However, according to highly optimistic forecasts, we could not have a COVID-19 vaccine until September 2020. This is due to the fact that a successful COVID-19 vaccine will necessitate a careful validation of effectiveness and adverse reactivity given that the target vaccine population includes high-risk people over 60, particularly those with severe co-morbid conditions, frontline healthcare professionals, and those involved in essential industrial sectors. For passive immunization, which is being considered for Covid-19, there are several platforms for vaccine development, each with its own advantages and disadvantages. The COVID-19 pandemic, which is arguably the deadliest in the last 100 years after the Spanish flu, necessitates a swift assessment of the various approaches for their ability to incite protective immunity and safety to prevent unintended immune potentiation, which is crucial to the pathogenesis of this virus. Considering the pandemic's high fatality rate and rapid spread, an efficient vaccination is critical for its management. As a result, academia, industry, and government are collaborating in unprecedented ways to create and test a wide range of vaccinations. In this review, we summarize the Covid-19 vaccine development initiatives, recent trends, difficulties, comparison between traditional vaccines development and Covid-19 vaccines development also listed the approved/authorized, phase-3 and pre-clinical trials Covid-19 vaccines in different countries.

1. Introduction

Coronaviruses (CoVs) are a group of concerned viruses that can cause respiratory tract infections in humans, with symptoms ranging from moderate to fatal [1,2]. There are currently-seven types of CoVs known to infect humans (Fig. 1) [3]. Human Coronavirus 229E (HCoV-229E), Human Coronavirus OC43 (HCoV-OC43), Human Coronavirus NL63 (HCoV-NL63), and Human Coronavirus HKU1 (HCoV-HKU1) are four of these that induce only moderate and self-limiting respiratory symptoms. The other three CoVs, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), on the other hand, are extremely pathogenic and can cause severe respiratory diseases as well as death in infected patients [4,5].

China's health officials detected a suspicious pneumonia with no known cause in late December 2019 [6]. The disease was caused by a novel coronavirus, according to a prompt genome analysis [7]. This novel virus was given the name SARS-CoV-2 by the World Health Organization (WHO), and the disease COVID-19, or Coronavirus Disease 2019 [8]. On March 11, 2020, the World Health Organization (WHO) had no choice but to declare the outbreak a pandemic due to its rapid spreading [9]. COVID-19 can cause a wide range of symptoms, from asymptomatic to moderate flu-like symptoms to severe respiratory distress syndrome and death [10]. COVID-19 incidences have also been linked to long-term pulmonary, cardiological, and neurological problems [11]. Other than treating symptomatic patients, monitoring of asymptomatic infections, follow-up and monitoring after cure and discharge, close contact tracking, high-risk population screening, and disinfection of the epidemic source have all been used to prevent and control the epidemic, but effective vaccination would be the only way to

* Corresponding author.
E-mail address: skm@dpsru.edu.in (S. Kumar).

https://doi.org/10.1016/j.intimp.2022.109175
Received 8 June 2022; Received in revised form 8 August 2022; Accepted 14 August 2022
Available online 17 August 2022

completely eliminate COVID-19 infections [12–14]. A vaccine is a biological substance that gives active acquired immunity against a specific infectious disease [15]. A vaccine usually comprises an antigen that resembles a disease-causing microorganism and is manufactured from weakened or killed microbes, their toxins, or one of their surface proteins [16]. Vaccines can be used for both prevention and treatment [17,18]. Many processes are involved in bringing a new vaccine to the public, including vaccine development, clinical trials, FDA authorization or approval, production, and distribution [19]. To make COVID-19 vaccinations available to the general population, a number of public and private institutions collaborated [20]. While the COVID-19 vaccines were created quickly, every precaution was taken to assure their safety and efficacy [21].

2. COVID-19 vaccine development

Vaccines are among the most extensively studied biological medications on the market [22,23]. The development of a vaccine is a lengthy and difficult procedure that differs from the development of regular medicines [24]. In terms of scope and pace, the efforts of researchers around the world to develop vaccines against SARS-CoV-2 as a therapeutic remedy in the COVID-19 pandemic are unprecedented [25]. Because "speed" is the most important aspect of receiving these vaccines, it's possible that they'll be available under emergency or similar protocols [26]. However, this pressing requirement constitutes a significant shift from the classic and typical stages of vaccine development, which take on average ten years to complete, compared to the five years required for Ebola vaccines [27]. The quick and pressing need for COVID-19 vaccines involves novel development concepts:

(i) parallel and adaptive development phases,
(ii) innovative regulatory processes, and.
(iii) Big manufacturing capacity [28].

In the preclinical stage of standard vaccine development, the technology that will be used in the vaccine is chosen, and the efficiency, safety, and efficacy on human cells (*in vitro*) and animal models (*in vivo*) are evaluated [29]. *In vivo* animal studies are carried out if the anti-infective activity *in vitro* is expected and many cells do not perish excessively [30]. The preclinical stage lasts between 1 1/2 [31] and 2 1/2 [32] years and is by far the most selective; less than 20 % [30] of studies survive the human test, according to estimates. Some studies fail because the product is ineffective, while others fail because financing is no longer available [33]. These factors could be a result of the failure of prospective anti-COVID vaccinations that have been designated as "preclinical testing" by the World Health Organization [34]. Human testing is the second step, which includes FDA (USA) and EMA (Europe) approvals [35,36]. Testing on tens of individuals (phase I), testing on hundreds of people (phase II), and testing on thousands of people (steps III/IV) are the three phases of this stage [37,38]. As the goal is to identify the vaccine's effective dose and, more importantly, to limit side effects, small-scale testing is always preferred [39].

3. Comparison of the development of traditional vaccines and COVID-19 vaccines

Traditional vaccine development can take up to 15 years, beginning with a protracted discovery phase during which vaccines are designed and exploratory preclinical studies are carried out (Fig. 2) [40]. This is frequently followed by a phase in which more formal preclinical investigations and toxicological studies are conducted, as well as the development of manufacturing methods [41]. During this time, an investigational new drug (IND) application is submitted, and the vaccine candidate is tested in phases I, II, and III. If the predefined end points are satisfied with the outcome of phase III trials, a biologics license application (BLA) is filed, examined by regulatory agencies, and the vaccine is finally licensed [42]. Large-scale production begins after that. The research of a vaccine for Covid-19 is moving at a tremendous speed (Fig. 3) [43,44]. The discovery phase was avoided due to knowledge gathered from the initial development of vaccines for SARS-CoV and MERS-CoV [45]. Existing procedures were implemented, and phase I/II trials began. After the interim review of phase I/II data, phase III studies began, with numerous clinical trial phases operating concurrently [46]. Meanwhile, vaccine manufacturers have begun large-scale production of numerous vaccine candidates, putting them in jeopardy. It's yet unclear how these vaccine candidates will be licensed, for example, through an initial emergency use authorization [47].

4. The difficulties in developing Covid-19 vaccines

In the last decade, empirical-based vaccination firms have made significant advancements in human health [48]. Nonetheless, vaccine research is still in its infancy in terms of modern immunology and molecular microbiology, necessitating a longer time to develop a new vaccine [49]. When producing new vaccines, increased health concerns, extremely advanced production techniques, and related research

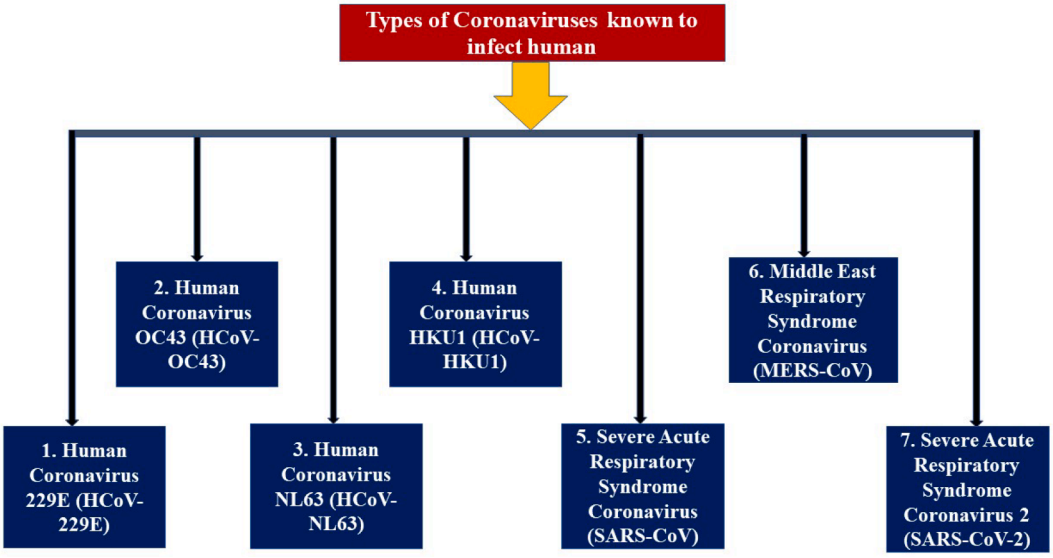

Fig. 1. Types of Coronaviruses known to infect Human.

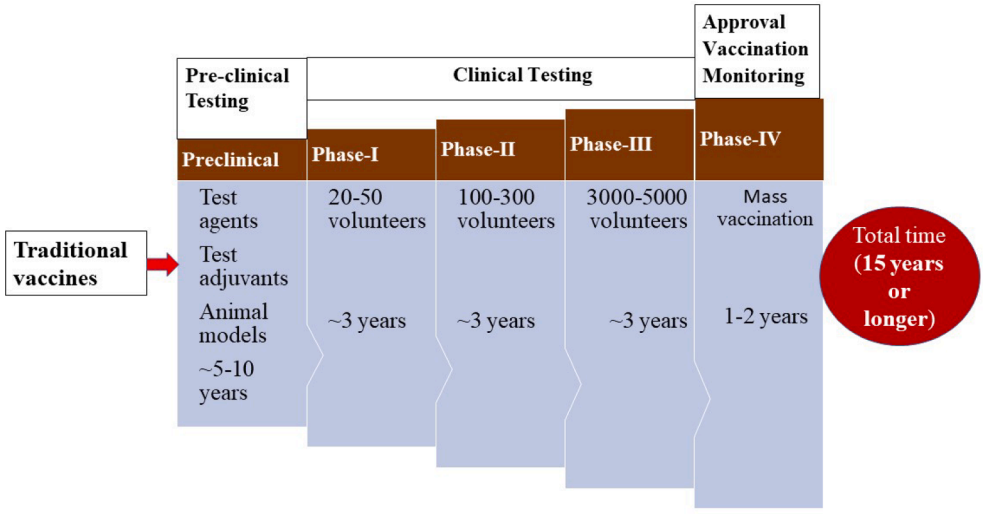

Fig. 2. Development of Traditional Vaccines.

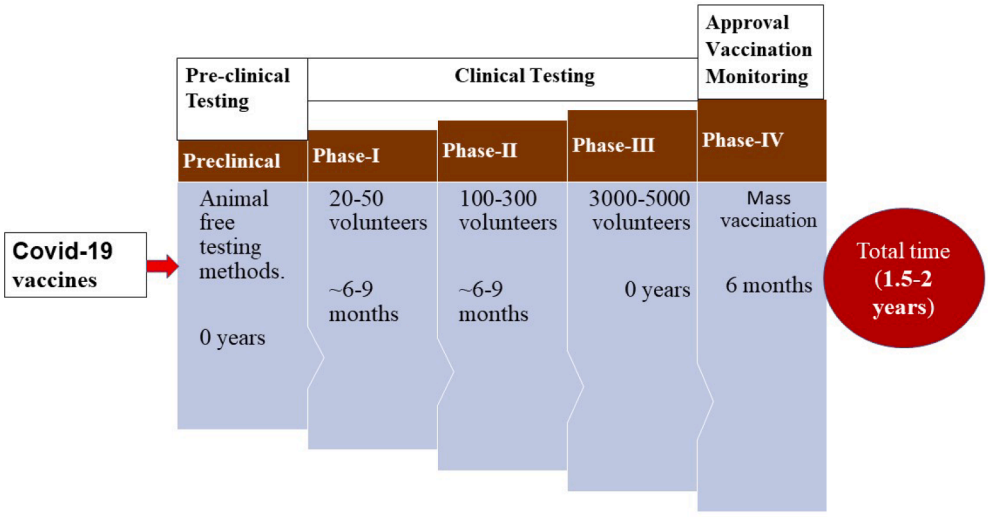

Fig. 3. Development of Covid-19 Vaccines.

requirements must all be carefully examined [50]. If a SARS-CoV-2 vaccine is produced on a fast-track basis for clinical use, a new set of regulations and guidelines will be needed to address overlapping medical, technological, regulatory, and public safety concerns [51]. In recent years, the relationship between immune responses and protective effects has been questioned for many vaccinations [52]. Structure-guided antigen production is quite popular [53]. Vaccine development, on the other hand, is far from being a well-established research topic. After nearly-four decades of study, the recent announcement of the discontinuation of HVTN702 reminded us of a considerable gap between research and the production of human immunodeficiency virus (HIV) vaccines [51]. Vaccine development today necessitates a wide range of skills. A wide range of advances has emerged over the last two decades [54]. In light of the challenging vaccination specifications against rapidly spreading novel viral illnesses, vaccine technologies with existing human research experience would provide significant benefits, particularly in terms of health concerns. It's also worth noting that the innovator might quickly scale up his or her vaccine production to a scale-up Good Manufacturing Practice (GMP) output of up to 10-million doses [55]. Those who already have facility and manufacturing experience would be in a much better position [51]. Regulatory agencies face a similar difficulty to vaccine companies when it comes to the quick development of COVID-19 vaccines [56]. The health assessment of potential vaccines against COVID-19 would be given top priority. The virus's immune-pathogenesis is critical in the COVID-19 infection, ensuring that immunization against such a virus does not cause the same types of immunological reactions [57]. This would have an impact on the vaccination formulation and immunogens used. If the global demand for COVID-19 vaccinations arises, the preparation will eventually begin to allow every-one in the world to have equal access to effective vaccines. To achieve total pandemic control, the following challenges must be addressed: vaccine ownership, unmatched development financing, pricing and supply networks, and coordinated delivery of such vaccines [58].

5. Major vaccine development initiatives for Covid-19

To combat the current coronavirus epidemic, much effort is being put into developing a vaccine against COVID-19 [59]. More than 150 companies and academic institutions are working on COVID-19 vaccines, using DNA-based vaccines, RNA-based vaccines, non-replicating viral vectors (NRVV), replicating viral vectors (RVV), inactivated vaccines (IAcV), live-attenuated vaccines (LAVs), and protein subunits, among other strategies. Several researchers are using computer-aided

and machine learning technologies to investigate the immune system's interaction with viral antigens in order to find prospective vaccine targets. These approaches have already been used to develop vaccines against a variety of different infections, and they are presently being used to develop a vaccine against COVID-19 [60–62]. We have also listed the authorized or approved vaccines (Table 1) by mentioning their platform, vaccines under the pre-clinical phase (Table 2) and vaccines under phase-3 (Table 3).

6. Nucleic acid vaccines

SARS-CoV-2 nucleic acid vaccines have been developed by a number of pharmaceutical companies [63,64]. Inovio Pharmaceuticals, for example, developed a DNA vaccine, while other businesses, such as Moderna Therapeutics and Curevac [65], are investigating RNA vaccine techniques. DNA vaccines were shown to induce protective immunity against influenza in mice models in 1993. For decades, however, these nonclinical investigations have not been transferred into clinical trials in humans [65]. The formulations of nucleic acid vaccines have lately improved significantly, boosting their safety. Although nucleic acid vaccines are now exclusively used in animals, it is becoming more likely that they will be utilized in people [66].

7. DNA vaccines

The DNA vaccine, which encodes for the antigen plus an adjuvant that triggers the adaptive immune response, is the most revolutionary technique for immunization [67]. This kind of vaccine preparation has possibilities for successful HCV viral hepatitis or viral pathology prophylaxis with high antigenic diversity (influenza virus or HIV) [68]. DNA vaccines can be administered in a variety of ways. They can be delivered intradermally, where a short electric pulse (electroporation) optimizes their uptake by cutaneous antigen-presenting cells (APCs) like macrophages, monocytes, and dendritic cells, which will process and present them to naive T cells in secondary lymph organs, resulting in increased cellular adaptive immune responses. The newly produced antigen will also reach these organs, where it will activate naive B cells, leading to antibody production [67]. Because DNA molecules are normally quite stable, DNA vaccines can be stored at + 4 °C, making the distribution of this type of vaccination much easier [69].

8. RNA vaccines

RNA vaccines are made up of viral antigen-encoding messenger RNAs that can be converted into antigenic proteins and trigger the immune system by human cells [70]. These vaccines aim to stimulate the production of antibodies against the viral protein spike, which can be detected on the virus's surface. These antibodies have a neutralizing effect, which means they prevent the protein that permits cells in the respiratory tract to get infected [71]. To boost their efficiency, RNA vaccines are frequently administered in combination with other agents such as protamine or lipid- and polymer-based nanoparticles. RNA vaccines can be administered via a variety of methods, including regular intravenous injection, but DNA vaccines need the use of specialized instruments such as electroporation or a gene gun [72,73]. Because of its flexibility and capacity to mimic antigen structure and expression as seen during a natural infection, this platform has aided the rapid vaccine development effort [74]. mRNA molecules, on the other hand, are much more unstable than DNA. As a result, long-term storage of mRNA vaccines typically necessitates temperatures between −70 °C and −20 °C, which complicates vaccine distribution logistics [71].

9. Whole virus vaccines

Conventional production processes are used to create live-attenuated viral vaccines and inactivated virus vaccines. Johnson & Johnson is one

Table 1
Authorized/approved vaccines for Covid-19 [96,97].

Name	Platform	Developers	Origin
Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech; Fosun Pharma	Multinational
Moderna COVID–19 Vaccine (mRNA-1273); also called Spikevax	mRNA-based vaccine	Moderna, BARDA, NIAID	US
COVID-19 Vaccine AstraZeneca (AZD1222); also known as Vaxzevria and Covishield	Adenovirus vaccine	BARDA, OWS	UK
Sputnik V	Recombinant adenovirus vaccine (rAd26 and rAd5)	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia
Sputnik Light	Recombinant adenovirus vaccine (rAd26)	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia
COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Non-replicating viral vector	Janssen Vaccines (Johnson & Johnson)	The Netherlands, US
CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China
BBIBP-CorV/ NVSI-06–07	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China
EpiVacCorona	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia
Convidicea (PakVac, Ad5-nCoV)	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	China
Covaxin (BBV152)	Inactivated vaccine	Bharat Biotech, ICMR; Ocugen; ViroVax	India
WIBP-CorV	Inactivated vaccine	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China
CoviVac	Inactivated vaccine	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	Russia
ZF2001 (ZIFIVAX)	Recombinant vaccine	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	China, Uzbekistan
QazVac (QazCovid-in)	Inactivated vaccine	Research Institute for Biological Safety Problems	Kazakhstan
Unnamed vaccine	Inactivated vaccine	Minhai Biotechnology Co.; Kangtai Biological Products Co. Ltd.	China
COVIran Barekat	Inactivated vaccine	Shifa Pharmed Industrial Group	Iran
Unnamed vaccine	Inactivated vaccine	Chinese Academy of Medical Sciences,	China

(continued on next page)

Table 1 (*continued*)

Name	Platform	Developers	Origin
		Institute of Medical Biology	
Abdala (CIGB 66)	Protein subunit vaccine	Center for Genetic Engineering and Biotechnology	Cuba
Soberana 02/ Soberana Plus	Conjugate vaccine	Finlay Institute of Vaccines; Pasteur Institute	Cuba, Iran
MVC-COV1901	Protein subunit vaccine	Medigen Vaccine Biologics Corp.; Dynavax	Taiwan
ZyCoV-D	DNA vaccine (plasmid)	Zydus Cadila	India
Spikogen (COVAX-19)	Monovalent recombinant protein vaccine	Vaxine Pty Ltd.; CinnaGen	Iran
FAKHRAVAC (MIVAC)	Inactivated vaccine	The Stem Cell Technology Research Center; Organization of Defensive Innovation and Research	Iran
NVX-CoV2373 (Nuvaxovid; Covovax in India)	Recombinant nanoparticle vaccine	Novavax; CEPI, Serum Institute of India	US
Corbevax	Adjuvanted protein subunit vaccine	Biological E, Baylor College of Medicine, Dynavax, CEPI	India, United States
Covifenz (CoVLP)	Plant-based adjuvant vaccine	Medicago; GSK; Dynavax	Canada
VLA2001	Inactivated vaccine	Valneva;UK National Institute for Health Research; Dynavax	France, United States
Noora	Recombinant protein vaccine	Baqiyatallah University of Medical Sciences	Iran

of the major pharmaceutical companies that set out to produce COVID-19 vaccines, according to corporate publications [75]. They used Janssen's AdVac® adenoviral vector and PER.C6® cell line technologies to manufacture an Ebola vaccine based on their Ebola vaccine concept [75,76]. In addition, Hong Kong University researchers have developed a live influenza vaccination that includes SARS-CoV-2 proteins [77]. One of the most important advantages of whole virus vaccines is their ability to activate toll-like receptors (TLRs), such as TLR3, TLR7/8, and TLR9, which are found on innate immune cells [78]. Codagenix has developed a "codon deoptimization" technology for attenuating viruses and developing vaccines for SARS-CoV-2 [79]. Nonetheless, it is critical to investigate live viruses for safety profiles and protective effects. It's very important to figure out if antibody-dependent enhancement happens following immunization with live or killed COVID-19 viral vaccines [78].

10. Inactivated vaccines

It contains viral copies that have been killed (inactivated). COVID-19 inactivated vaccines are made by cultivating the virus in cell culture, commonly on Vero cells, and then chemically inactivating it [80,81]. CoronaVac (formerly known as PiCoVacc), which is being developed by Sinovac Biotech in China, is an example of an inactivated vaccine candidate [81,82]. These vaccines are often given intramuscularly and may include alum (aluminium hydroxide) or other adjuvants. Immune responses are anticipated to target not just the SARS-CoV-2 spike protein, but also the matrix, envelope, and nucleoprotein, because the entire virus is presented to the immune system. Clinical trials for a number of inactivated vaccine candidates have begun [83].

11. Live attenuated vaccines

It contains virus copies that have been weakened (attenuated). Live attenuated vaccines are made by creating a genetically weakened version of the virus that only replicates to a limited amount, causing no disease but eliciting immune responses similar to those elicited by natural infection [84]. Adapting the virus to unfavourable environments is one way to achieve attenuation (For example, growth at a lower temperature or in non-human cells) or by modifying the virus in a rational manner (For example, by de-optimizing codons or deleting genes that prevent innate immune recognition) [85,86]. These vaccines have the benefit of being able to be given intranasally, where they stimulate mucosal immune responses that protect the upper respiratory tract, which is the virus's main entry site. Furthermore, because the virus is multiplying in the vaccinated host, antibodies and cellular immune responses are likely to target both structural and non-structural viral proteins. However, there are safety problems with these vaccinations, as well as the necessity to alter the virus, which is time-consuming with traditional methods and technically difficult using reverse genetics [87,88].

12. Viral vectored vaccines

A vector virus is a virus that has been modified in some way. To send vital instructions to our cells, viral vector vaccines use a modified version of a virus that is not the virus being targeted [89]. The cells then create antigens, which are harmless fragments of the virus that elicit an immunological response in the body. Your immune system will recognize and fight the true virus if you are exposed to it later. Vaccines based on viral vectors have been approved to prevent Ebola and COVID-19, and others, such as malaria, influenza, and HIV, are being developed. There are two types of viral vector vaccines: replicating and non-replicating. Non-replicating viral vectors vaccines- contains viral genetic material packaged in another virus that is incapable of replicating itself. Replicating viral vectors vaccines- contains viral genetic material packaged in a harmless virus capable of replicating itself. COVID-19

Table 2
Vaccines under the pre-clinical phase [96,97].

Name	Platform	Sponsor	Institutions
ChAd-SARS-CoV-2-S	Adenovirus-based vaccine	Washington University School of Medicine in St. Louis	Washington University School of Medicine in St. Louis
LineaDNA	DNA vaccine	Takis Biotech	Takis Biotech
AAVCOVID	Gene-based vaccine	Massachusetts Eye and Ear; Massachusetts General Hospital; University of Pennsylvania	
No name announced	gp96-based vaccine	Heat Biologics	University of Miami Miller School of Medicine
No name announced	Ii-Key peptide COVID-19 vaccine	Generex Biotechnology; Beijing Youfeng Biological Technology, Ltd	Generex
PittCoVacc	Recombinant protein subunit vaccine (delivered through microneedle array)	UPMC/University of Pittsburgh School of Medicine	University of Pittsburgh
HaloVax	Self-assembling vaccine	Voltron Therapeutics, Inc.; Hoth Therapeutics, Inc.	MGH Vaccine and Immunotherapy Center

Table 3
Vaccines under the Phase-3 [96,97].

Name	Platform	Sponsor	Trial Phase	Institutions
No name announced	Adenovirus-based vaccine	ImmunityBio; NantKwest	Phase 2/3	
S-268019	Recombinant protein vaccine	Shionogi & Co., Ltd; Japan Agency for Medical Research and Development	Phase 2/3	
HDT-301 (HGCO19)	RNA vaccine	University of Washington; National Institutes of Health Rocky Mountain Laboratories; HDT Bio Corp; Gennova Biopharmaceuticals; SENAI CIMATEC; Quratis Inc.	Phase 2/3	
INO-4800	DNA vaccine (plasmid)	Inovio Pharmaceuticals; Advaccine	Phase 2/3	Center for Pharmaceutical Research, Kansas City. Mo.; University of Pennsylvania, Philadelphia
GRAd-COV2	Adenovirus-based vaccine	ReiThera; Leukocare; Univercells	Phase 2/3	Lazzaro Spallanzani National Institute for Infectious Diseases
SCB-2019	Protein subunit vaccine	GlaxoSmithKline, Sanofi, Clover Biopharmaceuticals, Dynavax and Xiamen Innovax; CEPI	Phase 2/3	Linear Clinical Research (Australia)
GX-19N	DNA vaccine	Genexine	Phase 2/3	PT Kalbe Farma TBK
UB-612	Multitope peptide-based vaccine	Vaxxinity	Phase 2/3	United Biomedical Inc. (UBI)
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
BBV154	Intranasal vaccine	Bharat Biotech	Phase 2/3	Various
CVnCoV	mRNA-based vaccine	CureVac; GSK	Phase 2b/3	CureVac
Unnamed vaccine candidate	Recombinant protein vaccine	Laboratorios HIPRA, S.A.	Phase 2b/3	Hospital Clínic de Barcelona; Hospital Universitari Dr. Josep Trueta
Unnamed vaccine candidate	Recombinant vaccine (Sf9 cells)	WestVac Biopharma Co., Ltd.; West China Hospital; Sichuan University;	Phase 3	Jiangsu Province Centers for Disease Control and Prevention
ARCoV (Awcorna)	mRNA-based vaccine	Walvax Biotechnology Co., Ltd.; Abogen Biosciences Co. Ltd.; Yuxi Walvax Biotechnology Co., Ltd.	Phase 3	Xiangfen CDC
Vidprevtyn	Recombinant protein vaccine	Sanofi; GlaxoSmithKline	Phase 3	Various
Nanocovax	Recombinant vaccine (Spike protein)	Nanogen Biopharmaceutical	Phase 3	Military Medical Academy (Vietnam)
V-01	Recombinant protein vaccine	Guangdong Provincial Center for Disease Control and Prevention; Gaozhou Municipal Center for Disease Control and Prevention; Zhuhai Livzonumab Biotechnology Co., Ltd.	Phase 3	Livzon Mabpharm Inc.
Razi Cov Pars	Recombinant vaccine (Spike protein)	Razi Vaccine and Serum Research Institute	Phase 3	Tehran Rasoul Akram Hospital; Karaj, Hesarak, Razi Vaccine and Serum Research Institute
GBP510	Nanoparticle vaccine	SK bioscience Co., Ltd.; GSK; University of Washington; CEPI	Phase 3	Various
SCB-2019	Protein subunit vaccine	GlaxoSmithKline, Sanofi, Clover Biopharmaceuticals, Dynavax and Xiamen Innovax; CEPI	Phase 3	Linear Clinical Research (Australia)

vaccines are non-replicating, requiring higher dosages but being safer than replicating viral vectors [68,90].

13. Protein subunit vaccines

Subunit vaccinations include only the components, or antigens, that best stimulate the immune system. There is no risk of disease because there is no live fragment involved [91]. Protein-based subunit vaccines, polysaccharide vaccines, and conjugate subunit vaccines are all types of subunit antibodies [92]. Live attenuated and inactivated/killed vaccinations are less consistent and safer than protein subunit vaccines. When compared to other types of vaccinations, they can be generated at a lower cost [93]. SPs, which include spike (S), envelope (E), membrane (M), and nucleocapsid (N), are viral antigens that elicit neutralizing antibodies and a protective immunological response in SARS-CoV2 [94]. The S and N proteins of coronaviruses are the most widely used structural proteins. Intravacc., in conjunction with EpiVax, is developing an outer membrane vesicle (OMV) delivery platform using synthetically created SARS-CoV2 epitopes. It's one of a number of platforms being researched for the development of a subunit vaccine. Preclinical testing is currently being conducted on the candidate. The GP-96 backbone and the li-key peptide are two other innovative platforms being researched as part of this strategy [95].

14. Additional factors for the development of the Covid-19 vaccine

Given COVID-19′s rapid transmission and asymptomatic spread, an effective vaccine with worldwide immunization coverage is clearly needed to restore people's lives to normalcy. Even if a safe and efficient COVID-19 vaccine is developed, the longevity of vaccine-induced protection remains uncertain. SARS-specific IgG and neutralizing antibodies were only retained for around 2 years in patients who recovered from COVID-19 infection, according to previous SARS research [98,99]. As a result, lifelong protection from COVID-19 vaccinations is less likely, and a regular vaccination regimen may be required in the future. Furthermore, the minimum neutralizing antibody titer that can confer protection against COVID-19 infection is still unknown. It is thought that the larger the level of neutralizing antibodies induced by vaccination, the better the protective effect. This is in line with the finding that most COVID-19 reinfection cases have relatively minor or no symptoms during their initial infection, which may not be enough to develop

robust neutralizing antibodies [100,101]. As a result, more research is needed to describe the relationship between neutralizing antibody and protective effect in order to guide COVID-19 vaccine development. Finally, numerous mutations have been discovered in the SARS-CoV-2 genome, with the D614G mutation being the most common [102]. D614G is a missense point mutation in the S protein that promotes SARS-CoV-2 infectivity by reducing S1 shedding and enhancing S protein incorporation into the virion [103,104]. The D614G mutation, fortunately, does not prevent neutralizing antibodies from attaching to SARS-CoV-2, and so does not confer vaccine resistance [104]. However, such immune-escaping mutations may arise in the future, making the development of the COVID-19 vaccine much more difficult.

15. Conclusion

New forms of coronaviruses have emerged since the discovery of human coronaviruses in the 1960 s, and they have steadily become a severe threat to worldwide public health. Despite the fact that the first coronavirus outbreak occurred almost two decades ago, the scientific and medical communities are still unprepared to confront these diseases. One thing we learned from this is that the current pharmaceutical market's financial and regulatory mechanisms do not give enough incentive to support vaccine development before a catastrophic outbreak occurs. To compensate, academic institutions and enterprises all around the world are already creating an unprecedented number of vaccine candidates with extremely short clinical trial timelines. COVID-19 vaccine research studies are in various phases of development. Some methods use messenger RNA, while others use DNA, which is then translated, resulting in the production of specific immunogenic proteins. Beyond the basic research that identifies which antigens can cause a virus-neutralizing immune response, the development of a vaccine must take into account two extremely crucial factors. More research is urgently needed to find the most effective vaccine candidate in order to reduce the rising number of COVID-19 patients for this we believe that countries from all around the world, regardless of political orientations, can join and collaborate in the near future to create a speedy and viable COVID-19 vaccine.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] L. Chang, Y. Yan, L. Wang, Coronavirus disease 2019: coronaviruses and blood safety, Transfus. Med. Rev. 34 (2) (2020) 75–80.
[2] K. McIntosh, Coronaviruses: a comparative review. Current topics in microbiology and immunology/Ergebnisse der Mikrobiologie und Immunitätsforschung, 1974, 85–129.
[3] A. Syed, Coronavirus: a mini-review, Int. J. Curr. Res. Med. Sci. 6 (1) (2020) 8–10.
[4] Centers-for-Disease-Control-and-Prevention. Human Coronavirus Types. 2020. Available from: <https://www.cdc.gov/coronavirus/types.html>.
[5] L. van der Hoek, Human coronaviruses: what do they cause? Antivir. Ther. 12 (4 Pt B) (2007) 651–658.
[6] Y.C. Liu, R.L. Kuo, S.R. Shih, COVID-19: The first documented coronavirus pandemic in history, Biome. J. 43 (4) (2020) 328–333.
[7] R.A. Khailany, M. Safdar, M. Ozaslan, Genomic characterization of a novel SARS-CoV-2, Gene Rep. 1 (19) (2020), 100682.
[8] H. Ouassou, L. Kharchoufa, M. Bouhrim, N.E. Daoudi, H. Imtara, N. Bencheikh, A. ELbouzidi, M. Bnouham, The pathogenesis of coronavirus disease 2019 (COVID-19): evaluation and prevention, J. Immunol. Res. 2020 (2020).
[9] J.T. Wu, K. Leung, M. Bushman, et al., Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China, Nat. Med. 26 (4) (2020) 506–510.
[10] I. Madabhavi, M. Sarkar, N. Kadakol, COVID-19: a review, Monaldi Arch. Chest Dis. 90 (2) (2020).
[11] C. Del Rio, L.F. Collins, P. Malani, Long-term health consequences of COVID-19, JAMA (2020), https://doi.org/10.1001/jama.2020.19719.
[12] Z.P. Yan, M. Yang, C.L. Lai, COVID-19 vaccines: a review of the safety and efficacy of current clinical trials, Pharmaceuticals 14 (5) (2021) 406.
[13] S. Jamil, N. Mark, G. Carlos, C.S. Cruz, J.E. Gross, S. Pasnick, Diagnosis and management of COVID-19 disease, Am. J. Respir. Crit. Care Med. 201 (10) (2020) P19–P20.
[14] H.R. GÜNER, İ. Hasanoğlu, F. Aktaş, COVID-19: prevention and control measures in community, Turkish J. Med. Sci. 50 (SI-1) (2020) 571–177.
[15] S. Yesh, C. Devendra, N. Ravi, B. Atul, T. Tangutoori, R. Eliezer, Dental caries vaccine–a change, Acta Sci. Dental Sci. 2 (10) (2018) 41–44.
[16] T. Gualu, A. Dilie, Vaccination coverage and associated factors among children aged 12–23 months in debre markos town, Amhara regional state, Ethiopia, Adv. Public Health. 1 (2017) 2017.
[17] R. Edelman, The development and use of vaccine adjuvants, Mol. Biotechnol. 21 (2) (2002) 129–148.
[18] O.C. Brennan, J.E. Moore, P.J. Moore, B.C. Millar, Vaccination terminology: A revised glossary of key terms including lay person's definitions, J. Clin. Pharm. Ther. 47 (3) (2022) 369–382.
[19] G.A. Poland, D. Murray, R. Bonilla-Guerrero, New vaccine development, BMJ 324 (7349) (2002) 1315–1319.
[20] L. Corey, J.R. Mascola, A.S. Fauci, F.S. Collins, A strategic approach to COVID-19 vaccine R&D, Science 368 (6494) (2020) 948–950.
[21] Centers-for-Disease-Control-and-Prevention. Developing COVID-19 Vaccines. 2021. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/distributing/steps-ensure-safety.html>.
[22] JM Muzumdar, RR Cline, Vaccine supply, demand, and policy: a primer, Journal of the American Pharmacists Association 49 (4) (2009 Jul 1) e87–e99.
[23] E. Medina, C.A. Guzmán, Use of live bacterial vaccine vectors for antigen delivery: potential and limitations, Vaccine. 19 (13–14) (2001) 1573–1580.
[24] J. Petricciani, R. Sheets, E. Griffiths, I. Knezevic, Adventitious agents in viral vaccines: lessons learned from 4 case studies, Biologicals 42 (5) (2014) 223–236.
[25] S. Machingaidze, C.S. Wiysonge, Understanding COVID-19 vaccine hesitancy, Nat. Med. 27 (8) (2021) 1338–1339.
[26] O.J. Wouters, K.C. Shadlen, M. Salcher-Konrad, A.J. Pollard, H.J. Larson, Y. Teerawattananon, M. Jit, Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment, Lancet 397 (10278) (2021) 1023–1034.
[27] J. Powlson, et al., Characterization of antigenic MHC-class-I-restricted t cell epitopes in the glycoprotein of ebolavirus, Cell Rep. 29 (9) (2019) 2537–2545.e3.
[28] M.S. Khuroo, M. Khuroo, M.S. Khuroo, A.A. Sofi, N.S. Khuroo, COVID-19 vaccines: a race against time in the middle of death and devastation!, J. Clin. Exp. Hepatol. 10 (6) (2020) 610–621.
[29] E.S. Pronker, T.C. Weenen, H.R. Commandeur, A.D. Osterhaus, H.J. Claassen, The gold industry standard for risk and cost of drug and vaccine development revisited, Vaccine 29 (35) (2011) 5846–5849.
[30] M. Daneshian, F. Busquet, T. Hartung, M. Leist, Animal use for science in Europe. Alternatives to animal experimentation, ALTEX 32 (4) (2015) 261–274.
[31] E.S. Pronker, T.C. Weenen, H. Commandeur, E.H.J.H.M. Claassen, A.D.M. E. Osterhaus, Risk in vaccine research and development quantified, PLoS ONE 8 (3) (2013), e57755.
[32] M.-M. Struck, Vaccine R&D success rates and development times, Nat. Biotechnol. 14 (5) (1996) 591–593.
[33] M. Kremer, Pharmaceuticals and the developing world, J. Econ. Perspectives 16 (4) (2002) 67–90.
[34] Organization, W.H., DRAFT landscape of COVID-19 candidate vaccines. World. 2020.
[35] FDA, Investigational new drug (IND) Application, 2020.
[36] Agency, E.M., Clinical Trial Regulation, 2019.
[37] N.B. Bulik, et al., Reactogenicity and medically attended adverse events following hexavalent vaccination: an observational prospective study, Farmacia 67 (6) (2019) 1018–1024.
[38] C. Bucsa, et al., Adverse events following measles-mumps-rubella vaccination. A prospective observational study, Farmacia 68 (2) (2020) 219–224.
[39] D. Calina, T. Hartung, A.O. Docea, et al., COVID-19 vaccines: ethical framework concerning human challenge studies, DARU J. Pharm. Sci. (2020) 1–6, https://doi.org/10.1007/s40199-020-00371-8.
[40] M.S. Gebre, L.A. Brito, L.H. Tostanoski, D.K. Edwards, A. Carfi, D.H. Barouch, Novel approaches for vaccine development, Cell 184 (6) (2021) 1589–1603.
[41] H.H. Mao, S. Chao, Advances in vaccines, Curr. Appl. Pharm. Biotechnol. (2019) 155–188.
[42] A.S. Kesselheim, J.J. Darrow, M. Kulldorff, B.L. Brown, M. Mitra-Majumdar, C. C. Lee, O. Moneer, J. Avorn, An overview of vaccine development, approval, and regulation, with implications for COVID-19: analysis reviews the food and drug administration's critical vaccine approval role with implications for COVID-19 vaccines, Health Aff. 40 (1) (2021) 25–32.
[43] S. Ullah, A.G. Al-Sehemi, J.J. Klemeš, S. Saqib, S.M. Gondal, S. Saqib, A. Arshad, H. Saqib, A. Mukhtar, M. Ibrahim, A.S. Saira, A review of the progress of COVID-19 vaccine development, Duzce Med. J. 23 (Special Issue) (2021) 1–23.
[44] N. Lurie, J.M. Sharfstein, J.L. Goodman, The development of COVID-19 vaccines: safeguards needed, JAMA 324 (5) (2020) 439–440.
[45] J. Begum, N.A. Mir, K. Dev, B. Buyamayum, M.Y. Wani, M. Raza, Challenges and prospects of COVID-19 vaccine development based on the progress made in SARS

and MERS vaccine development, Transboundary Emerg. Dis. 68 (3) (2021) 1111–1124.
[46] D. van Riel, E. de Wit, Next-generation vaccine platforms for COVID-19, Nat. Mater. 19 (8) (2020) 810–812.
[47] Development and Licensure of Vaccines to Prevent COVID-19. Available from: <https://www.fda.gov/ media/139638/download> (FDA, 2020).
[48] C. Rueckert, C.A. Guzmán, Vaccines: from empirical development to rational design, PLoS Pathog. 8 (11) (2012), e1003001.
[49] E.S. Pronker, T.C. Weenen, H. Commandeur, E.H. Claassen, A.D. Osterhaus, Risk in vaccine research and development quantified, PLoS ONE 8 (3) (2013), e57755.
[50] F. Stauffer, T. El-Bacha, A.T. Da Poian, Advances in the development of inactivated virus vaccines, Recent Pat. Anti-Infect. Drug Discovery 1 (3) (2006) 291–296.
[51] S. Lu, Timely development of vaccines against SARS-CoV-2, Emerging Microbes Infect. 9 (2020) 542–544.
[52] B.F. Haynes, P.B. Gilbert, M.J. McElrath, S. Zolla-Pazner, G.D. Tomaras, S. M. Alam, et al., Immune-correlates analysis of an HIV-1 vaccine efficacy trial, N. Engl. J. Med. 366 (2012) 1275–1286.
[53] P.R. Dormitzer, J.B. Ulmer, R. Rappuoli, Structure-based antigen design: a strategy for next generation vaccines, Trends Biotechnol. 26 (12) (2008 Dec 1) 659–667.
[54] S. Lu, Editorial overview: vaccines against challenging viral pathogens and new vaccine technology, doi: 10.1016/j.coviro.2014.04.006. 2014.
[55] B. Buckland, R. Boulanger, M. Fino, I. Srivastava, K. Holtz, N. Khramtsov, C. McPherson, J. Meghrous, P. Kubera, M.M. Cox, Technology transfer and scale-up of the Flublok® recombinant hemagglutinin (HA) influenza vaccine manufacturing process, Vaccine 32 (42) (2014) 5496–5502.
[56] S. Jiang, Y. He, S. Liu, SARS vaccine development, Emerg. Infect. Dis. 11 (7) (2005) 1016.
[57] L.J. Saif, Animal coronavirus vaccines: lessons for SARS, Dev. Biol. (Basel) 1 (119) (2004) 129–140.
[58] C.J. Silva, C. Cruz, D.F. Torres, A.P. Muñuzuri, A. Carballosa, I. Area, J.J. Nieto, R. Fonseca-Pinto, R. Passadouro, E.S. Santos, W. Abreu, Optimal control of the COVID-19 pandemic: controlled sanitary deconfinement in Portugal, Sci. Rep. 11 (1) (2021) 1–5.
[59] M.A. Kabir, R. Ahmed, R. Chowdhury, S.M. Iqbal, R. Paulmurugan, U. Demirci, W. Asghar, Management of COVID-19: Current status and future prospects, Microbes Infect. 23 (4–5) (2021), 104832.
[60] C. Chakraborty, G. Agoramoorthy, India's cost-effective COVID-19 vaccine development initiatives, Vaccine 38 (50) (2020) 7883.
[61] R.P. Saha, A.R. Sharma, M.K. Singh, S. Samanta, S. Bhakta, S. Mandal, M. Bhattacharya, S.S. Lee, C. Chakraborty, Repurposing drugs, ongoing vaccine, and new therapeutic development initiatives against COVID-19, Front. Pharmacol. 1258 (2020).
[62] G. Salvatori, L. Luberto, M. Maffei, L. Aurisicchio, L. Aurisicchio, G. Roscilli, G. Roscilli, F. Palombo, E. Marra, E. Marra, SARS-CoV-2 spike protein: an optimal immunological target for vaccines, J. Transl. Med. (2020), doi: 10.1186/s12967-020-02392-y.
[63] W.H. Chen, U. Strych, P.J. Hotez, M.E. Bottazzi, The SARS-CoV-2 vaccine pipeline: an overview, Curr. Tropical Med. Rep. 7 (2) (2020) 61–64.
[64] R. Piyush, K. Rajarshi, A. Chatterjee, R. Khan, S. Ray, Nucleic acid-based therapy for coronavirus disease 2019, Heliyon 6 (9) (2020), e05007.
[65] W.-H. Chen, U. Strych, P.J. Hotez, M.E. Bottazzi, The SARS-CoV-2 vaccine pipeline: an overview, Curr. Tropical Med. Rep. (2020:) 1–4, https://doi.org/10.1007/s40475-020-00201-6.
[66] F.R. Vogel, N. Sarver, Nucleic acid vaccines, Clin. Microbiol. Rev. 8 (3) (1995) 406–410.
[67] D. Hobernik, M. Bros, DNA vaccines-how far from clinical use? Int. J. Mol. Sci. 3605 (2018) https://doi.org/10.3390/ijms19113605. PMID: 30445702; PMCID: PMC6274812.
[68] S. Rauch, E. Jasny, K.E. Schmidt, B. Petsch, New vaccine technologies to combat outbreak situations, Front. Immunol. 9 (2018) 1963.
[69] S.K. Misra, K.A. Pathak, D.E. Pathak, R.A. Yadav, Current updates on COVID-19 vaccines, Asian J. Pharma. Clin. Res. 7 (2021) 17–23.
[70] S.H. Shahcheraghi, J. Ayatollahi, A.A. Aljabali, M.D. Shastri, S.D. Shukla, D. K. Chellappan, N.K. Jha, K. Anand, N.K. Katari, M. Mehta, S. Satija, An overview of vaccine development for COVID-19, Therapeutic Delivery 12 (3) (2021) 235–244.
[71] N. Pardi, M.J. Hogan, F.W. Porter, D. Weissman, mRNA vaccines—a new era in vaccinology, Nat. Rev Drug Discov. 17 (4) (2018) 261–279.
[72] K.J. Kaufman, M.J. Webber, D.G. Anderson, Materials for non-viral intracellular delivery of messenger RNA therapeutics, J. Control. Release 240 (2016) 227–234.
[73] U. Sahin, K. Kariko, O. Tureci, mRNA-based therapeutics–developing a new class of drugs, Nat. Rev. Drug Discov. 13 (10) (2014) 759–780.
[74] M.J. Mulligan, K.E. Lyke, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, K. Neuzil, V. Raabe, R. Bailey, K.A. Swanson, P. Li, Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults, Nature 586 (7830) (2020) 589–593.
[75] J&J. working on coronavirus vaccine. thepharmaletter 2020. Available from: <https://www. thepharmaletter.com/article/j-j-working-on-coronavirusvaccine>. Accessed 28 Feb 2020. 2020.
[76] ClinicalTrials.gov. National Institutes of Health. Available from: <https://clinicaltrials.gov/ct2/show/NCT02543567>. Accessed February 7, 2020. 2020.
[77] E. C. China coronavirus: Hong Kong researchers have already developed vaccine but need time to test it, expert reveals. South China Morning Post. Available from: <https://www.scmp.com/news/hong-kong/health-environment/article/3047956/china-coronavirus-hongkong-researchers-have>. Accessed 28 Feb 2020, 2020.
[78] S. Jiang, M.E. Bottazzi, L. Du, S. Lustigman, C.-T.K. Tseng, E. Curti, et al., Roadmap to developing a recombinant coronavirus S protein receptor-binding domain vaccine for severe acute respiratory syndrome, Expert Rev. Vaccines 11 (2012) 1405–1413.
[79] J. S. Codagenix raises $20 million for a new flu vaccine and other therapies. Tech Crunch. Available from: <https://techcrunch.com/2020/01/13/codagenix-raises20-million-for-a-new-flu-vaccine-and-othertherapies/>. Accessed 28 Feb 2020, 2020.
[80] H. Wang, et al., Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2, Cell 182 (2020) 713–721.e9.
[81] Q. Gao, et al., Development of an inactivated vaccine candidate for SARS-CoV-2, Science 369 (2020) 77–81.
[82] Y.-J. Zhang et al., Immunogenicity and safety of a SARS-CoV-2 inactivated vaccine in healthy adults aged 18–59 years: report of the randomized, double-blind, and placebo-controlled phase 2 clinical trial, 2020. Preprint at doi: 10.1101/2020. 07.31.20161216.
[83] Draft Landscape of COVID-19 Candidate Vaccines. Available from: <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines> (WHO, accessed 26 September 2020).
[84] P.L. Fidel Jr, M.C. Noverr, Could an unrelated live attenuated vaccine serve as a preventive measure to dampen septic inflammation associated with COVID-19 infection? MBio 11 (3) (2020) e00907-20.
[85] J. Talon, et al., Influenza A and B viruses expressing altered NS1 proteins: a vaccine approach, PNAS 97 (2000) 4309–4314.
[86] A.J. Broadbent, et al., Evaluation of the attenuation, immunogenicity, and efficacy of a live virus vaccine generated by codon-pair bias de-optimization of the 2009 pandemic H1N1 influenza virus, in ferrets, Vaccine 34 (2016) 563–570.
[87] S. Okamura, H. Ebina, Could live attenuated vaccines better control COVID-19? Vaccine 39 (39) (2021) 5719–5726.
[88] J.W. Alsulaiman, A.I. Khasawneh, K.A. Kheirallah, Could "trained immunity" be induced by live attenuated vaccines protect against COVID-19? Review of available evidence, J. Infect. Dev. Countries 14 (09) (2020) 957–962.
[89] K.B. Lauer, R. Borrow, T.J. Blanchard, Multivalent and multipathogen viral vector vaccines, Clin. Vaccine Immunol. 24 (1) (2017) e00298–e00316.
[90] R. Vanaparthy, G. Mohan, D. Vasireddy, P. Atluri, Review of COVID-19 viral vector-based vaccines and COVID-19 variants, Le Infezioni in Medicina. 29 (3) (2021) 328.
[91] NIH: NIAID, vaccine types | NIH: national institute of allergy and infectious diseases, NIH Natl. Inst. Allergy Infect. Dis. (2019), doi: 10.1016/0021- 8707(56) 90057-0.
[92] World Health Organization, MODULE 2- Types of Vaccine and Adverse Reactions, WHO, 2018, pp. 41–42.
[93] M. Wang, S. Jiang, Y. Wang, Recent advances in the production of recombinant subunit vaccines in Pichia pastoris, Bioengineered (2016), doi: 10.1080/21655979.2016.1191707.
[94] S.C. Pandey, V. Pande, D. Sati, S. Upreti, M. Samant, Vaccination strategies to combat novel corona virus SARS-CoV-2, Life Sci. (2020), https://doi.org/10.1016/j.lfs.2020.117956.
[95] World Health Organization, Draft Landscape of COVID-19 Candidate Vaccines - 28th July, Who, 2020.
[96] Available from: <https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker>.
[97] Available from: <https://covid19.trackvaccines.org/vaccines/>.
[98] W.C. Cao, W. Liu, P.H. Zhang, F. Zhang, J.H. Richardus, Disappearance of antibodies to SARS-associated coronavirus after recovery, N. Engl. J. Med. 357 (11) (2007) 1162–1163.
[99] L.P. Wu, N.C. Wang, Y.H. Chang, X.Y. Tian, D.Y. Na, L.Y. Zhang, L. Zheng, T. Lan, L.F. Wang, G.D. Liang, Duration of antibody responses after severe acute respiratory syndrome, Emerg. Infect. Dis. 13 (10) (2007) 1562–1564.
[100] A. Iwasaki, What reinfections mean for COVID-19, Lancet. Infect. Dis (2020), https://doi.org/10.1016/S1473-3099(20)30783-0.
[101] J.H. Ko, E.J. Joo, S.J. Park, J.Y. Baek, W.D. Kim, J. Jee, C.J. Kim, C. Jeong, Y. J. Kim, H.J. Shon, E.S. Kang, Y.K. Choi, K.R. Peck, Neutralizing antibody production in asymptomatic and mild COVID-19 patients, in comparison with pneumonic COVID-19 patients, J Clin Med. 9 (7) (2020) 2268.
[102] E. Callaway, The coronavirus is mutating—does it matter? Nature 585 (7824) (2020) 174–177.
[103] B. Korber, W.M. Fischer, S. Gnanakaran, H. Yoon, J. Theiler, W. Abfalterer, N. Hengartner, E.E. Giorgi, T. Bhattacharya, B. Foley, K.M. Hastie, M.D. Parker, D. G. Partridge, C.M. Evans, T.M. Freeman, T.I. de Silva, C.-G.G. Shefeld, C. McDanal, L.G. Perez, H. Tang, A. Moon-Walker, S.P. Whelan, C.C. LaBranche, E.O. Saphire, D.C. Montefori, Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus, Cell 182 (4) (2020) 812–827 e819.
[104] L. Zhang, C.B. Jackson, H. Mou, A. Ojha, E.S. Rangarajan, T. Izard, M. Farzan, H. Choe, The D614G mutation in the SARS-CoV-2 spike protein reduces S1 shedding and increases infectivity, bioRxiv, 2020, doi: 10.1101/2020.06.12.148726.