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A Review on Ongoing Research for Potential COVID-19 Vaccine

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Abstract
Novel corona virus is a communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first recognizing in December 2019 in Wuhan, China, and has since expanded globally, resulting in an ongoing epidemic. As of 11 May 2020, more than 4.16 million cases have been arrive across 187 countries and territories, resulting in more than 285,000 deaths. More than 1.45 million people have recovered. common symptoms include fever cough, fatigue, loss of appetite, sputum production, shortness of breath, and muscle and joint pains. While sever cases show acute respiratory distress syndrome (ARDS), multi-organ failure, septic shock, and blood clots. The standard diagnosis method is by real-time reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab. Nowadays, the outbreak is still spreading and there is no effectual means to prevent the infection. Several organizations and institutions began work on produce vaccines for 2019 n-CoV based on the published genome. Vaccines are showed to be the most effective and economical means to prevent and control infectious diseases. Several countries, companies, and institutions declare their programs and advancement on vaccine development in opposition to the virus. While most of the vaccines are undergoing design and preparation, there are some that have entered efficacy assessment in animals and initial clinical trials. This review largely focused on the advancement and our prospects on field of vaccine development in opposition to SARS-CoV-2.

Keywords
SARS-CoV-2, rRT-PCR, vaccine development, animal model, clinical trials.

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INTRODUCTION
Novel corona virus is an communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] It was first recognize in December 2019 in Wuhan, China, and has since expand globally, resulting in an ongoing epidemic.[2] As of 11 May 2020, more than 4.16 million cases have been arrive across 187 countries and territories, resulting in more than 285,000 deaths. More than 1.45 million people have recovered.[3] Common symptoms include fever, cough, fatigue, shortness of breath, and loss of smell and taste.[4] While the majority of cases result in mild symptoms, some progress to acute respiratory distress syndrome (ARDS), multi-organ failure, septic shock, and blood clots.[5] The time from exposure to onset of symptoms is typically around five days but may range from two to fourteen days.[6] The virus is primarily spread between people during close contact, most often via small droplets produced by coughing, sneezing, and talking. The droplets usually

drop to the ground or onto surfaces rather than transfer through air over long distances.[7] Less commonly, people may become infected by touching a contaminated surface and then touching their face.[8] It is most contagious during the first three days after the onset of symptoms, although spread may be possible before symptoms appear, or from people who do not show symptoms.[9] The standard method of diagnosis is by real-time reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab.[10] Chest CT imaging may also be helpful for diagnosis in individuals where there is a high suspicion of infection based on symptoms and risk factors; however, guidelines do not recommend using it for routine screening.[11] Recommended measures to prevent infection include frequent hand washing, maintaining physical distance from others (especially from those with symptoms), quarantine, covering coughs, and keeping unwashed hands away from the face.[12] In addition, the use of a face covering is recommended for those who suspect they have the virus and their caregivers.[13] According to the World Health Organization, there are no available vaccines nor specific antiviral treatments for COVID-19.[14] On 1 May 2020, the United States gave Emergency Use Authorization to the antiviral remdesivir for people hospitalized with severe COVID-19.[15] Management involves the treatment of symptoms, supportive care, isolation, and experimental measures.[16] The World Health Organization (WHO) announced the COVID-19 outbreak a Public Health Emergency of International Concern (PHEIC)[17] on 30 January 2020 and a pandemic on 11 March 2020.[18] Local transmission of the disease has occurred in most countries across all six WHO regions.[19].

Epidemiology

As of April 6, 2020, a total of 1,285,257 cases of COVID-19 happen in at least 170 countries and territories were appearing, with approximately 5.4 % of fatality rate (70,344/1,285,257). A previous overview from China that cover 72,314 confirmed, suspected, and asymptomatic patients revealed several important epidemiological features of COVID-19. In general, the majority of confirmed cases are aged 30–79 years-old (86.6%).[20] Several measures are commonly used to quantify mortality.[21] These numbers vary by region and over time and are influenced by the volume of testing, healthcare system quality, treatment options, time since the initial outbreak, and population characteristics such as age, sex, and overall health.[22] The death-to-case ratio show the number of deaths divided by the number of identify cases within a given time interval. Based on Johns Hopkins University statistics, the global death-to-case ratio is 6.8% (285,445/4,168,427) as of 11 May 2020.[23] The figure varies by region other measures encompass the case fatality rate (CFR), which consider the percent of diagnosed independent who die from a disease, and the infection fatality rate (IFR), which reflects the percent of infected individuals (diagnosed and undiagnosed) who die from a disease. These statistics are not time-sensitive and keep to a specified people from infection through case resolution. Many instructor have attempted to calculate these figure for specific populations.[24] Outbreaks have occurred in prisons due to crowding and an inability to enforce adequate social distancing.[25] In the United States, the prisoner population is aging and many of them are at high possibility for poor outcomes from COVID-19 due to high rates of accompany heart and lung disease, and poor access to high-quality healthcare.[26] Our World in Data states that as of March 25, 2020, the IFR cannot be precisely calculated.[27] In February, one research group gauge the IFR at 0.94%, with a dependence interval between 0.37 percent to 2.9 percent.[28] The University of Oxford Centre for Evidence-Based Medicine (CEBM) approximate a global CFR of 0.72 percent and infection fatality rate of 0.1 percent to 0.36 percent.[29] According to CEBM, random antibody testing in Germany recommend an infection fatality rate of 0.37% (0.12% to 0.87%) there, but there have been concerns about faulty positives.[30] Firm under limitation of infection fatality rates have been confirmed in a number of locations. In New York City, with a population of 8.4 million, as of May 7, 14,162 (0.17% of the population) have died from COVID-19.[31] To get a better view on the number of people infected initial antibody testing have been carried out, but there are no valid scientific reports based on any of them as of yet.[32]

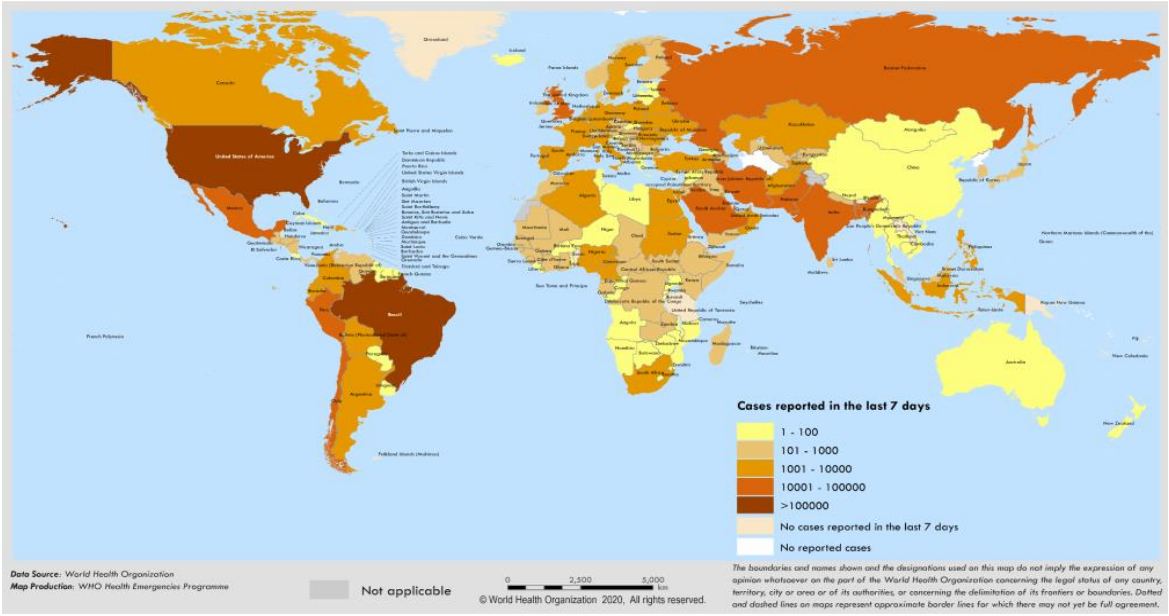

Fig.1.Number of confirmed COVID-19 cases reported in the last seven days by country, territory or area, 17 May to 23 May.[33]

History

Vaccines have been produced against several diseases caused by coronaviruses for animal use, including for infectious bronchitis virus in birds, canine coronavirus and feline coronavirus.[34] above projects to develop vaccines for viruses in the family Coronaviridae that influence humans have been aimed at severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). [35] As of 2020, there is no cure or protective vaccine for SARS that has been shown to be both of them are safe and effectual in humans.[36] As per research papers published in 2005 and 2006, development of novel vaccines and medicines to treat SARS was a priority for governments and public health agencies around the world.[37] There is also no proven vaccine in opposition to MERS. When MERS became widespread, it was trust that existing SARS research may give a useful template for developing vaccines and therapeutics against a MERS-CoV infection.[38] As of March 2020, there was one (DNA based) MERS vaccine which finished Phase I clinical trials in humans, and three others in development, all of which are viral-vectored vaccines, two adenoviral-vectored (ChAdOx1-MERS, BVRS-GamVac), and one MVA-vectored (MVA-MERS-S).[39]

Pathophysiology

The lungs are the organs mostly affected by novel corona virus because the virus attack host cells via the enzyme angiotensin-converting enzyme 2 (ACE2), which is most abundant in type II alveolar cells of the lungs. The virus uses a distinct surface glycoprotein called a "spike" (peplomer) to connect to ACE2 and go in to the host cell.[40] The density of ACE2 in each tissue correlates with the severity of the disease in that tissue and some have suggested that decreasing ACE2 activity might be protective.[41] though another view is that increasing ACE2 using angiotensin II receptor blocker medications could be protective and these hypotheses need to be tested.[42] As the alveolar disease progresses, respiratory failure might develop and death may follow.[43] SARS-CoV-2 may also infect respiratory system through influence the brainstem as other coronaviruses have been found to invade the central nervous system (CNS). While corona virus has been detected in cerebrospinal fluid of autopsies, the exact mechanism by which it occupy the CNS remains unclear and may first involve invasion of peripheral nerves given the low levels of ACE2 in the brain.[44] The virus also influence gastrointestinal organs as ACE2 is copiously demonstrate in the glandular cells of gastric, duodenal and rectal epithelium as well as endothelial cells and enterocytes of the small intestine.[45] The virus can cause acute myocardial injury and chronic damage to the cardiovascular system.[46] An acute cardiac injury was found in 12% of infected people admitted to the hospital in Wuhan, China, and is more persistent in severe disease.[47] Rates of cardiovascular symptoms are high, owing to the systemic inflammatory response and immune system disorders during disease progression, but acute myocardial injuries may also be related to ACE2 receptors in the heart.[48] Another common source of death is problem associated to the kidneys SARS-CoV-2 directly infects kidney cells, as confirmed in post-mortem studies. Acute kidney have found diffuse alveolar damage (DAD), and lymphocyte-containing inflammatory

infiltrates within the lung.[50]injury is a common issue and cause of death; this is more notable in patients with already compromised kidney function, especially in people with pre-existing persistent conditions such as high blood pressure and diabetes which specifically cause nephropathy in the long run.[49] Autopsies of people who died of COVID-19

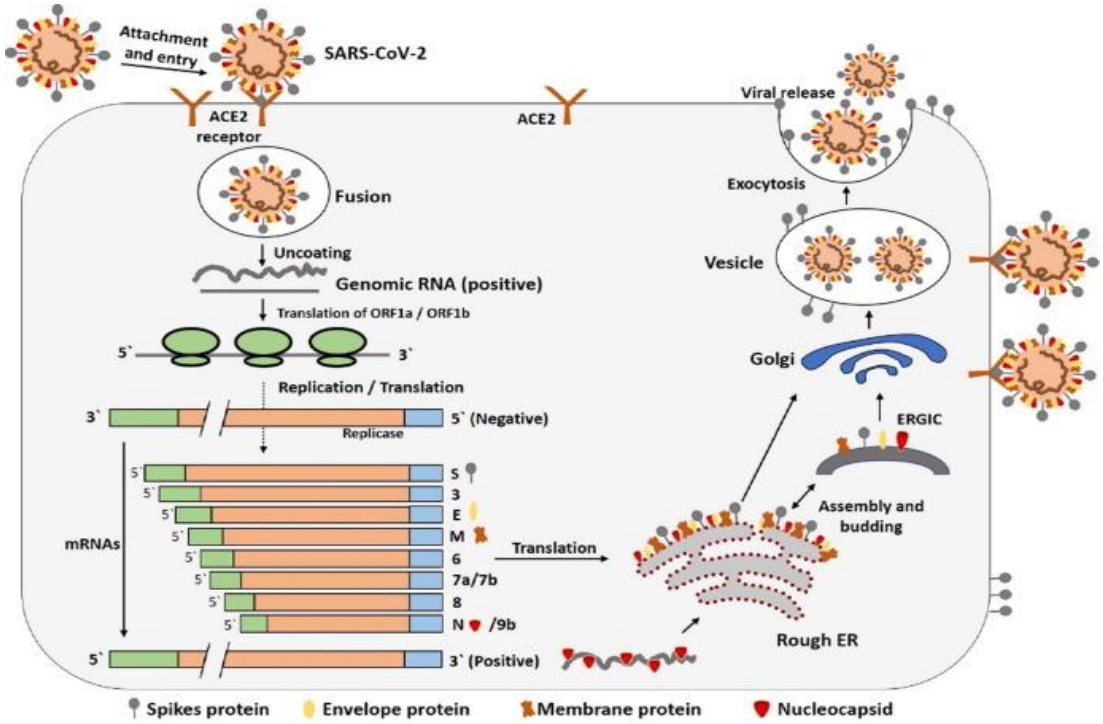

Fig.2. Pathophysiology of novel corona virus [SARS-CoV-2].[51]

Signs and symptoms

Fever is the almost usual symptom, in spite of the fact that some older people and those with other health issue experience fever later in the disease. In one investigation, 44% of people had fever when they admitted to the hospital while 89% went on to evolve fever at some point during their hospitalization. Other common symptoms include cough, fatigue, loss of appetite, sputum production, shortness of breath, and muscle and joint pains.[52] Symptoms such as nausea, vomiting, and diarrhoea also observed in varying percentages.[53] Less common symptoms include sneezing, runny nose, or sore throat. Some patient in China firstly presented with only chest tightness and palpitations.[54] A lower sense of smell or disturbances in taste may occur. The incubation period for COVID-19 is typically five to six days but may range from two to 14 days.[55] although 97.5% of people who develop symptoms will do so within 11.5 days of infection. A minority of patients do not develop observable symptoms at any point in time.[56] These asymptomatic transporter tend not to get tested, and their role in transmission is not yet fully known.[57] However, preliminary evidence suggests they may contribute to the spread of the disease.[68]In March 2020, the Korea Centers for Disease Control and Prevention (KCDC) announce that 20% of confirmed patient remained asymptomatic through their hospital stay.[59] For several weeks from January and February, initial study from China establish that about 13% of transmission from pre-symptomatic persons.[60]

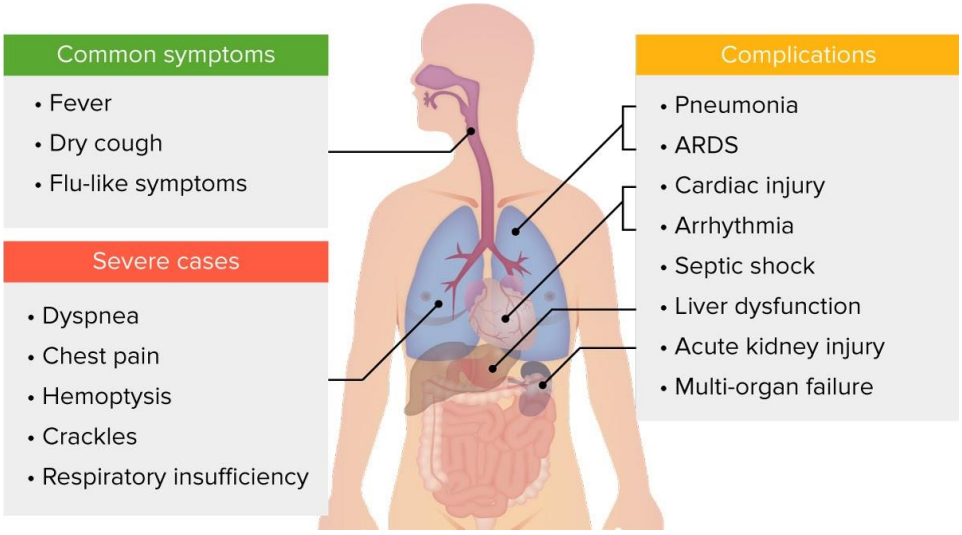

Fig .3. Clinical presentation of COVID-19.[61]

COVID-19 vaccine research

A novel corona virus (COVID-19) vaccine is a hypothetical vaccine in opposition to coronavirus disease 2019 (COVID-19). In spite of the fact that no vaccine has finished clinical trials, there are several attempts in progress to begin such a vaccine. [62] about US$2 billion fund develop by Epidemic Preparedness Innovations (CEPI) worldwide for rapid investment and development of vaccine candidates indicated in April that a vaccine may be accessible under emergency use protocols in less than 12 months or by early 2021.[63] On 4 May 2020, the WHO organized a telethon to raise US$8 billion from forty countries to support rapid development of vaccines to prevent COVID-19 infections.[64] also announcing deployment of an international "Solidarity trial" for simultaneous evaluation of several vaccine candidates reaching Phase II-III clinical trials.[65] By May, 120 vaccine candidates were in development, with five having been initiated in Phase I–II safety and efficacy studies in human subjects, and six in Phase I trials.[66]

Partnerships and competition

WHO Solidarity trial

The world health organization has set up a multinational partnership of vaccine scientists defining a Global Target Product Profile (TPP) for COVID-19, recognize approving allocate of safe and effective vaccines under two broad categories: "vaccines for the long-term protection of people at excessive risk of COVID-19, such as healthcare workers", and other vaccines to provide rapid-response immunity for new epidemic.[67] The international Target Product Profile (TPP) team was create to assess the evolution of the most successful candidate vaccines [68] rapidly evaluate and screen for the most promising candidate vaccines simultaneously before they are tested in humans; and design and coordinate a multiple-site, international randomized controlled trial the Solidarity trial for vaccines[to authorize concurrent assessment of the wellbeing and danger of different type of vaccine candidates under clinical trial in countries where there are high level of novel corona virus disease, make sure that fast explanation and sharing of results all over the world. The WHO vaccine should go into Phase II and III clinical trials, and discover harmonized Phase III protocols for all vaccines attain the pivotal trial stage.[69]

Vaccine candidates

Total 120 vaccine candidates are in primary stages of evolution as either established active projects or in "exploratory" or "preclinical" development, as of May.[70] Phase I trials test initial for safety and preliminary dosage in a small no of healthy subjects, while Phase II trials following success in Phase I trials to judge immunogenicity, dose levels (efficacy based on biomarkers) and harmful effects of the candidate vaccine, typically in hundreds of people. A Phase I–II trial carries out to determining more accurate, efficacious doses. Phase III trials typically involve additional participants, including a control group, and test efficacy of the vaccine to stop the disease, while keep track of adverse effects at the optimal dose.[71,72]

Preclinical research

In April, the WHO provide a number of vaccine scientists around the world, pledging partnership to speed development of a vaccine in opposition to COVID-19.[73] The WHO union is inspire international cooperation between organizations developing vaccine candidates, national regulatory and policy agencies, financial contributors, public health associations, and governments for ultimate

manufacturing of a successful vaccine in sufficient number to distribute all affected areas, particularly low-resource countries. The failure rates of 84-90% of vaccine development[74,75] Because COVID 19 is a novel virus target with possession still being discovered and need inventive vaccine technologies and development policy, the risks probability with developing a victorious vaccine covering all steps of preclinical and clinical research are high level. To evaluate possible vaccine efficacy, unparalleled computer simulations, and novel corona virus specific animal models are being developed, but these techniques remain untested by unknown feature of the COVID-19 virus and are being organized multinational during 2020. Researchers stated that 115 vaccine candidates were in development as either "exploratory/preclinical" The committed active vaccine candidates, about 70% are being found by private industries, with the persist projects go through development by government federation, academic, and health organizations. In early April, CEPI projects or in Phase I safety trials in human participants.[76] Table.1. Show COVID: 19 Candidate vaccines scheduled for phase I trials in 2020. [77,78] and table.2. Show COVID-19: Candidate vaccine in Phase I-II trials.

Vaccine candidate (developer)	Technology	Start date announced
NVX-CoV2373 (Novavax)	protein subunit, nanoparticles	May
DPX-COVID-19 (IMV, Inc., Canadian Immunization Research Network)	protein subunit, lipid based – delivery	mid-2020
PittCoVacc (University of Pittsburgh)	protein subunit, microneedle arrays	mid-2020
unnamed (University of Cambridge)	protein subunit, S protein	mid-2020
unnamed (Imperial College London)	RNA; saRNA	mid-2020
CureVac (CEPI)	RNA; saRNA	mid-2020
LUNAR-COV19 (Arcturus Therapeutics, Duke University-National University of Singapore)	RNA; saRNA	mid-2020
Unnamed (Sanofi Pasteur, GlaxoSmithKline)	protein subunit, S protein	mid-2020
Unnamed (Cobra Biologics, Karolinska Institute)	DNA plasmid	mid-2020
Unnamed (Generex Biotech)	synthetic viral peptides combined with Ii-key immune activation	mid-2020
Unnamed (Clover Biopharm)	fragments of the SARS-CoV-2 spike protein	mid-2020
Unnamed (Medicago, Inc.)	plant-derived virus-like particle	July–August
Unnamed (Janssen; Beth Israel Deaconess Medical Center)	non-replicating viral vector	September
CoroFlu (University of Wisconsin-Madison; FluGen; Bharat Biotech)	self-limiting influenza virus	late 2020
AdCOVID (Altimmune; University of Alabama at Birmingham	non-replicating viral vector; intranasal	late 2020
Unnamed	pan-coronavirus	No earlier than December 2020

(VBI Vaccines; National Research Council of Canada)		
Unnamed (Vaxart; Emergent BioSolutions)	non-replicating viral vector; oral	late 2020
Unnamed (Takis; Applied DNA Sciences; Evvivax)	DNA	late 2020
Unnamed (SK Biosciences, Government of Saskatchewan; Korea Centers for Disease Control and Prevention)	COVID-19 antigen subunits	September

Table.1. COVID: 19 Candidate vaccines scheduled for phase I trials in 2020. [77,78]

Vaccine candidate (developer/sponsor)	Technology	Phase of trial (participants)	Location	Duration
Ad5-nCoV (CanSino Biologics, Institute of Biotechnology of the Academy of Military Medical Sciences)	recombinant adenovirus type 5 vector	Phase I-II interventional trial for dosing and side effects (500)	China	March 2020 to December 2020[79]
Ad5-nCoV (CanSino Biologics, Institute of Biotechnology of the Academy of Military Medical Sciences)	recombinant adenovirus type 5 vector	Phase I (108)	China	March 2020 to December 2020[80]
ChAdOx1 nCoV-19 (University of Oxford)	adenovirus vector	Phase I-II randomize, placebo-controlled, multiple sites (1000)	United Kingdom	April 2020 to May 2021[81]
BNT162 (a1, b1, b2, c2) (BioNTech, Fosun Pharma, Pfizer)	RNA	Phase-I-II Of four vaccines, randomized, placebo-controlled, dose-finding, vaccine candidate-selection (7600)	Germany United States	April 2020 to May 2021[82]
unnamed (Sinovac Biotech)	inactivated SARS-CoV-2 virus	Phase-I-II randomized, double-blinded, single-center, placebo-controlled (744)	China	April 2020 to December 2020[83]
INO-4800 (Inovio Pharmaceuticals, CEPI, Korea National Institute of Health, International Vaccine Institute)	DNA plasmid delivered by electroporation	Phase-I-II (40)	United States South Korea	April 2020 to November 2020[84]
INO-4800 (Inovio Pharmaceuticals, CEPI, Korea National Institute of Health, International Vaccine Institute)	DNA plasmid delivered by electroporation	Phase-I-II (40)	United States South Korea	April 2020 to November 2020[84]

mRNA-1273 (Moderna, US National Institute of Allergy and Infectious Diseases)	lipid nanoparticle dispersion containing messenger RNA	Phase I (45)	United States	March 2020 to Spring-Summer 2021[85,86]
Covid-19/aAPC (Shenzhen Geno-Immune Medical Institute)	lentiviral vector, pathogen-specific artificial antigen presenting dendritic cells	Phase I (100)	China	March 2020 to 2023[87]
LV-SMENP-DC (Shenzhen Geno-Immune Medical Institute)	lentiviral minigene vaccine, dendritic cells modified with lentiviral vector	Phase I (100)	China	March 2020 to 2023[88]
bacTRL-Spike (Symvivo Corporation, University of British Columbia, Dalhousie University)	DNA, bacterial medium (oral)	Phase I (84)	Canada	April 2020 to December 2021[89]
unnamed (Beijing Institute of Biological Products, Wuhan Institute of Biological Products)	inactivated COVID-19 virus (vero cells)	Phase I (288)	China	April 2020 to November 2021[90]

Table.2. COVID-19: Candidate vaccine in Phase I-II trials.

Challenge studies of proposed vaccines

During the global outbreak of the novel corona virus pandemic, strategies are under consideration to fast-track the timeline for licensing a vaccine against COVID-19, especially by compressing (to a few months) the usually lengthy duration of Phase II–III trials (typically, many years).[91] Following preliminary proof of safety and efficacy of a candidate vaccine in laboratory animals and healthy humans, controlled "challenge" studies may be implemented to bypass typical Phase III research, providing an accelerated path to license a vaccine for widespread prevention against COVID-19.[92] The design of a challenge study involves first, testing a vaccine candidate for immunogenicity and safety in laboratory animals and healthy adult volunteers (100 or fewer) – which is usually a sequential process using animals first – and second, quickly advancing its effective dose into a large-scale Phase II–III trial in previously-uninfected, low-risk volunteers (such as young adults), who would then be deliberately infected with COVID-19 for comparison with a placebo control group.[93] Following the challenge, the volunteers would be monitored closely in clinics with life-saving resources, if needed. Volunteering for a vaccine challenge study during the COVID-19 pandemic is likened to the emergency service of healthcare personnel for COVID-19-infected people, firefighters, or organ donors.[94] In spite of the fact challenge studies are morally questionable due to the unknown hazards for the volunteers of possible COVID-19 disease enhancement and whether the vaccine received has long-term safety (among other cautions), challenge studies may be the only option available as the COVID-19 pandemic worsens, according to some infectious disease experts.[95] to rapidly produce an effective vaccine that will minimize the projected millions of deaths worldwide from COVID-19 infection.[96]

CONCLUSIONS

With the emergence of 2019-nCoV, there are about 120 potential vaccine candidates in the pipeline globally (Table 1,and 2), in which a wide range of technology (such as DNA-based, messenger RNA, nanoparticle, synthetic and modified virus-like particle) was applied. It will likely take around a year for most candidates to initiate phase 1 clinical trials except for those funded by Coalition for Epidemic Preparedness Innovations (CEPI). Researchers are investigating for effectual and satisfactory vaccine candidates and therapeutics for manage the deadly COVID-19. There are no effectual vaccines or specified antiviral drugs for novel corona virus (COVID-19). Hence, we have to rely exclusively on enforcing strict preventive and control measures that reduce the risk of possible disease transmission. Results obtained from the recently conducted in vitro study in opposition to COVID 19 are favorable. Direct clinical trials can be carrying out among the patients infected

with novel corona virus. Since these drugs are being used for treating other diseases and have well-established safety profiles, making the more estimation of these drugs much easier. In spite of the fact research is in progress to enhance Epidemiology, pathology, prevention, treatment, vaccine development and control of COVID-19, the documented clinical data on different therapeutic perspective for CoVs are scarce. Additional research should be carrying out toward the study of SARS-CoV-2 in suitable animal models for analyzing replication, transmission, and pathogenesis.

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