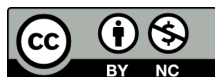


COVID-19 pandemic: potential phase III vaccines in development

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Abstract: By the end of the year 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated in China. With the passage of more than half of the year 2020, the virus has spread worldwide, making it the worst pandemic of our lifetime. The spread of the virus is controlled by imposing lockdown, which has led to severe economic slowdown around the globe. Coronaviruses are zoonotic as they spread from animals to humans. Factors such as rapid urbanization and poultry farming have permitted inter-mixing of species leading to crossing barriers and spreading of viruses to humans. Coronavirus disease (COVID-19) caused by SARS-CoV-2 is acute in most people, but it may progress to severe respiratory distress, especially in people with weak innate immunity leading to death. It is a contagious infection with the death toll mounting to above seven lakhs in the world, so there is an urgent need to find the vaccine to cure the virus, as there is no licensed drug or vaccine available. Global collaborations and increased research efforts among the scientific community have led to more than 150 clinical trials globally. This review discusses the SARS-CoV-2 replication mechanism and potential vaccine candidates in phase III COVID-19 clinical trials. Measures adopted to accomplish the fast pace of the COVID-19 trials are highlighted with an update on possible new drug targets or strategies to fight off the virus.

Keywords: coronavirus; COVID-19; SARS-CoV-2; Severe Acute Respiratory Syndrome; vaccines

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes novel coronavirus disease (COVID-19; CO-corona, VI-virus, D-disease, 19-originated in 2019) which has spread globally, affecting 21,756,357 people in 216 countries as per World Health Organization (WHO) as on 18 August 2020 [1]. This global pandemic started when pneumonia of unknown cause was detected in Wuhan, China, on 31 December 2019 as was first reported to the WHO country office. This outbreak was declared public health emergency internationally on 30 January 2020 [2].

SARS-CoV-2 causes severe respiratory illness and infects the upper and lower respiratory tract and spreads through person to person transmission when someone coughs or sneezes. Those droplets containing the virus are inhaled by the other person who is within the 6-feet distance. It can spread through people showing symptoms and asymptomatic, where people do not have any infection signs. The incubation period for the virus is for two weeks. The most common symptoms of the virus are fever, cough, tiredness and less common symptoms are sore throat, diarrhoea, aches and pains, a headache, conjunctivitis, loss of taste or smell or, a rash on the skin [3]. In advance stage,

symptoms progress from pneumonia to severe acute respiratory syndrome (SARS) or multiple organ failure (MOF) [4]. It can live in the air for up to 3 hours and on surfaces like plastic or steel for up to 2-3 days [5]. On 9 July 2020, WHO updated its guidelines after a group of researchers communicated that SARS-CoV-2 can even remain in the air in crowded indoor airspace with poor ventilation and can also spread through airborne transmission though this research requires further study [6]. We are not sure how much time it will take to eradicate the virus as we are still learning about it. Treatments provided are basically to manage the symptoms and prevent the development of complications. Many strategies like monoclonal antibodies, convalescent plasma transfusions, immunomodulators, antivirals are investigated to treat people who already have COVID-19 [7-9].

As of 18 August 2020, worldwide cases of COVID-19 have surpassed two crores and are growing swiftly. Scientists are moving forward to develop the vaccines to stop the virus from spreading. Research has shown that some degree of pre-existing immunity against SARS-CoV-2 is present in the human population, but it is not verified whether it might be due to common cold coronaviruses [10]. Therefore, herd immunity is an option by mass vaccination of the people to eradicate the virus in such a situation slowly. Herd immunity also protects at-risk populations such as babies or people who have a weak immune system and cannot resist of their own. Vaccines can build resistance by activating memory cells of the immune system. Memory cells retain the memory of the virus attack for years and regenerate antibodies when a virus attack occurs in the future. But the memory may or may not last for a lifetime for all viral infections; in such cases, repetitive booster doses of



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vaccines would be given at regular intervals as advised by the doctors. Vaccination is one of the means to set in the herd immunity in a population. Herd immunity occurs when an appropriate number of people in a community have become immune to an infectious disease reducing the likelihood of infection for individuals who lack immunity. Reproduction number (R_0) is a measure for herd immunity, which tells the average number of people that a single person with the virus can infect if they are not already immune. As per the researchers, R_0 is between 2 and 3 for COVID-19 infection, which means that one person can infect two to three people and, 50% to 67% of the people would need to be resistant before herd immunity kicks in and the infection rate starts to slow down [11].

This global issue of the current time is addressed by discussing a brief overview of coronaviruses with the proposed action mechanism of SARS-CoV-2 to enter the human cells. Potential vaccine candidates in the final race are highlighted as multiple successful vaccines that may be needed to meet the demand to vaccinate billions of people worldwide. This review also gives insight into the research community's scientific efforts, which has come together to form new initiatives to complete the trials rapidly.

Overview of Coronaviruses

Coronaviruses belong to the family Coronaviridae and belongs to four genus- Alpha, Beta, Gamma and, Delta. They were first discovered in the 1930s in domesticated chicken [12] with the first case identified in humans in the 1960s [13]. Coronaviruses are enveloped RNA viruses with positive sense single-strand RNA in its genome. Their genome size ranges from 26.4 to 31.7 kilobases. They are large spherical particles with surface projections. The viral

envelope consists of a lipid bilayer in which the structural proteins are anchored [14]. The four common coronaviruses circulating in humans and causes mild respiratory illness are; 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), and HKU1 (beta coronavirus) [15]. The other three human coronaviruses, namely severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2, belong to the beta coronavirus genus. They have spread by a crossover from animals to humans in the past [16]. SARS-CoV was the first, which occurred in 2002-2003 in the Guangdong province of China. It causes SARS infection and has origin in the bats and spread to humans via an intermediary host of palm civet cats. After almost a decade in 2012, MERS-CoV also of bat origin with camel as an intermediary host causes Middle East respiratory syndrome (MERS) originated in Saudi Arabia [17]. Similarly, in December 2019, SARS-CoV-2, which causes COVID-19, was first identified in Wuhan in China's Hubei province. Several of the first reported cases of COVID-19 had visited Huanan Seafood Wholesale Market. Bat is an animal reservoir for SARS-CoV-2 with Pangolins that were suggested to be its intermediate hosts as their genome shows 85.5%–92.4% similarity to SARS-CoV-2 [18-20]. In 2003, 774 people died by SARS-CoV with a fatality rate of 9.3%. Since September 2012, 866 deaths were confirmed by MERS-CoV with a 34.3% fatality rate. From December 2019 till 18 August 2020¹, 771, 635 deaths were reported by SARS-CoV-2 and are still counting, though it shows a less fatality rate of 1.34-3.4% compared to SARS-CoV and MERS-CoV [21]. Viral genome sequencing established that SARS-CoV-2 is 96.2% identical to the bat coronavirus and about 79% to SARS-CoV and 50% to MERS-CoV [22, 23]. There is no approved

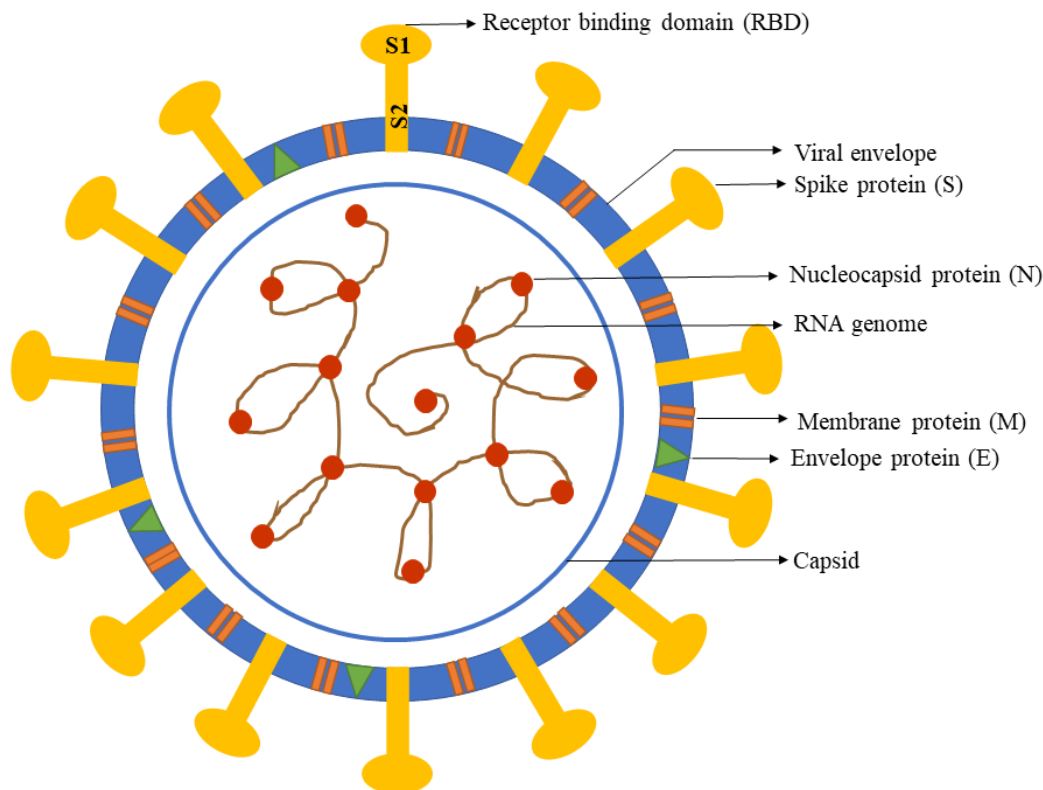


Figure 1: The structure of SARS-CoV-2 depicts structural proteins spike (S), membrane (M), envelope (E), and nucleocapsid (N).

antiviral drug or vaccine available for all the three SARS-CoV, MERS-CoV or SARS-CoV-2, though many clinical trials are in progress to find the drugs or vaccines against SARS-CoV-2 [7, 24].

Mechanism of action of SARS-CoV-2

Every day as COVID-19 research is making progress, there is an explosion of articles detailing the various aspects of SARS-CoV-2, such as structural assembly, replication, neuroinvasion [8], receptor usage [25], and cytokine storm [26]. Here, a discussion about the entry mechanism and replication of SARS-CoV-2 in human cells is done. These entry points tested in clinical trials in different protocols and combinations, can serve as targets for antiviral drugs. Still, no one has yet shown any real efficacy and safety against SARS-CoV-2 [27].

Cellular Entry of SARS-CoV-2

The structural proteins essential for the assembly and infection of the coronavirus are spike glycoprotein (S), membrane protein (M), an envelope protein (E) present on the surface of the virus, and nucleocapsid protein (N) which is present with the viral RNA genome (Figure 1). The spike protein has three major segments, a large ectodomain, a single-pass transmembrane anchor, and a short intracellular tail, which plays a significant role in anchoring the host cells. The ectodomain consists of two subunits: S1 and S2. S1 and S2 subunits are in clover-trimeric shape and form spike-like projections on its surface which give it a crown-like appearance hence the name corona, i.e., crown [27]. The S1 subunit contains the receptor-binding domain (RBD), which binds to the host cellular receptor angiotensin-converting enzyme 2 (ACE2) [28, 29]. In the endocytosis mechanism, after interaction between the S1 domain and host ACE2 receptor, spike protein is cleaved by proteases (TMPRSS2 and furin) to be primed for S2 mediated membrane fusion with the host cell [31]. S glycoprotein and ACE2 are critical in SARS-CoV-2 infection and are exciting targets for antiviral agents [32].

Membrane (M) protein on SARS-CoV-2 is a transmembrane dimeric glycoprotein that is most abundant and defines the viral envelope's shape. It increases membrane curvature and promotes viral assembly. Envelope (E) protein is the smallest hydrophobic integral membrane protein essential to release the virus. Underneath the surface proteins is the viral envelope derived from the host cell membrane and consists of a fatty layer that is broken down by soaps or detergents, thus killing the virus. The viral capsid is a protein shell that encloses the virus's genetic material and protects it from extracellular agents. Inside the capsid is the nucleocapsid protein bound to the RNA genome strand. The nucleocapsid protein of SARS-CoV-2 is interferon antagonistic and suppresses the initial innate host immune response and helps in viral replication.

SARS-CoV-2 lacks the hemagglutinin-esterase gene, which is characteristically found in lineage A of beta coronaviruses (HKU1) [33]. Though SARS-CoV-2 is 79% identical to SARS-CoV but, RBD of SARS-CoV-2 has a higher binding affinity to ACE2 than SARS-CoV supporting efficient cell entry. SARS-CoV-2 contains a furin-like cleavage site in the spike protein, which is also

present in other pathogenic viruses but not in SARS-CoV [34]. Furin preactivation enhances SARS-CoV-2 entry into target cells while in SARS-CoV, it does not have any effect. TMPRSS2 and lysosomal cathepsins (cellular proteases) have a cumulative impact with furin on SARS-CoV-2 access. Furin preactivation helps SARS-CoV-2 enter some types of cells with low expression of TMPRSS2 and lysosomal cathepsins [35]. Host protease activation is a significant factor for the spread of coronavirus infection and is an essential target for the host immune system and human intrusion strategies. The strong binding of S glycoprotein of SARS-CoV-2 to human ACE2 receptor along with furin dependent activation, makes it to spread effectively.

Replication of SARS-CoV-2

As SARS-CoV-2 enters the human host cells (such as Type II alveolar cells in the lungs), it releases its viral genome with nucleocapsid protein (N) into the cytoplasm. The released genomic RNA (positive strand) of SARS-CoV-2 act as a messenger mRNA (mRNA), and host ribosomal machinery will translate open reading frames (ORF1a and ORF1ab) into polyproteins (pp1a and pp1ab). These polyproteins are proteolyzed by cysteine like proteases ($M^{pro}/3CL^{pro}$ and PL^{pro}) into non-structural proteins (Nsp 1-16) [36]. These Nsps have an essential role in transcription and replication, thus acting as replicase and transcriptase proteins. They can block the host immune system to support viral replication such as Nsp 15, a target to control viral infections [35, 37, 38]. These Nsps establish the replicase-transcriptase complex (RTC) by combining with genomic RNA (positive strand) and replicates the positive genomic RNA to negative genomic RNA. From the negative RNA strand, more positive RNA genomes are produced via replication and sub-genomic mRNAs by discontinuous transcription. Translation of the sub-genomic mRNAs makes the respective N, M, E, and S structural proteins. Nucleocapsid protein (N) combines with the new RNA genomes (positive strand) to form ribonucleoprotein (RNP) complex [39]. Synthesized M, E and S proteins enter the endoplasmic reticulum for folding. Assembly of the RNP complex and M, E, S proteins occurs at the Endoplasmic reticulum (ER)-Golgi intermediate compartment (ERGIC) complex, making the structure of a viral envelope. From the ERGIC complex, new virions come out by making a bud-like structure. These mature viruses fuse with the plasma membrane by forming a vesicle and release the virus particles into the extracellular region by exocytosis [40]. On infection, SARS-CoV-2 causes excessive production of massive inflammatory cytokines and chemical mediators, called cytokine storm and causes damage to the lung tissue, deterioration of lung function, lung failure and is a crucial cause of death from COVID-19 [26].

As discussed above, the critical entry points of SARS-CoV-2 into human host cells, different interventional strategies are explored to suppress the spread of the virus. Antibody drugs having a high affinity to bind to RBD on SARS-CoV-2 than ACE2 can be developed, blocking the viral attachment. Vaccines can be designed to target the S2 subunit of the spike protein, which helps in membrane fusion with the host cell. Host ACE2 protein, which is relatively stable and does not mutate frequently, can be one of the targets. As virus entry requires protease activation,

cell protease inhibitors can be developed to block the SARS-CoV-2 entry [35].

Insight into the COVID-19 vaccine research

As COVID-19 posed the most significant challenge currently, there is an upsurge in the research efforts globally to find the vaccine. As SARS-CoV-2 is an RNA virus, it is challenging to make vaccines against RNA viruses compared to the DNA viruses due to their ever-changing and continuously evolving genomes. Genetic material on single-stranded RNA viruses can get cut, remixed easily compared to the double-stranded DNA viruses that are more stable. Though, negative-sense viruses have slower mutation rates as compared to positive-sense viruses [41]. For a virus to become more severe, multiple genes would have to be mutated, which is unlikely in SARS-CoV-2 in such a short time. These SARS-CoV-2 strains are still so genetically similar that mutations would not escape from the new vaccines. Though once the vaccine is made, a virus could adapt to it and develop resistance. Therefore, these mutations should be monitored as due to genetic mutations, vaccines made specifically for one strain of RNA virus may become obsolete and may lead to significant genomic variations. However, other RNA viruses that cause measles, mumps, and yellow fever have not yet developed any vaccine resistance. Research efforts made during the SARS and MERS infection provided a stimulus to start the

COVID-19 vaccine research as the groundwork was already done [42]. As COVID-19 posed the most significant challenge currently, there is an upsurge in the research efforts globally to find the vaccine. As SARS-CoV-2 is an RNA virus, it is challenging to make vaccines against RNA viruses compared to the DNA viruses due to their ever-changing and continuously evolving genomes. Genetic material on single-stranded RNA viruses can get cut, remixed easily compared to the double-stranded DNA viruses that are more stable. Though, negative-sense viruses have slower mutation rates as compared to positive-sense viruses [41]. For a virus to become more severe, multiple genes would have to be mutated, which is unlikely in SARS-CoV-2 in such a short time. These SARS-CoV-2 strains are still so genetically similar that mutations would not escape from the new vaccines. Though once the vaccine is made, a virus could adapt to it and develop resistance. Therefore, these mutations should be monitored as due to genetic mutations, vaccines made specifically for one strain of RNA virus may become obsolete and may lead to significant genomic variations. However, other RNA viruses that cause measles, mumps, and yellow fever have not yet developed any vaccine resistance. Research efforts made during the SARS and MERS infection provided a stimulus to start the COVID-19 vaccine research as the groundwork was already done [42].

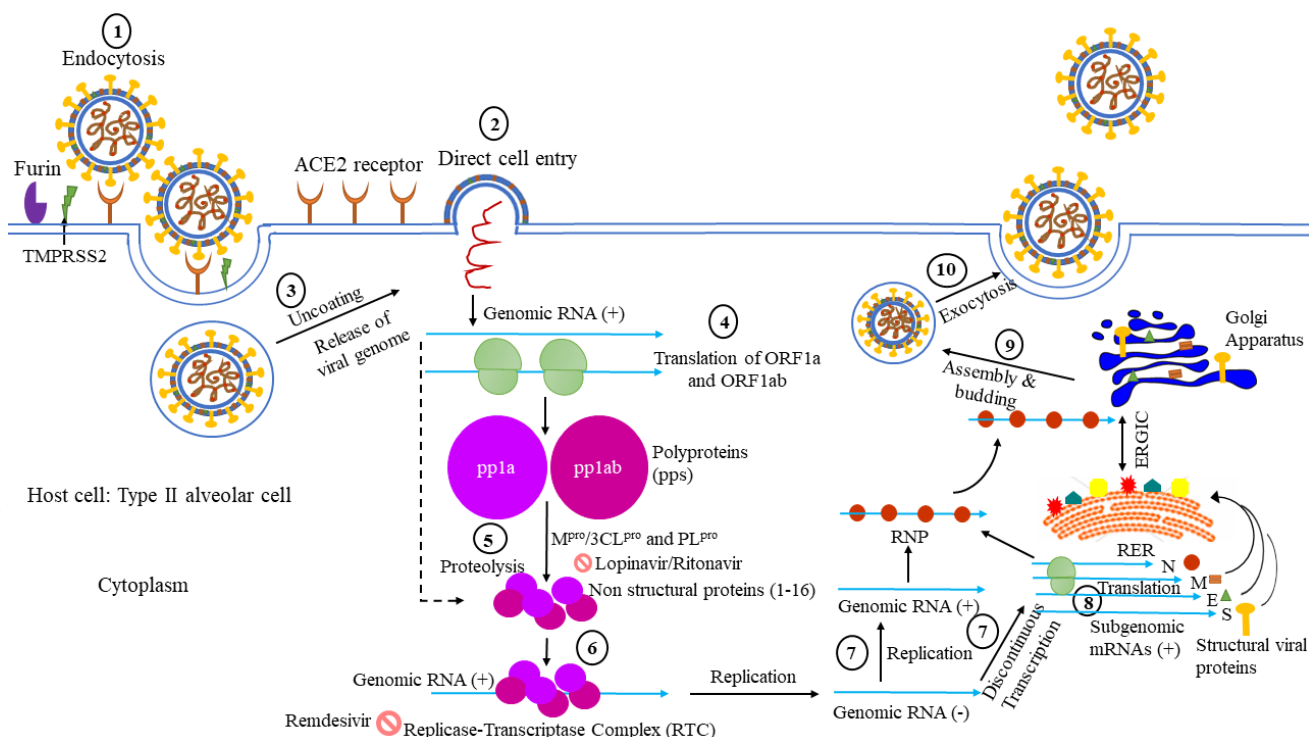


Figure 2: Various steps involved in the cell entry and replication of SARS-CoV-2 in the host cell. SARS-CoV-2 enters the host cell either by 1) endocytosis or 2) direct cell entry. The receptor-binding domain on S1 interacts with the angiotensin-converting enzyme 2 receptor on the host cell and triggering the viral cell entry. 3) & 4) Viral RNA genome is released and translated into polyproteins. 5) & 6) Polyproteins are proteolyzed into non-structural proteins that form RTC complex with genomic RNA (+). 7) RTC replicates and transcribes genome RNA (-) to develop more RNA and sub-genomic RNAs. 8) Sub-genomic mRNAs translate into structural viral proteins. 9) & 10) Genomic RNA and proteins assembled into new virions are released by the process of exocytosis. RER: Rough endoplasmic reticulum; RNP: Ribonucleoprotein complex; ERGIC: Endoplasmic reticulum Golgi intermediated complex. The figure also shows drug targets for repurposed antiviral drugs lopinavir/ritonavir and remdesivir, currently being investigated in WHO's clinical trials.

Interferons are a group of signalling proteins made and released by host cells in response to the presence of viruses causing nearby cells to heighten their antiviral defenses. Interferon β -1a has the same amino acid sequence as the naturally occurring protein called interferon β , which belongs to the class of type 1 interferons.

Interferon β has both antiviral and anti-inflammatory properties. Insufficient production of interferon β in lung cells in older people leads to increased susceptibility to SARS-CoV-2; therefore, administration of interferon β -1a results in a significant reduction in viral load and disease severity [48]. Dexamethasone, a synthetic corticosteroid, is administered to terminally ill patients of COVID-19, which suffer a hyperinflammatory state called a cytokine storm. Every inflammation begins with a series of biochemical reactions. Initially, the phospholipid membrane of cells secretes arachidonic acid by an enzyme called phospholipase A2. Another enzyme cyclooxygenase converts secreted arachidonic acid to several inflammatory mediators, including cytokines, prostaglandins, and leukotrienes. These mediators induce the body's cells and blood vessels to fight the infection. Dexamethasone forms a complex by binding to receptors, that are expressed by nearly all cells of the body. The dexamethasone formed complex inhibits the enzyme phospholipase A2 and blocks the synthesis of the inflammatory mediators [49]. While antiviral drugs like remdesivir try to stop the replication of SARS-CoV-2 inside the cells, dexamethasone counters the body's heightened inflammatory response. Thus, dexamethasone is useful as an immunosuppressant in severely ill patients and depends on ventilator support. In contrast, immune suppression during the early phase of the viral infection might allow increased viral replication and aggravate the disease. These combined antiviral drugs are helping patients who are already infected with SARS-CoV-2. In several research articles, various repurposed drugs which are currently used in COVID-19 treatment are mentioned [7, 8, 50, 51]. Among them, individual treatments of lopanivir/ritonavir and hydroxychloroquine have been discontinued for COVID-19. The interim results of these drugs in the clinical trials have shown little or no reduction in the mortality rate of hospitalized COVID-19 patients than a standard of care [43]. Many drug repurposing studies have demonstrated promising candidates from cheap and common drugs. Still, more extensive research is needed, and many big pharma giants do not want to invest in drugs whose patents have already lapsed.

Typically, drug development involves various stages, starting with discovering several drug candidates, then filtering them in the pre-clinical stage where the safe dosage is determined to start trials in humans and assess their potential toxicity (Figure 3). The clinical stage involves phase I, which evaluates the potential vaccine candidates for safety and immune response in healthy volunteers at different doses in 20-100 people and takes 1-2 years to complete. Phase II is double-blind, randomized placebo-controlled study involving 100-500 volunteers having the disease and evaluates safety, efficacy, optimal dose and vaccine schedule for 2-3 years, in phase III researchers,

assess the drug's effectiveness, monitor side effects, compare it to other commonly used treatments or placebo in 1000-5000 of volunteers and typically takes 2-4 years [52]. The trial data is reviewed by the regulatory authority that approves new drugs, which can take up to 1-2 years. The next stage is the manufacturing of vaccines which is highly specialized and regulated and should be of the same standard as the drugs used in clinical trials [53]. In phase IV or post-marketing studies, long-term risks and benefits of medication, interaction with other medicines, and side effects are evaluated. Overall, the clinical trial is completed in approximately ten years if it goes serially, but for COVID-19 vaccine development, this long duration cannot be afforded. Thus, the international community, governments, and industry are working together and taking many measures to accelerate clinical trials to produce coronavirus vaccine [54]. In COVID-19 vaccine trials, regulators have allowed testing the vaccine parallelly in animals and patient's severe cases. They have permitted a combination of phases I and II, which has dramatically reduced the timeline. Follow up for a response in volunteers is done in a lesser amount of time [55].

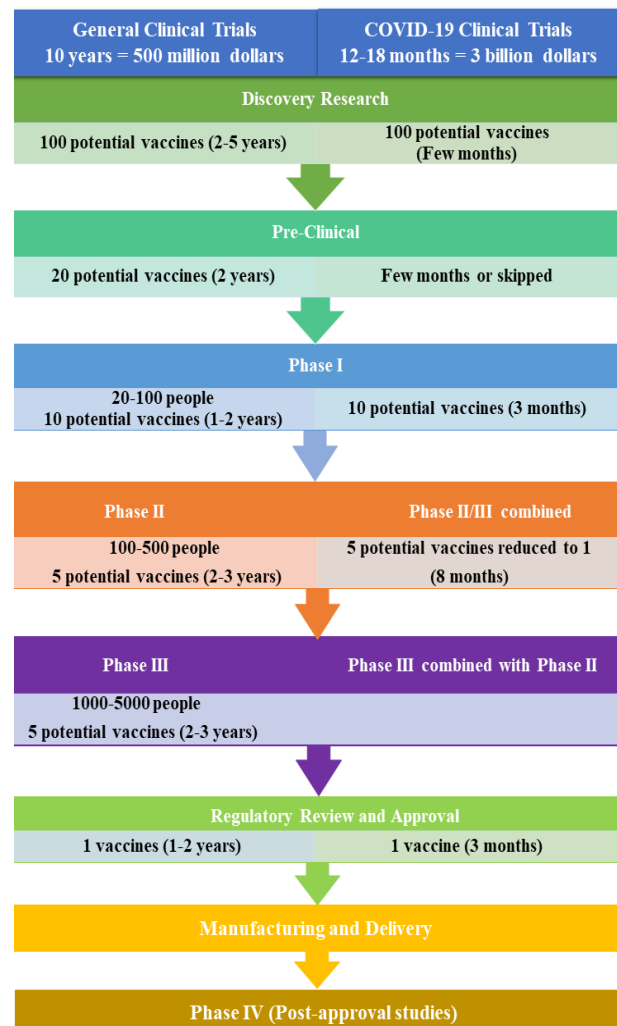


Figure 3: Comparison of drug development stages in terms of timeline in general and COVID-19 clinical trials.

Figure 3 compares the steps of vaccine development in general clinical trials to COVID-19 clinical trials. Although the timeline for generalized clinical trials cannot be shortened to 10-18 months while maintaining the integrity of science and research, it can pave the way for future reforms in regulatory policies sustaining trials efficiency in a faster way. The development, production, and equitable distribution of COVID-19 vaccines are accelerated by global collaboration among various countries that have been launched by WHO as the COVID-19 Vaccine Global Access (COVAX) Facility. The COVAX Facility forms a vital part of the COVAX (vaccine) pillar of the Access to COVID-19 Tools (ACT) Accelerator. ACT brings together governments, scientists, industrialists, civil society, and philanthropists and global health organizations [Bill & Melinda Gates Foundation, Coalition for Epidemic Preparedness Innovations (CEPI), Foundation for Innovative New Diagnostics (FIND), Global Alliance for Vaccines and Immunizations (GAVI), Global Fund, Unitaid, Wellcome, WHO and World Bank]. COVAX is co-led by GAVI, CEPI, and WHO. They are working in partnership with developed and developing country vaccine manufacturers to accelerate the COVID-19 vaccine development and fair access to every country in the world (Figure 4). The goal of COVAX is to deliver 2 billion doses by the end of 2021 after regulatory approval and WHO pre-qualification [56].

COVID-19 vaccine candidates in phase III clinical trials

Due to worldwide research efforts in COVID-19 vaccine development, more than 165 candidates are in a clinical development stage as on 18 August 2020. Strong global governance and cooperation are required between governments and pharmaceutical companies for the research, manufacturing, and to share the costs of SARS-CoV-2 vaccines to be available [57].

The US National Institutes of Health (NIH) has partnered with 18 biopharmaceutical companies to speed up the drug and vaccine candidate's development. Table 1 list the selected phase III COVID-19 vaccine candidates. The data was compiled for vaccine candidates by searching the tracker resources from World Health Organization (<https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>), Regulatory Affairs Professional Society ([https://www.raps.org/news-and-articles/2020/3/covid-19-vaccine-tracker](https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker)), The New York Times (<https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html>) and the Milken Institute (<https://covid-19tracker.milkeninstitute.org/>). The US government has chosen three vaccine candidates to fund for phase III clinical trials under programme Operation Warp Speed (OWS); Moderna's mRNA-1273 in July 2020, The University of Oxford and AstraZeneca's AZD1222 in August 2020, and Pfizer and BioNTech's BNT162 in September 2020 [58]. The six COVID-19 vaccine candidates discussed ahead have advanced to phase III clinical trials.

1. The University of Oxford and AstraZeneca

The work on the AZD1222 vaccine developed by Oxford University's Jenner Institute with the Oxford Vaccine Group began on 20 January 2020. AstraZeneca has joined the university and its spinout company Vaccitech in April. Vaccitech has shared rights with Oxford University to the platform technology behind the vaccine candidate. It is expected that phase III trials will end by November in the United States and Brazil. AZD1222 (ChAdOx1 nCoV-19) is a SARS-CoV-2 vaccine candidate made from a virus (ChAdOx1), which is a weakened version of a common cold virus (adenovirus) that causes infection in chimpanzees. It is expected that phase III trials will end by November in the United States and Brazil. AZD1222

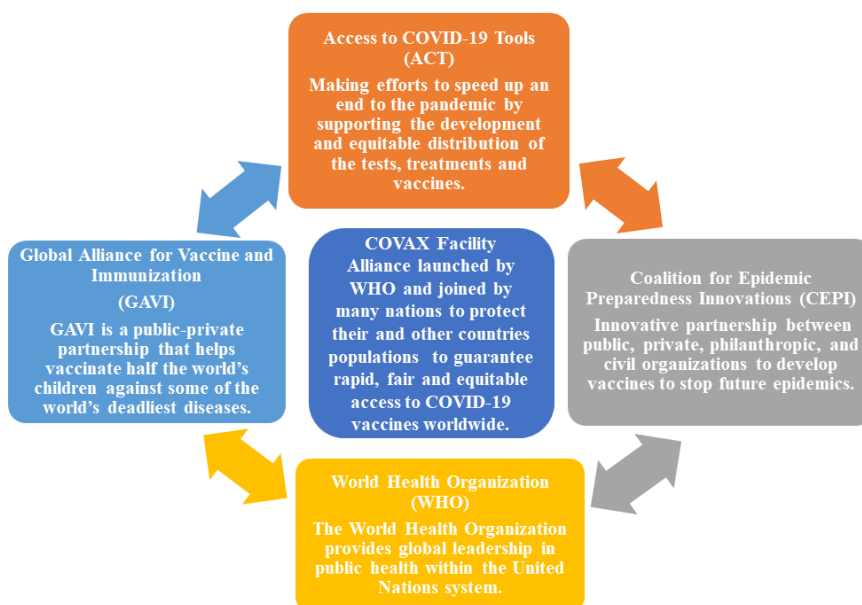


Figure 4: Global alliance among various organizations for the equitable distribution of COVID-19 vaccine in developed and developing countries.

(ChAdOx1 nCoV-19) is a SARS-CoV-2 vaccine candidate made from a virus (ChAdOx1), which is a weakened version of a common cold virus (adenovirus) that causes infection in chimpanzees. This adenovirus is genetically modified so that it does not replicate in humans. After vaccination, cells express surface spike protein that travels

to the lymph nodes and primes the immune system to make neutralizing antibodies that bind to spike glycoprotein and attack SARS-CoV-2 if it later infects the body [59]. In addition to this, the vaccine also induces a type of white blood cell called T-cells, which can destroy the body cells if they get infected by the virus (Figure 5A).

Table 1: Selected COVID-19 vaccine candidates in phase III clinical trials.

Sponsor	Vaccine candidates	Vaccine platform	Type of candidate vaccine	Clinical trial registration number
University of Oxford, AstraZeneca	AZD1222	Non-replicating viral vector	Adenovirus vaccine	Phase III (ISRCTN89951424)
Moderna/NIAID	mRNA-1273	RNA-based	LNP encapsulated-mRNA	Phase III (NCT04470427)
Sinovac	CoronaVac	Inactivated virus	Inactivated virus	Phase III (NCT04470427)
Pfizer, BioNTech, Fosun Pharma	BNT162	RNA-based	3-LNP-mRNAs vaccine	Phase III (NCT04368728)
Wuhan Institute of Biological Products, Sinopharm	New Crown	Inactivated virus	Inactivated virus	Phase III (ChiCTR2000034780)
Beijing Institute of Biological Products, Sinopharm	BBIBP-CorV	Inactivated virus	Inactivated virus	Phase III (ChiCTR2000034780)

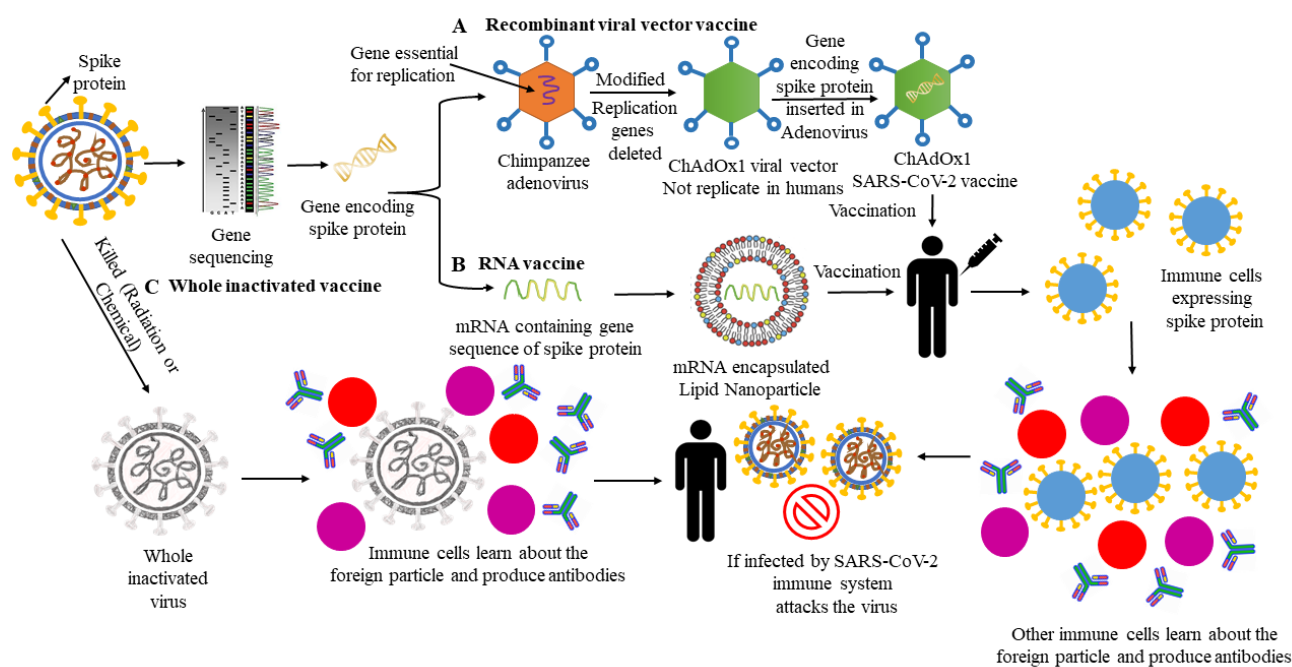


Figure 5: Different approaches used in SARS-CoV-2 vaccine development for candidates which are in phase III clinical trials. The whole-genome sequence of SARS-CoV-2 is deposited in the public database from where gene sequence encoding for spike protein is taken. A) Recombinant viral vector vaccine- This approach is used by the University of Oxford group, which uses a modified adenovirus vector (inactivated, non-replicating) to express spike protein of SARS-CoV-2. When an individual is vaccinated, the spike proteins are recognized by the immune system to elicit an immune response. B) RNA vaccine- Moderna and Pfizer are using the RNA vaccine development method. In this technology, the mRNA of the spike protein is encapsulated into lipid nanoparticle. When injected, the encapsulated mRNA then translates to the spike proteins expressed on the immune cells. Other immune cells learn about the spike proteins, and, when infected by SARS-CoV-2, recognize it as foreign. C) Whole inactivated vaccine- Sinovac, Wuhan Institute of Biological Products, and Beijing Institute of Biological Products use this approach where the killed pathogen is vaccinated, which is recognized as foreign by the host's immune system to produce antibodies. When re-infected by SARS-CoV-2, the body has a robust immune response against it.

2. Moderna and the National Institute of Allergy and Infectious Diseases (NIAID)

In collaboration with investigators from the Vaccine Research Center at the NIAID (a part of the US NIH), Moderna has selected an mRNA vaccine candidate (mRNA-1273) against SARS-CoV-2 [60]. There are not yet any licensed RNA or DNA vaccines to be used in humans. The phase III clinical trials of mRNA-1273, called the COVE (Coronavirus Efficacy), have already begun. mRNA used in vaccination is safe to use since they cannot become part of the person's chromosomes. The mRNA vaccine contains only a short synthetic version of the viral mRNA, which encodes only the antigen protein and mimics the natural infection of the SARS-CoV-2. This synthetic viral mRNA is recognized by the host body, which then produces the viral protein itself. However, as mRNA is not a very stable molecule, but through chemical modifications, mRNA is stabilized and is packaged into an injectable form using liquid nano-particles [61]. The mRNA-1273 is a lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes a stable form of the spike protein of SARS-CoV-2. The encapsulated mRNA-1273 then travels to the immune cells (lymph nodes) and instructs them to make copies of the spike protein on their surface as if SARS-CoV-2 infects them. Other immune cells learn about the spike protein and prepare themselves for the future response to SARS-CoV-2. Moderna has collaborated with Catalent on 25 June 2020 to perform large-scale, commercial fill-finish manufacturing of Moderna's mRNA-1273 COVID-19 vaccine at Catalent's biologics facility in Indiana, US [62] (Figure 5B).

3. Sinovac

Sinovac Biotech Ltd. (China-based biopharmaceutical company) developed a vaccine candidate CoronaVac based on an inactivated version of the SARS-CoV-2 whole virus. CoronaVac is made by growing the pathogen in the lab and then killing it by heat, chemicals, radiation, or any other method. After virus destruction, some of its integrity is maintained to be recognized by the immune system to produce an adaptive immune response (Figure 5C). This technology is different as compared to the next-generation platforms that involve using RNA or DNA of SARS-CoV-2. In comparison to the newer technologies, these inactivated vaccines take a longer time to manufacture as the virus needs to be cultured in the lab and then inactivated. Since the killed pathogens do not reproduce in a properly produced vaccine, booster shots are required periodically to reinforce the immune response [63]. CoronaVac's large-scale phase III clinical trials are launched in Indonesia.

4. Pfizer, BioNTech, and Fosun Pharma

Biopharmaceutical New Technologies (BioNTech) vaccine development programme (BNT162) is also based on mRNA technology and supported by Pfizer's global vaccine development capabilities. BioNTech has collaborated with Fosun Pharma (a Chinese pharmaceutical company) to manufacture BNT162 in China, where it is expected to conduct clinical trials.

BioNTech is developing four experimental vaccines in the BNT162 vaccine evaluating programme. Each BNT162 vaccine has a unique combination of mRNA format with a target antigen. Among the four vaccine candidates, two of them include modified nucleoside mRNA, one comprises uridine containing mRNA, and the fourth contains self-amplifying mRNA. Each mRNA vaccine candidate combines with LNP formulation. The smaller RBD of the spike protein (essential for eliciting antibodies that can inactivate the virus) includes two of the vaccine candidates (one of them is BNT162b1), and the full-length spike protein antigen includes the other two candidates (such as BNT162b2). BNT162b1 and BNT162b2 are both nucleoside-modified RNAs, formulated in LNPs (Figure 5B). BioNTech's BNT162b2 candidate is in phase II/III stage of clinical trials [64].

5. Wuhan Institute of Biological Products and Sinopharm

Sinopharm (China National Pharmaceutical Group Co., Ltd.) is the largest pharmaceutical group in China. Wuhan Institute of Biological Products Co. under the Sinopharm and the Wuhan Institute of Virology under the Chinese Academy of Sciences of Biological Products Co. developed a COVID-19 inactivated vaccine "New Crown." New Crown is made of virus particles grown in a lab culture, usually in Vero cells (kidney cells extracted from an African green monkey) (Figure 5C). These viruses lose the capacity to cause infection and lack disease-producing capability [65]. Phase III trials for the same started on 17 July 2020 in United Arab Emirates.

6. Beijing Institute of Biological Products and Sinopharm

China National Biotec Group, a unit of the Sinopharm, is developing another similar inactivated novel coronavirus vaccine in collaboration with the Beijing Institute of Biological Products in Phase III testing in humans (Figure 5C).

Many countries are running the race to become the first one to approve the COVID-19 vaccine. On 29 June 2020, China's military has received the nod to use the Ad5-nCoV vaccine (Adenovirus vaccine) candidate as a "especially needed drug" developed by China's CanSino Biologics Inc. as it was proved safe and efficient in the clinical trials [NCT04341389](https://clinicaltrials.gov/ct2/show/study/NCT04341389) [59]. On 11 August 2020, Russia has announced to become the first country to approve the anti-SARS-CoV-2 vaccine named "Sputnik V" (a reference to the world's first satellite) developed by Moscow's Gamaleya Institute. There is skepticism about Russia's vaccine as the only phase I clinical trial results have been made public. It is not specified whether all the three phases of the clinical trials have been completed. Earlier, it was said that phase III human trials for its effectiveness would be done in real-life situations after the shot receives regulatory approval [66]. Sputnik V uses non-replicating viral vector "adenovirus" containing gene-specific spike protein as in other vaccine candidates. The difference in comparison to other strategies is that Sputnik V uses two adenovirus vectors: Ad26 and Ad5, instead of a single

adenovirus variant. In the first dose, Ad26 is administered, and after 21 days, the second dose of Ad5 is given. This double vector approach has an advantage as after the first dose, antibodies are produced against the Ad26 serotype. The second dose is of Ad5 serotype; therefore, the body is stimulated to produce enhanced immune response [67]. Phase I/II trial results of Sputnik V have shown antibody production in all the trial participants though, the sample size was small, and further studies will be carried out in elderly [68]. It seems remarkable to see the COVID-19 vaccines finally reaching the market, but this should not only be in haste to boast it off. The results should be validated by published scientific data and registered clinical trials so that the launched vaccines should not be ineffective, unsafe, and with side effects.

The scenario of COVID-19 vaccine trials in India

With time, India has become the third-worst affected country struck by COVID-19, with more than 51,797 deaths up to 18 August 2020. Thirty Indian companies are in various stages of developing COVID-19 vaccines. Among them, at least seven companies—Bharat Biotech, Zydus Cadila, Serum Institute, Indian Immunologicals, Mynvax, Panacea Biotec, and Biological E, have got approvals to work further on the coronavirus vaccine.

Among them, Covaxin™ is India's first indigenous COVID-19 vaccine developed by Bharat Biotech International Limited (BBIL) in collaboration with the Indian Council of Medical Research (ICMR)-National Institute of Virology (NIV). The vaccine is the first to get a regulatory nod from the Drug Controller General of India (DCGI) for phase I & II human clinical trials. These double-blind, randomized clinical trials commenced on 15 July 2020. Scientists have isolated and cultured 11 strains of SARS-CoV-2, which can develop vaccines and aid in research. The strains of SARS-CoV-2 were isolated by ICMR-NIV and transferred to Bharat Biotech in May. Pre-clinical trials completed by Bharat Biotech have shown promising results with extensive safety and effective immune responses [69]. Covaxin is an inactive virus vaccine developed by killing the SARS-CoV-2 virus that could not infect or replicate and then use its particles in dosage form to build immunity by helping the body create antibodies against the dead virus [70].

Zydus Cadila, Healthcare Ltd., is the second drug manufacturer in India to develop COVID-19 vaccine candidate ZyCoV-D at its Vaccine Technology Centre at Ahmedabad, India. It has also received the approval from DCGI for Phase I/II clinical trials [69]. ZyCoV-D is a DNA vaccine where DNA codes for specific proteins (antigens) from the pathogen SARS-CoV-2. DNA injected in vaccine form in the patient is taken up by the cells. Proteins are synthesized based on the plasmid's genetic code that contains amino acid sequences characteristic of the SARS-CoV-2 virus. These proteins are recognized as foreign when processed by the host cells and displayed on their surface, thus alerting the immune system. In animal studies, ZyCoV-D induced a 'strong immune response' in mice, rats, guinea pigs, and rabbits. The antibodies generated entirely neutralized the wild type virus when tested using a virus neutralization assay, which indicates the protective potential of the vaccine [71]. Both BBIL and Zydus Cadila

have started the phase II trials in India. Indian Immunologicals Limited (IIL), another pharmaceutical company, is developing a vaccine in partnership with Griffith University, Australia, using a deoptimization technology that directly targets the cells infected by SARS-CoV-2. The vaccine is in its initial stage with pre-clinical and clinical studies still going on. Mynvax, a Bengaluru-based medical pharmaceutical startup associated with the Indian Institute of Science (Bengaluru), is conducting pre-clinical trials for the protein-based COVID-19 vaccine. AstraZeneca working with the University of Oxford to develop an adenovirus vector vaccine in phase III trials has tied up with the Serum Institute of India (SII) to produce the vaccine on a large scale. SII has also got the approval to start phase III human trials of Oxford's vaccine in India. Panacea Biotec Limited, a Delhi-based biotechnology company, is developing an inactivated virus strain that has shown significant pre-clinical trial results conducted in the US. It has also signed a partnership with Refana Inc., a US-based pharma company, to develop, manufacture, and distribute an investigational COVID-19 vaccine. Biological E, a Hyderabad based company, is also developing a vaccine against SARS-CoV-2, which is in pre-clinical stage [72].

Recent research on potential future vaccine candidates or targets to treat COVID-19

In this section, the purposed new drugs or their targets for COVID-19 treatment are discussed. In a rare neurological disorder known as IgM monoclonal gammopathy, the immune system targets Human Natural Killer-1 (HNK-1; a sulfated trisaccharide) epitope, a component of the myelin sheath known as MAG (myelin-associated glycoprotein). To treat the disease, investigators have developed a biodegradable poly-l-lysine backbone with multiple copies of this sulfated HNK-1 trisaccharide, poly(phenyl disodium 3-O-sulfo- β -glucopyranuronate)-(1 \rightarrow 3)- β -d-galactopyranoside (PPSGG) to remove anti-MAG IgM autoantibodies from the blood while not activating the immune system [73]. Based on this strategy to impair the cellular uptake of the SARS-CoV-2 virus complex, polysaccharides (high mannose, hybrid and complex-type glycans across the N-glycosylation sites) can be constructed similar to the RBD (22 glycan-binding sites) of spike protein in SARS-CoV-2 which might block the binding of SARS-CoV-2 to its receptor (ACE2) [74]. These carbohydrate mimics of the spike protein conjugated to a carrier or a backbone serve as potential vaccine candidates who might provoke an immune response to the spike protein, successfully preventing life-threatening disease.

In research by Araujo *et al.*, the administration of amantadine in patients who have Parkinson's disease and have also tested positive for the SARS-CoV-2 virus have not shown any COVID-19 related medical implications [75]. Amantadine is an antiviral drug against the influenza A virus and blocks the initial stage of viral replication. The proposed mechanism for influenza A virus replication is as it enters the cell, an endosome is formed with an acidic pH of 5. The M2 protein forms a proton channel, which carries the protons inside the virus particle. Amantadine can cross the endosomal membrane as it is lipophilic and interrupt the virion's release into the cell blocking the early viral

replication of influenza A virus. Similarly, docking studies suggest that amantadine interaction with the amino acids ALA22 and PHE26 blocks the proton channel [76]. From this study, it is envisioned that amantadine being a lipophilic molecule, may enter the E-channel of the SARS-CoV-2, preventing the release of the viral nucleus into the cell. Amantadine is also one of the drugs studied (*in vitro*) at the time of SARS [77].

SARS-CoV-2 relies on the activity of viral proteases: M^{pro} (the main protease) or 3CL^{pro} (the chymotrypsin-like protease) present in Nsp 5 and PL^{pro} (the papain-like protease) present in Nsp 3 to generate functional replicase complex and enable viral spread (Figure 2). PL^{pro} is also involved in cleaving proteinaceous post-translational modifications (ubiquitin-like protein ISG15) on host proteins from interferon responsive factor3 (IRF3) as an evasion mechanism against the host antiviral immune responses. Shin *et al.* have shown that GRL-0167 (naphthalene based inhibitor) mediated inhibition of PL^{pro} in SARS-CoV-2 exhibits a dual therapeutic strategy to hamper the viral replication by blocking the ongoing viral synthesis and increasing IRF3ISGylation (protein modification process), thereby increasing antiviral signalling via TBK1 (a kinase) and IRF3 regulating antiviral immune response [78]. Hence, exploring different therapeutic options will help in finding the treatment for COVID-19 in the future.

Conclusion and Future Perspectives

As COVID-19 has created a stressed environment worldwide and to overcome this global life and health crisis, several therapeutic strategies are adopted. To provide immediate relief to the COVID-19 patients, already proven and licensed antiviral drugs are being repurposed for its treatment until SARS-CoV-2 vaccines become commercially available. For better solutions, multifaceted collaborations are done between government organizations, pharma companies, academic, and research institutions to bring a positive outcome to the masses. This review gives the recent update about the potential vaccine candidates, the frontrunners in COVID-19 clinical trials, and will be available for the masses to achieve herd immunity. Different technologies are used for vaccine development worldwide, and each type offers unique benefits and challenges that implies more chances to control the virus even if one of the potential candidates does not work.

Technological advancement in vaccine development coupled with publicly data sharing, reporting, and working in partnerships has led the foundation for rapid vaccine progress, with six of them already in phase III trials. Fast-paced and parallelly conducted stages in COVID-19 vaccine trials can help make future policies to shorten the trial time while maintaining the efficiency of the clinical trials. This global pandemic has prepared the world to work together responsively to deal with future outbreaks. As SARS-CoV-2 vaccines are in phase III clinical trials, it is assumed that the vaccine will be available in early 2021, bringing relief to the jeopardized economy.

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