COVID-19: An Overview of Current progress and prospects in the frantic race to develop upcoming safe and effective SARS-CoV-2 vaccine Candidates

Lahcen WAKRIM, Mohammed Timinouni, Salsabil HAMDI.

Instiutt Pasteur du Maroc, Casablanca, Morocco
*Corresponding Author E-mail: Lahcen WAKRIM

SUMMARY

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It quickly spread around the world after its first emergence in Wuhan in December 2019 to become a global pandemic with millions of infections worldwide. As of 1 November 2020, nearly 46 million cases have been reported globally and 1.2 million patients succumbed to the viral disease. Due to the lack of efficient and specific therapeutic and prophylactic options available and the need to contain the epidemic, and its economic, political, cultural, demographic and societal consequences, there is a strong consensus globally only the development of a safe and effective vaccine against COVID-19 is the best way to control and ultimately end the pandemic. Faced with the urgency imposed by the speed of expansion of covid-19, scientists are led to launch themselves into a race against the clock to produce a safe and effective coronavirus vaccine by next year. Once the vaccine has been developed, strong international coordination and cooperation between all stakeholders in the vaccine production process will be needed to ensure equitable availability of the vaccine to the global population.

Introduction

On March 11, 2020, the World Health Organization declared the Coronavirus disease 2019 (COVID-19) outbreak as a pandemic (Wu et al. 2020). COVID-19 was firstly reported in Wuhan city, the capital of Hubei, China (Lam et al. 2020). The etiological agent of COVID-19 has been confirmed on 7 January 2020 as a novel severe acute respiratory syndrome coronavirus 2 which is originally hosted by bats and might have been transmitted from zoonotic coronaviruses to humans by means of pangolin (Lam et al. 2020, WHO 2020) or other wild animals before
subsequently spread by means of human-to-human transmission within a few months after the first case (Lu et al. 2020, Zhang et al. 2020). In a preliminary report, complete viral genome analysis revealed that the virus shared 88% sequence identity to two bat-derived SARS-like coronaviruses, but more distant from SARS coronavirus (Zhou et al. 2020).

As COVID-19 outbreak has triggered enormous critical challenges for the public health, research and medical communities and serious economic loss that weigh heavily on the world order, it is urgent to understand the ongoing situation and to build strategies to contain the viral spread. It is now evident that the best way to control and ultimately end the pandemic is to develop a safe and effective vaccine against coronavirus SARS-CoV-2. Currently, global institutions and companies have started to develop vaccines for the prevention of COVID-19. Here, we review the current status of vaccine development for COVID-19. The publication of the genetic sequence of SARS-CoV-2 on 11 January 2020 (Wu et al. 2020), had elicited intense Research and development activity worldwide to develop a vaccine against the disease.

Under normal circumstances, the development of a vaccine goes through several stages which can last up to 12 years before its approval. This process requires years of research and testing before reaching the clinical stage, but the scale of the humanitarian and economic impact of the COVID-19 pandemic is driving evaluation of next-generation vaccine technology platforms through novel paradigms to accelerate development of a safe and effective coronavirus vaccine, and the first COVID-19 vaccine candidate entered human clinical testing with unprecedented rapidity on 16 March 2020. As of December 17, 2020, more than 223 vaccine candidates are under active investigation, among which 166 are in pre-clinical development and 57 in clinical development (WHO 2020b). These vaccines are developed using various technology platforms including 17 protein subunits, 9 non-replicating viral vectors, 7 inactivated viruses, 7 DNA vaccines, 7 RNAs, 3 replicating viral vectors and 1 live attenuated virus (WHO 2020b). Although COVID-19 is caused by a new coronavirus, previous research on other coronavirus vaccines, such as Feline-CoVs, MERS-CoV, SARS-CoV has provided valuable information for the rapid development of COVID-19 vaccine.

**Different stages of vaccine development:**

Even before starting clinical trials on humans, a test phase known as the "preclinical studies" is necessary. In the first step, researchers work on cells and animals such as mice or monkeys to determine the immunogenicity of a new vaccine. This step also makes it possible to verify the safety of the vaccine formulation, either the optimal doses which make it possible to protect without causing undesirable effects, and finally the tolerance of the subjects, or the side effects of the product. In these preclinical tests carried out on different animal species researchers use the same route of administration as that which will be used in humans.

Once the preclinical tests have been successfully carried out, the vaccine enters the stage of clinical trials, carried out on humans, which comprises three phases.

During phase 1, the product is administered to a small group of healthy people, between 10 to 100 volunteers. The objective is then to ensure the safety of the vaccine in injected subjects.

In phase 2, hundreds of healthy volunteers are recruited to determine the efficacy of the vaccine, its ability to produce antibodies and also the amount of vaccine to be administered for each subject.

A crucial phase 3 is finally carried out on a much larger sample of people, around several thousand split into
groups, such as children and the elderly. The vaccine is administered to confirm its safety and effectiveness taking into account its side effects. This phase involve a control group which will receive a placebo.

Once a vaccine has been placed on the market, pharmacovigilance activities make it possible to detect, evaluate, understand, prevent and communicate any undesirable effects resulting from vaccination or any other problem linked to the vaccine or vaccination. Long-term follow-up is often carried out in order to demonstrate that the protection provided by the vaccine is safe and durable.

During a pandemic, researchers are often forced to speed up vaccine development by combining phases. This is the case with coronavirus vaccines for which phases 1 and 2 are combined to test the vaccines directly on hundreds of people. If investigators observe worrying symptoms in the volunteers, they can temporarily suspend a trial to take the time to identify and mitigate the risks, and the development process can resume or be abandoned.

There are many approaches to vaccine development which vary depending on the type of formulation. This difference affects how they are used, how they are administered and they are stored. Vaccines may be viral (live or inactivated), viral vector, subunit (protein or polysaccharide) or nucleic acid (DNA or RNA). Combination vaccines may include inactivated, protein-based and/or protein-conjugated polysaccharide vaccine components. There has been an increased focus on vaccine development using the viral-vector and nucleic-acid based platforms since the appearance of the SARS-CoV-2 virus and COVID-19 disease in late 2019. Different vaccines can cause different side effects, and it is important to be familiar with these different types and know how to manage them to ensure their safety and effectiveness and to take into account their suitability for all sections of the population, especially pregnant women and immunocompromised recipients.

**Vaccines can be divided into:**

**Live attenuated vaccines**

Live attenuated vaccines are derived from whole alive and functional disease-causing virus or bacteria which have been weakened under laboratory conditions so it can replicate in the body for long time and elicited a strong and lasting protective immune response without causing the disease in healthy people. Live attenuated microorganisms will grow in a vaccinated individual providing continual antigenic stimulation during sufficient time for memory cell production. Attenuated vaccines are mostly produced passing the wild-type pathogen through a series of cell cultures or animal embryos. With each passage, the pathogen loses its ability to replicate in human cells. Eventually, an attenuated virus will be unable to replicate well (or at all) in human cells, and can be used in a vaccine. However, live vaccines are not suitable for people who have a compromised immune system response. Administration of a live attenuated vaccine to these people may cause severe disease as a result of uncontrolled replication of the vaccine virus.

One concern to be considered is the possibility that the vaccine virus will revert to a wild type capable of causing disease due to mutations that are frequently generated during replication of the viruses composing a live attenuated vaccine. However, it is taken into consideration to limit the ability of the vaccine virus to replicate when developing an attenuated vaccine. Protection against a live attenuated vaccine generally lasts longer than that provided by an inactivated vaccine. The protective immunity conferred by a live attenuated vaccine is generally stronger and lasts longer than that provided by inactivated vaccine.

**Inactivated vaccines**

One alternative to attenuated vaccines are inactivated vaccines produced by inactivating a pathogen, using heat or chemicals such as formaldehyde or formalin. This
destroys the pathogen’s ability to replicate, but keeps it “intact” so that the immune system can still recognize it. Because inactivated pathogens can’t replicate at all, they can’t revert to a more virulent form capable of causing disease as live attenuated vaccines. However, they tend to provide a shorter length of protection than live vaccines, and are more likely to require adjuvants to generate strong and lasting immune response.

Unlike live attenuated vaccines, the administration of inactivated vaccines to people with impaired immune system response does not carry any potential risk; however, a person with an impaired immune system response may not develop the same level of protection after vaccination as a healthy person receiving the vaccine (Goossen et al. 2009, Bat et al. 2010, Meerveld-Eggink et al. 2011, Altamirano-Diaz et al. 2011). Some inactivated vaccines may also require repeated doses to strengthen and lengthen the immune response to the vaccine conferring protection against disease (Duchini et al. 2001, Soesman et al. 2000).

Subunit vaccines also called ‘acellular’

Subunit vaccines contain only components, or antigens, chosen as targets for their key role in neutralizing infection. Unlike whole vaccines, subunit vaccines are safer and easier to produce. However, antigens alone are not sufficiently immunogenic to induce long-term protective immunity, hence the need to often complex them with adjuvants to generate a strong protective immune response (Zhang et al. 2020b). The strength of the use of only essential antigens in the vaccine preparation is the reduction of the risk of inducing side effects.

Subunit vaccines can be classified into protein-based subunit vaccines, polysaccharide vaccines and conjugate subunit vaccines (WHO 2020c).

Protein-based subunit vaccines

Protein-based subunit vaccines may be obtained by isolating a specific protein from a pathogen via genetic engineering. A gene coding for a vaccine protein is inserted into genetic material of producer cells in culture. When the carrier producer cell grows, the vaccine protein is also produced. The immune system will recognize the expressed protein and provide future protection against the target virus (Bill 2015, Alexandra et al. 2019, Bellini et al. 2020). Unlike vaccines based on the whole pathogen, subunit vaccines include only components, or antigens, that best stimulate the immune system. While this technology can make vaccines safer, cheaper, easier to produce and more stable than those containing whole viruses or bacteria, inoculation of protein subunits alone are not sufficient to induce adequate long-term immunity. These immunogens often requires the incorporation of adjuvants to elicit a strong protective immune response (Steven et al. 2009, Dennis et al. 2009). The risk of side effects is also minimized by restricting the immune system’s access to the whole pathogen.

Polysaccharide Vaccines

Some bacteria, when infecting humans, are protected by a polysaccharide capsule that allows them to evade the body's defense systems, especially in infants and young children (Barrett 1985, Bruyn et al. 1991). Polysaccharide vaccines trigger an immune response against molecules present in the capsule of the pathogen. These molecules are small and their immunogenicity is often lower. They induce only short-term immunity, lack of immune memory and not effective in infants and young children under 18 to 25 months. The association of polysaccharide antigens with protein antigens in conjugate form induces a higher and more durable antibody response (Cadoz 1998, Moore et al. 2000).
Conjugate subunit vaccines

Conjugate subunit vaccines induce an immune response against molecules expressed on the pathogen’s capsule. Compared to single polysaccharide vaccines, they are produced by a technological process that binds the polysaccharide to a carrier protein to increase its immunogenicity when used as a vaccine and induce a long-term protective response even in infants. Various protein carriers are used for conjugation, including diphtheria and tetanus toxoid. Conjugate subunit vaccines, can therefore prevent common bacterial infections for which classical polysaccharide vaccines are either ineffective or provide only short-term protection (Obaro et al. 2002, Rino et al. 2019, Lindberg 1999). The advent of conjugate subunit vaccines heralded a new age for immunization against diseases caused by encapsulated organisms.

Toxoid vaccines

Toxoid vaccines are based on the toxin produced by certain bacteria as immunogen (tetanus or diphtheria). The toxin produced by the bacteria is responsible for the symptoms of the disease (Rinaldo et al. 1999, Dhillon et al. 2017) (et al. 2001, Penina et al. 2020). The protein-based toxin is inactivated to produce an anatoxin and used as an antigen in the vaccine to elicit immunity. To increase the immune response, the toxoid must bind to an adjuvant (Edel et al. 2004).

Nucleic Acid Vaccines

Although they have been the subject of work for several years, DNA/RNA based vaccination technologies have never yet been authorized for use in humans. Only four DNA vaccines have received regulatory approvals for commercial use in animals. The approach of nucleic acid based vaccines involves introducing genetic material encoding the target antigen into the body’s own cells that use its machinery to produce the antigens from target genetic material. While DNA is fired directly in the host cells using a brief electrical pulse, RNA must be encapsulated into lipid nanoparticle and injected. Potential advantages of this approach include the stimulation of broad long-term immune responses, excellent vaccine stability and relative ease of large-scale vaccine manufacture. Like other vaccine types, nucleic acid-based vaccines have proven to be safe and tolerable (Robinson 1999, Gurunathan et al. 2000, Kutzler et al. 2008, Ulmer et al. 2012). Although none of nucleic acid based vaccines are currently licensed for human use, many such vaccines are currently in the research pipeline. The manufacturing process for DNA vaccines is well-established, allowing experimental vaccines to be quickly developed to address emerging infectious diseases. Many candidate DNA vaccines are developed to address several viral disease threats during outbreaks, including SARS coronavirus (SARS-CoV) in 2003, H5N1 avian influenza in 2005, H1N1 pandemic influenza in 2009, and Zika virus in 2016. The time from selection of the viral genes to be included in the vaccine to initiation of clinical studies in humans was shortened from 20 months with SARS-CoV to slightly longer than three months with Zika virus.

Vaccines based on messenger RNA also are being developed. Recent technological advances have largely overcome issues with the instability of mRNA and the difficulty of delivering it into cells, and some mRNA vaccines have demonstrated encouraging early results.

Rather than delivering DNA or mRNA directly to cells, some vaccines use a harmless virus or bacteria as a vector, or carrier, to introduce genetic material into cells. Several such recombinant vector vaccines are approved to protect animals from infectious diseases, including rabies and distemper. Many of these veterinary vaccines are based on a technology that uses weakened versions of a poxvirus to deliver the pathogen’s genetic material.

All of these vaccine forms are now involved in the frantic race to develop an effective and safe vaccine against Covid-19 including new technologies based on the use of
mRNAs that have never been used in humans until now. The majority of vaccine candidates currently in clinical trials target the spike (S) protein and its variants as the primary antigen. However, candidates that target other or multiple antigens are progressing, including candidates that target N protein, attenuated vaccines, inactivated vaccines and peptide vaccines. The multiplicity of vaccine formulations used in the development of an effective vaccine against Covid-19 is prompted by the desire to produce a vaccine capable of inducing a potent and effective antibody response as well as long-term protection. The exact mechanism required to induce long-lived plasma cells, hence, long-term antibody responses, is in fact a fundamental immunological question that is central to vaccine design in general and, yet, not well understood. Studies have shown that monoclonal antibodies isolated from the COVID-19 patients can neutralize SARS-CoV-2 (Ju et al. 2020, Chen et al. 2020, Chi et al. 2020). Moreover, the use of convalescent plasma from the COVID-19 recovery patients as a treatment strategy has led to positive outcome (Duan et al. 2020, Shen et al. 2020). These results confirm that protective antibody response against SARS-CoV-2 can be elicited. Nevertheless, whether long-lasting protective antibody response can be elicited by vaccination remains elusive. Three previous studies on vaccine development against other coronaviruses have shown that vaccines against SARS-CoV or MERS-CoV using either inactivated virions or plasmid DNA have been tested in healthy adult cohort at phase I clinical trials (Lin et al. 2007, Martin et al. 2008). Although the majority of the recipients were found to seroconvert and produce neutralizing antibody against MERS-CoV, antibody levels were only maintained at a level for around 30 weeks and dropped to the level of baseline 60 weeks after vaccination. Similar phenomenon was observed in patients recovered from MERS-CoV infection, where neutralizing antibodies dropped to an undetectable level as early as 6 months post-infection (Beigel et al. 2018). Studies have suggested that long-lived plasma cells play a critical role in maintaining serum antibody level (Zhao et al. 2017).

The COVID-19 vaccine R&D landscape has developed at unprecedented scale and speed since viral genome sequencing. There are over 223 confirmed COVID-19 candidate vaccine under development of which 57 have already entered clinical phase in humans and at least 18 vaccines are in phase 3 clinical trials, the final phase of testing. Geographically, the United States dominates the market with a 20% share of COVID-19 vaccine development activities worldwide, followed by China with 8% and France with 6%.

Pfizer/BioNTech

On November 18, Pfizer and the German biotechnology company BioNTech developed one of the candidate vaccines, BNT162b2, and showed it was 95% effective in preventing Covid-19 and has passed its safety checks, with no severe side effects beyond fatigue which affected 3.7 per cent of participants and it was 94 percent effective in older adults, who usually are more vulnerable to developing severe COVID-19 (Joseph 2020). This vaccine candidate consists in injecting nucleoside-modified messenger RNA (mRNA) which functions as a blueprint for the virus spike protein. Once administered, the vaccine stimulates the human immune system to produce antibodies against this protein and thus the virus. Any successful vaccine based on this technology would be the first mRNA vaccine approved for human use. This vaccine requires two doses taken 21 days apart. Its German partner BioNTech have submitted an application to the US Food and Drug Administration (FDA) for an emergency use authorization of their vaccine against COVID-19. If FDA authorization does come in the first half of next December, Pfizer and BioNTech will be
ready to distribute the vaccine candidate in US within hours.

**Moderna Therapeutics**

After Pfizer, on November 16, another US drugmaker, Moderna Inc, announced that preliminary data of its phase three study of its mRNA-1273 experimental vaccine shows 94.5 percent effective in preventing COVID-19, more than that of Pfizer, without any significant safety concerns (Mahase 2020). Like Pfizer, Moderna has not presented underlying data on how the vaccine produced these effects. In a separate announcement, the company also said its vaccine can be safely stored on ice or in a normal refrigerator for 30 days. Moderna intends to apply FDA for an emergency use authorization of their vaccine against COVID-19.

Like Pfizer, however, Moderna released only early data from their trial. There’s more work to be done before they’ll know if the vaccine really is safe and effective. And even if Moderna’s vaccine gets the approval from the F.D.A., it will take months to reach widespread distribution.

**AstraZeneca/Oxford University**

The Oxford vaccine, developed with AstraZeneca vaccine is the third to produce efficacy results, following Pfizer/BioNTech and Moderna whose vaccines were made with a different technology. Oxford’s candidate is a viral vector vaccine constructed by transferring the SARS-CoV-2 spike protein into a weakened version of an adenovirus. When this adenovirus is injected into humans, the hope is that the spike protein will trigger an immune response.

On November 23, Oxford and AstraZeneca announced interim results from two of its phase three trials (Folegatti et al. 2020, Callaway 2020). One conducted in the United Kingdom showed the vaccine was 90-percent effective in preventing COVID-19 when given as a half dose followed by a full dose one month later. But in a second trial conducted in Brazil, in which volunteers received two full doses one month apart, the effectiveness dropped to 62 percent. When averaged, the efficacy is 70 percent. The benefit of this vaccine is that it can be stored in normal refrigeration. AstraZeneca and Oxford University plan to apply to an “emergency use listing” from the World Health Organization, which would set up their candidate for distribution in lower income countries. Oxford and AstraZeneca expect to produce up to three billion doses of the vaccine in 2021.

**Sputnik-V**

Russia's Sputnik Vaccine developed by Gameleya National Center of Epidemiology and Microbiology has also drawn widespread attention, after the Russian government approved it for general use on August 11 without completing Phase 3 trials. Sputnik V is based on similar viral vector technology to that used in the Oxford-AstraZeneca coronavirus vaccine candidate, which early results indicate may be up to 90 per cent effective (Burki 2020). But a full comparison between the two vaccines will only be possible when all the data is released. According to preliminary results obtained on volunteers 42 days after the injection of the first dose, the Russian vaccine candidate, Sputnik V, would be 95% effective after two doses according to Russian Ministry of Health and the Russian Federation.

China is the second competitor in the vaccine race behind the USA with 10 vaccine candidates of which four were in Phase 3 clinical trials, the final and most important step before regulatory approval. The most advanced are Sinovac and Sinopharm.

**Sinovac**

Sinovac Biotech, a private Chinese company, developed an inactivated vaccine called CoronaVac, one of four Chinese vaccines in last-stage human trials. In June the company
announced that Phase 1/2 trials on 743 volunteers found no severe adverse effects and produced an immune response. Sinovac published the details of the trial in November in a medical journal, showing a comparatively modest production of antibodies (Palacios et al. 2020). Only a Phase 3 trial would demonstrate if that was enough to protect people from Covid-19. CoronaVac is capable of inducing a quick antibody response within four weeks of immunization by giving two doses of the vaccine at a 14-day interval.

In July, Sinovac launched a Phase 3 trial in Brazil, followed by others in Indonesia and Turkey. Although Sinovac has yet to release late-stage trial data, on October 19, Brazilian officials said that CoronaVac was the safest of five vaccines they were testing in Phase 3 trials. The Chinese government gave the Sinovac vaccine emergency approval for limited use in July. Meanwhile, Sinovac has been preparing to manufacture the vaccine for global distribution. The company planned on worldwide distribution of the vaccine in early 2021, including the United States.

**Sinopharm:**

The Wuhan Institute of Biological Products developed an inactivated virus vaccine, which the state-owned Chinese company Sinopharm put into clinical tests. The Phase 1/2 trial showed that the vaccine produced antibodies in volunteers, some of whom experienced fevers and other side effects. They launched Phase 3 trials in the United Arab Emirates in July and in Morocco and Peru the following month. In summer, although Sinopharm has yet to release Phase 3 data on either vaccine to demonstrate that they are safe and effective, the Chinese government had authorized Sinopharm vaccine inoculation to government officials, health workers and other selected groups. As of November, nearly one million people in China had received the vaccines. In addition to their Wuhan vaccine, Sinopharm also began testing an inactivated virus vaccine developed by the Beijing Institute of Biological Products. After running early clinical trials in China, they launched Phase 3 trials in the United Arab Emirates and Argentina. In October, the chairman of Sinopharm said the company was gearing up manufacturing for their two vaccines, with plans for producing a billion doses a year.

**Conclusion**

Faced with the threat that SARS-CoV-2 represents on the world population through its ability to cause repeated epidemics and their consequences on mortality serious economic disruptions and major upheavals in our style of life, rapid development of an efficacious vaccine against SARS-CoV-2 is essential to avoid repeated or continuous outbreaks, but rigorous studies are required to determine the safety of candidate vaccines. It’s really important that we pursue trials of many different vaccines from many different manufacturers and be able then to ensure the supply of safe vaccine to the global population. Due to the constraint to accelerating the vaccine development process, conclusions and decisions are often made on the basis of interim data from ongoing clinical and preclinical vaccine studies. As a result, crucial information on longevity and the quality of the protective immunity induced by the vaccine are not available. Finally, strong international coordination and cooperation between vaccine developers, regulators, policymakers, funders, public health bodies and governments will be needed to ensure that promising vaccine candidates can be manufactured in sufficient
quantities and ensure their availability to all affected populations, particularly low-resource regions. We urge the global vaccine community to collectively mobilize the technical and financial support needed to successfully address the COVID-19 pandemic through a global vaccination programme, and provide a strong base to tackle future pandemics.

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