



(REVIEW ARTICLE)



Vaccines against SARS-COV-2

Julia San Miguel Rodríguez ¹, Julita Rodríguez Barbero ¹, Angel San Miguel Hernández ², Angel San Miguel Rodríguez ^{3,*} and María San Miguel Rodríguez ³

¹ Hospital Pharmacy Service. Río Hortega University Hospital, Valladolid, Spain.

² Clinical Analysis Service. Río Hortega University Hospital. Valladolid. International University of La Rioja. Spain.

³ Research Service, Río Hortega University Hospital, Valladolid, Spain.

GSC Advanced Research and Reviews, 2021, 08(02), 045–057

Publication history: Received on 05 June 2021; revised on 05 August 2021; accepted on 07 August 2021

Article DOI: <https://doi.org/10.30574/gscarr.2021.8.2.0143>

Abstract

Vaccines against Covid-19 were developed on the basis of protein S, before it had the mutations identified in these variants. Although research conducted so far is less effective against variants and continues to offer protection against severe forms of Covid-19, further research is ongoing.

WHO is working with every country in the world to help coordinate the key stages of this vaccine manufacturing and development process. In particular, to facilitate equitable access for all countries to vaccines against Covid-19 and that they are safe and effective for the billions of people who need them.

Keywords: Coronavirus; SARS-COV-2; Mutations; Vaccines

1. Introduction

SARS-CoV-2 is the causative agent of the Covid-19 pandemic that occurred and spread from the Wuhan market in China. This virus belongs to the B lineage of the betacoronavirus genus, which are viruses with single stranded RNA, approximately 30 kb, positive sense and relatively large envelope (Figure 1) [1]. SARS-Cov-2 is made up of an oily membrane packed with genetic instructions to make millions of copies of itself. The instructions are encoded in 30,000 letters of RNA that the infected cell reads and translates into many types of viral proteins. The SARS-CoV-2 genome encodes four structural proteins and other accessory or nonstructural proteins, including viral replicase (pp1a-pp1ab), 3C-like protease (3CLpro), papain-like protease (PLpro), and RNA-dependent RNA polymerase RdRp [2, 3].

The structural proteins of SARS-CoV-2 are:

- Spike (S), which forms large trimeric structures that are essential for entry into host cells after receptor binding and membrane fusion. Peak proteins are the target of host neutralizing antibodies.
- The envelope (E), which is only present in small amounts and most likely forms ion channels. E proteins are not required for viral replication, but are essential for infectivity and pathogenesis.
- Matrix/Membrane (M), which is the most abundant structural protein of the virus. M proteins are responsible for the curvature of the viral envelope membrane, especially through their interaction with E proteins.
- The Nucleocapsid (N), which binds to the viral RNA genome and ensures the maintenance of RNA in a bead-like conformation on a string.

* Corresponding author: Angel San Miguel Rodríguez
Research Service. Río Hortega University Hospital. Valladolid . Spain.

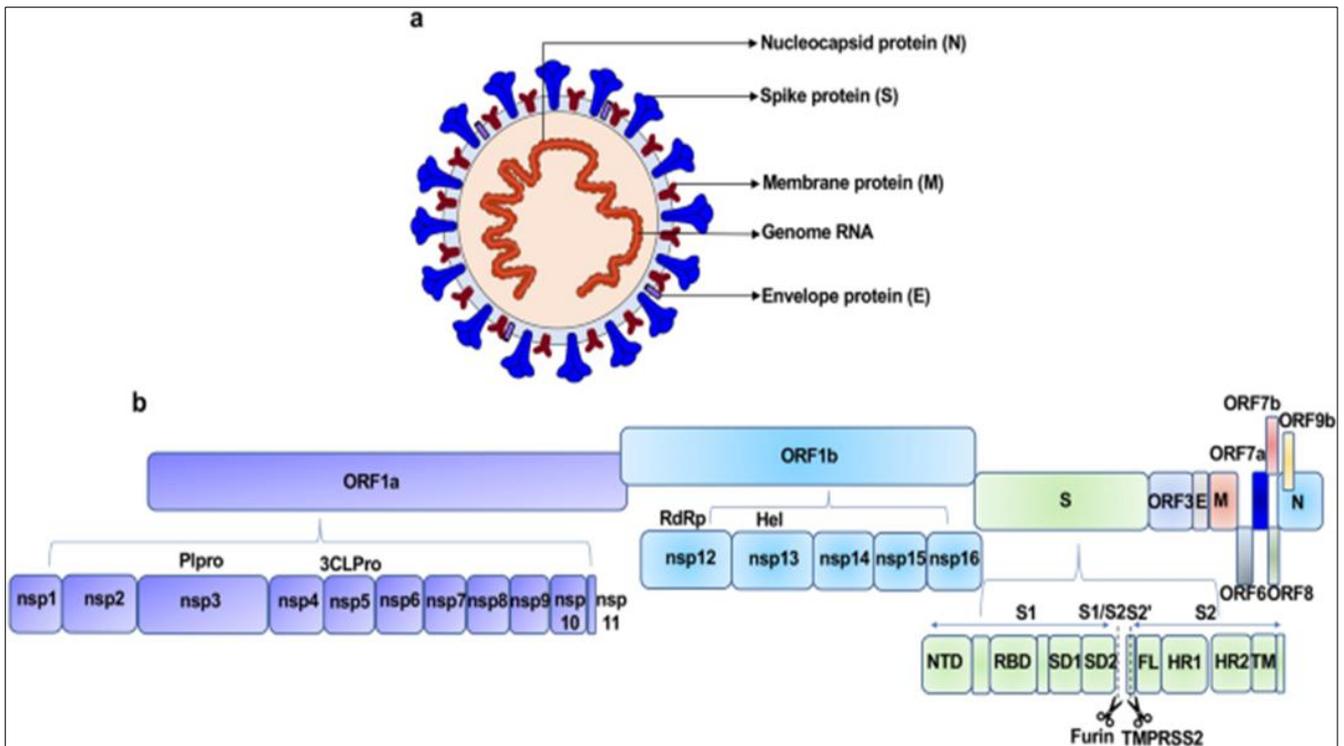


Figure 1 Structure and structural genes of SARS-CoV-2

1.1. Vaccine Development

Generally speaking, vaccines are intended to prevent the development of an infection. They are based on the introduction into an individual's body of a modified pathogen so that the immune system (IS) defends itself against it and generates the so-called "immunological memory". So, when the infection appears, the body can fight it effectively without developing the disease.

To develop any vaccine, the same steps must always be followed, such as: knowing its biology and the behavior of the pathogen that causes the infection and disease, identifying the domains or parts of that pathogen capable of inducing an immune response in the body when infection occurs, develop a vaccine prototype that generates this defensive response without generating disease, evaluate the safety, toxicity and efficacy of this prototype, a task carried out by health authorities through regulatory agencies, in Spain the AEMPS and manufacture the necessary doses of the new vaccine to make it available to the population, following the decisions of the health authorities regarding its use.

Since the SARS-CoV-2 infection and the subsequent Covid-19 pandemic have placed the world in an unprecedented health, economic and social crisis, the scientific and regulatory community is analyzing to what extent it would be feasible to speed up their development. phases in the research, development and production of commercialized vaccines. It was taken for granted that it would take at least a year, but the objective was to make the necessary procedures more flexible, guaranteeing safety and efficacy, to be able to have a vaccine against SARS-CoV-2 as quickly as possible, given the clinical and socioeconomic urgency that is causing the pandemic.

In SARS-COV-2, the domain of the virus that induces the immune response is known to be the target to act on, which is the spike protein.

Regarding the development of vaccine prototypes, it is possible to differentiate between research that is based on classic or traditional vaccines and innovative vaccines that opt for other methods.

Traditional developments are grouped into several types, some that work with inactivated viruses, those that work with attenuated viruses, and those that use protein subunits of the virus. The most innovative use the genetic material of the virus to trigger the immune response, either in naked form or by introducing this genetic material, DNA or RNA, in vectors, which are tools that allow its transport and distribution in the body.

As in all vaccine developments, the process will have to follow different phases. Once the part of the virus structure that will trigger the immune response without causing the disease has been located, with laboratory studies on the pathogen, the studies with animal models will be carried out, which is known as the preclinical phase. Of the investigation. If this phase is successful, the vaccine prototype will be tested in people, which is now known as a clinical trial, following the different phases I, II, III and IV, during which the safety and efficacy will be evaluated. of the vaccine in increasingly large groups of patients. Initiatives such as infection exposure trials, among other possible initiatives, are currently opening bioethical debates.

In addition, it is necessary to take into account the complexity that it would entail, to successfully develop a vaccine, to supply the world population in which its use is recommended. Industry capacity to manufacture doses may be limited and, on the other hand, there is debate around access to a potential vaccine, starring issues such as patents and licenses, equity in supply and prices. Therefore, it must be summarized that vaccination is like a simulation of infection, a way of provoking the immune system to activate against a certain microorganism. It is based on the ability of the immune system to generate immunological memory. Since the SI is, together with the nervous, the only ones capable of remembering, learning about themselves and being able to modify their response [4,5].

When we suffer an infection, memory lymphocytes are generated that keep the memory against that specific infection. This process takes several weeks, but our advantage is that if the individual faces the same pathogen again, the SI reacts in the following days with an immune response. Generating a vaccine is a very long process, since, until now, the vaccines currently in use have a development process of no less than 5-10 years. This process can be speeded up, but the requirements that must be met in order to be marketed are unlikely to be less than several years. These stages are clearly established by researchers, companies and drug regulatory agencies and can be summarized in the following points: Know the germ that causes the disease, its life cycle and its structure. Identify the domains or parts of that pathogen that induce an immune response. Prepare a prototype based on which the virus induces an immune response without causing disease. And to evaluate it, regarding the aspects of toxicity and efficacy, for which the different regulatory agencies generate a procedure in the development of vaccines. And once this effective prototype is defined, manufacture the number of doses necessary.

The effort that has been made in the development of vaccines worldwide with the current pandemic is unique and the investment made both economically and intellectually against SAR-COV-2 has been very important. Since, this pandemic is an infection that not only kills, but is also changing the current way of our social life and the economy.

Research in the development of vaccines has been guided by other respiratory viruses in which vaccines generate protection by inducing neutralizing antibodies that are directed against the envelope protein; therefore, the SARS-CoV-2 spike protein has been the target, due to the structure of said protein [4] and the determination of its immunogenic epitopes. Different studies and modeling works have defined epitopes of both B and T lymphocytes that would be the target of humoral, bone antibody or cell cytotoxicity responses [5,6].

To generate a specific immune response against SARS-COV-2, the vaccine must contain the whole virus or a part of it.

Two large groups of vaccines can be distinguished, the classic or traditional and the most advanced or innovative [7].

2. Traditional or classic vaccines, which are very safe but have drawbacks

These vaccines are grouped into three types: inactivated virus, attenuated virus, and protein subunit vaccines:

2.1. The inactivated vaccines

Which are preparations of the SARS-CoV-2 virus that grows in cell cultures and is destroyed by heat or fixation by chemical products. This virus, once injected, will induce an immune response against different components of its structure. The advantage of this vaccine is that it is very safe and relatively easy to manufacture.

The main drawback is that they are not very potent vaccines and that they have to be adequately purified for use in humans. This approach is under development and trials have already been conducted in animals that this vaccine appears to protect against infection [8,9].

2.2. The attenuated vaccines

which are live viruses modified so as not to be dangerous. In order to generate these vaccines, an in-depth knowledge of the virus is required to know which of its genes are the ones that cause the most damage, which is called virulence genes [10]. Once identified, deleted or mutated viruses are generated in these genes, a complex process that requires advanced reverse genetics techniques.

The advantage of this approach is that the resulting vaccines are very powerful because viral replication is reproduced, while they have the disadvantage that more exhaustive safety studies are required to guarantee the pursued viral attenuation.

2.3. Recombinant proteins

In the case of SARS-CoV-2, as previously explained, the target protein is that of its surface, protein S. Numerous vaccine prototypes are based on the synthesis and expression of this protein that synthesize and express the protein under different ways.

The advantage is that it is a very safe vaccine, but its potency may be low or insufficient when supplied as a soluble protein. To enhance its action, a strategy is to incorporate it anchored in a platform, such as Viral Like Particles or nanoparticles that give it greater stability and greater power in antigenic presentation.

In this type of vaccine, it is important to know the structure of the protein very well in order to induce neutralizing antibodies against it. Many viral proteins have different conformations, such as native, intermediate, prefusion, and it is necessary to immunize with the more immunogenic spicula structure that generates neutralizing antibodies.

2.4. Innovative or more advanced vaccines, which are riskier, but have more advantages

The prototypes currently selected by China and the US, in collaboration with large pharmaceutical companies working on vaccines, are not classic but innovative. A lot of money has been invested in each of these prototypes. In these models, the nucleic acids of the virus, with DNA or RNA, in naked form or inserted in viral expression vectors are used as immunogens.

2.4.1. Viral DNA and RNA

Both naked DNA and RNA are capable of inducing immunity, but sometimes they do not generate sufficiently powerful immune responses. Most prototypes in development encode the S protein of the virus. DNA must be administered by electroporation to be introduced into the cell. RNA is usually encapsidated in nanoparticles, generally by lipoparticles, to be internalized in cells. These prototypes are very safe and their production is simple, as well as their scaling, which represent great advantages for the rapid development and the urgency of obtaining a vaccine against SARS-CoV-2. However, its use has not been approved for any vaccine so far.

2.4.2. Viral vectors

In this type of model, among the SARS-CoV-2 genes, the one that codes for the S protein is inserted into infectious viral vectors that are used as transporters for the gene, which is carried and expressed inside the cell. The most commonly used viral vectors are poxviruses (MVA, modified Ankara virus), measles, and various adenoviruses (AD5, Chimp-Adeno). Some of these vectors are replicative and induce more potent responses, but require further safety studies. The question that arises with this type of vaccine is the impact of the response against the vector and whether it can affect the response against the insert.

Many prototypes are currently being developed. Half correspond to the category of novel vaccines, such as viral vectors and free nucleic acids; one third are soluble proteins, and only half a dozen prototypes are based on the more classical models of attenuated or inactivated viruses.

Regulatory agencies around the world have generated a whole procedure in the development of vaccines, since they must assess their safety, toxicity and efficacy, for which they have very strict protocols to approve a vaccine suitable for the market. And since it is a drug that is used in a healthy population, sometimes on a massive scale, so the side effects are not tolerable to the same degree that a drug is authorized. All the types of vaccines that are being developed against Covid-19 are summarized in Figure 2. This vaccine development process can be carried out in the following stages or phases, which are shown in Figure 3.

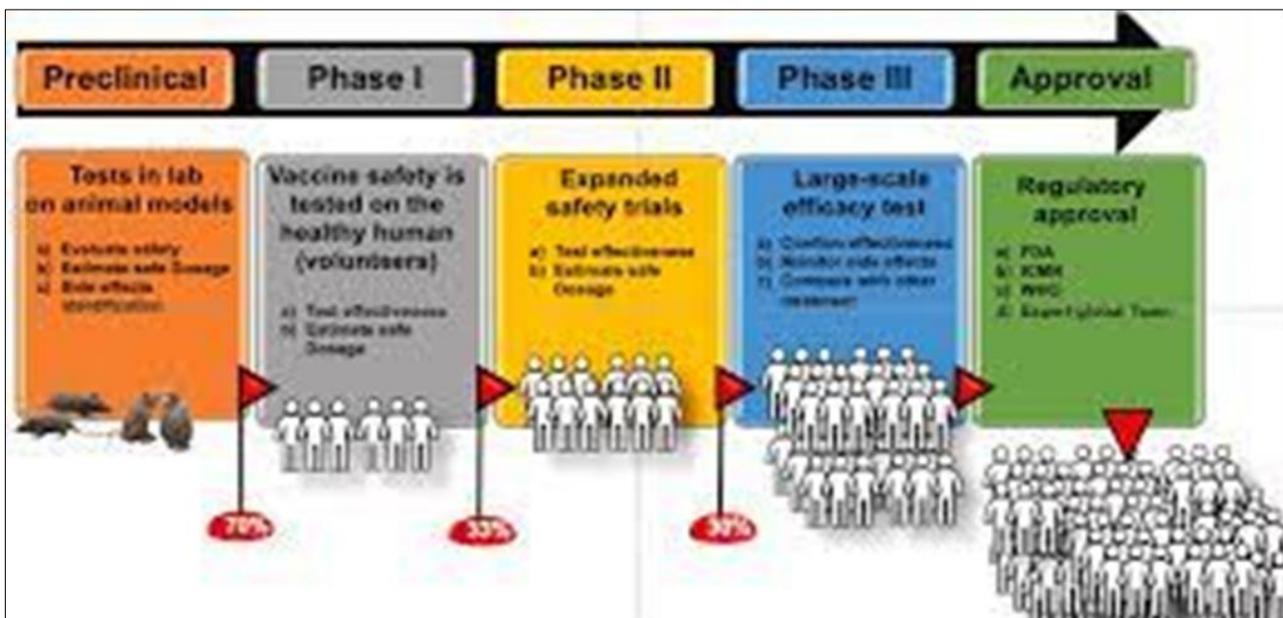
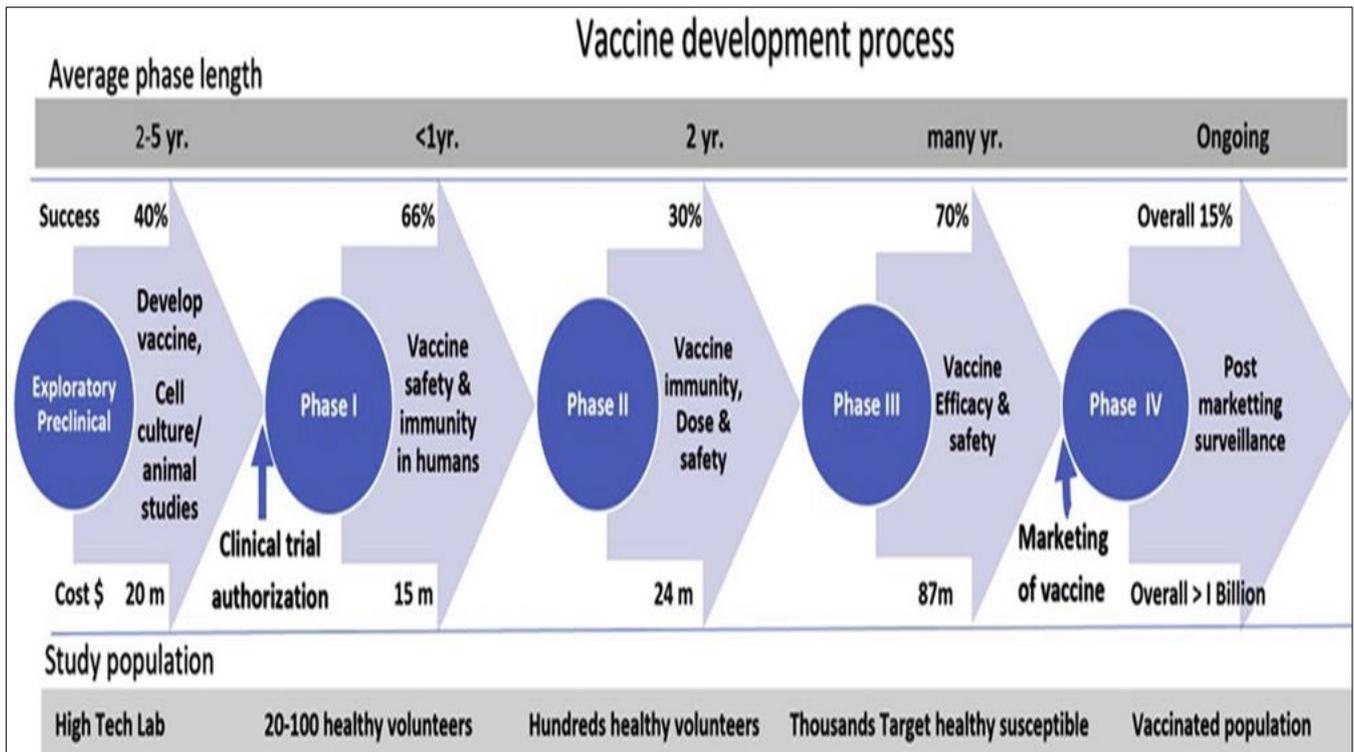


Figure 2 Basic diagram of the development phases of a vaccine. Taken from <https://corrientealterna.unam.mx/ciencia/cuales-son-las-fases-de-desarrollo-de-una-vacuna/>. Taken from: <https://corrientealterna.unam.mx/ciencia/cuales-son-las-fases-de-desarrollo-de-una-vacuna/>.

2.5. Basic science phase

For the development of an effective vaccine, the first thing to do is define an element of the pathogen that induces a powerful SI response capable of generating memory. This first phase is carried out through basic research, carrying out preliminary studies in the laboratory using cell cultures. Once the most immunogenic antigens have been identified, they must be exhaustively characterized to know all their physicochemical, functional and immunogenic properties.

They must then be purified to isolate them from other components and the vaccine specifications determined. Finally, the formulation is decided, including the most suitable excipients and adjuvants to improve the immune response.

2.6. Preclinical testing phase

This type of study is carried out in animal models, generally mice or monkeys, and allows evaluating the safety of the vaccine and its ability to generate an adequate humoral and / or cellular response. The results obtained during these studies support the subsequent investigation of the efficacy and safety of the vaccine in humans.

2.7. Production in conditions suitable for use in humans

During the production of the vaccine, very strict quality controls must be followed based on good manufacturing practices, which ensure the consistency of the production batches and the stability of the formulations during transport and storage until administration.

2.8. Phase I of clinical trials

It consists of testing the vaccine in a small group of no more than 100 healthy adults in order to determine the safety of the vaccine and its possible biological effects, including immunogenicity. During this phase, the safest dose is established and the best route of administration is established, which, in the case of a vaccine, is usually parenterally.

2.9. Phase II of clinical trials

In which the vaccine is administered to a much larger group of people, generally between 200-500 healthy individuals in order to verify the safety and efficacy of the vaccine. By increasing the number of participants, it is possible to determine whether the selected dose and route of administration are indeed the most appropriate.

2.10. Phase III of clinical trials

these are multicenter studies that include a greater number of volunteers following less strict inclusion criteria in the study, with the aim of having a more representative sample of the general population. There can be several thousand patients belonging to different countries, belonging to different age groups and also with risk factors for the disease that are divided into two groups: one of them receives the vaccine and the other receives a placebo that has no pharmacological activity. This phase is prior to the approval of the commercialization of a vaccine.

In the process to define the prototype and the manufacture of necessary doses, a large biotechnological investment is needed and necessary and includes up to two regulatory stages:

2.11. Production and scaling phase

Once the efficacy of the vaccine has been shown, comes the large-scale production phase, which is carried out in highly specialized factories that meet product quality control requirements.

2.12. Post-marketing phase IV

Once the arrival of a vaccine on the market is approved, the monitoring of its effects on individuals within a population of one or more countries continues. This study makes it possible to identify, in addition to the real efficacy of the vaccine, possible adverse effects not detected in the previous phases, as a larger and more varied population is available for analysis.

This would be the approval process for any type of vaccine; but given the seriousness of the Covid-19 pandemic that we are suffering and its health and economic repercussions, there has been and there is a debate about a possible acceleration of the process of development, approval and commercialization of a possible vaccine against SARS-CoV-2 [11]. Among other fronts, there are issues such as bioethics in the scientific process, as well as the possible regulation of trials based on controlled infection in humans; equitable access to a possible vaccine, the ability of the industry to manufacture it on a large scale, the guarantees that it will reach the whole world, etc. and the prominence of patents, licenses and prices, if the vaccine can be developed with success.

The WHO has recalled the regulatory aspects that must be considered in the development of a vaccine against the new coronavirus [12]. In a recent meeting of the International Coalition of Regulatory Authorities (ICMRA), which groups together the WHO, FDA and EMA, among others, the stages that could be avoided in this development were analyzed [13], which did not always have unanimous agreement. According to these guidelines, the passage to human trial phases could be started, without carrying out previous studies in animals, provided that safety was guaranteed. In fact, both the Cansino prototype from the Chinese Academy of Sciences, as well as the one from the US NIH with Moderna, have carried out these studies in parallel to the phase I trial in humans.

All the studies speak of a minimum of 18 months for the development and placing on the market of a vaccine against Covid-19. But ways have been sought to streamline the regulatory steps and accelerate the approval of the different prototypes that have been underway and of course taking into account quality and safety standards and always evaluating their effectiveness. The most advanced prototypes are very safe and scalable to large productions and probably for this reason they have been selected over the classic models, to be able to be used in humans in case of emergency.

In figure 3, the groups of vaccines that have been developed against Covid-19 and how they work are reviewed.

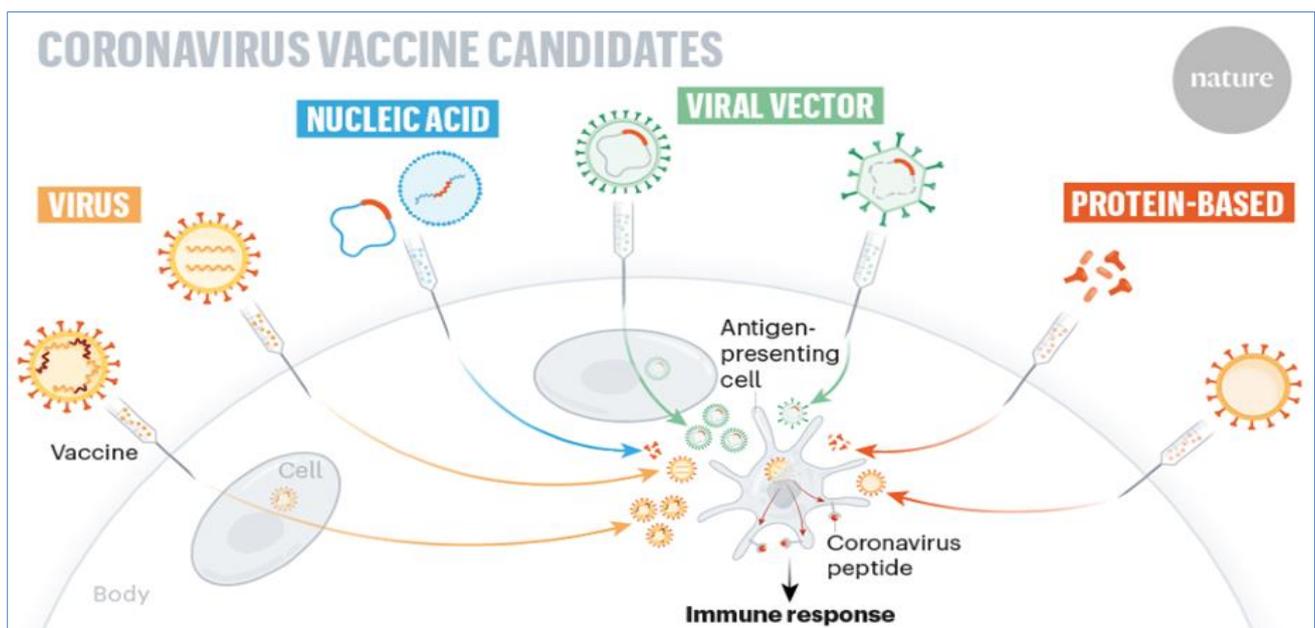


Figure 3 Diagram of the different vaccine developments and how they work. Source Ministry of Health

3. Genome sequencing of SARS-COV-2 and current vaccines

All living beings are made up of different types of macromolecules, which include carbohydrates, lipids, proteins, and nucleic acids. The latter are formed by the repetition of basic units called nucleotides that come together to form long chains. Nucleic acids have an important function, since they contain the genetic code necessary for the development and functioning of all living beings, that is, for life. There are two main types of nucleic acids, deoxyribonucleic acid (DNA), which is made up of two intertwined nucleotide strands that form a double helix structure, and ribonucleic acid (RNA), which is made up of a single strand. The basic structure of nucleic acids, the nucleotide, is always made up of three elements, a carbohydrate, a nitrogenous base and a phosphate group. The nitrogenous bases are those that differentiate some nucleotides from others and in the case of DNA they can be: adenine or A, thymine or T, cytosine or C and guanine or G.

Genetic sequencing is, therefore, the determination of the order of nucleotides in a nucleic acid molecule through physicochemical processes. Genetic sequencing is a technology that allows us to know and decipher the genetic code that all living beings have. So it is about reading that code, which contains the essential information for its development and operation, as if it were a genetic instruction book. These hallmarks, which define the characteristics and genetic signature of biological organisms, are inscribed in molecules called nucleic acids, which are made up of nucleotides.

The genomic sequencing of SARS-CoV-2 has been one of the main objectives since its discovery, since it is the gateway to knowing and fighting it. And throughout 2020, thousands and thousands of complete coronavirus genomes have been sequenced, thanks to the analysis of samples from patients affected by the Covid-19 disease. Achieving this sequencing is essential to better understand the virus and define its characteristics and behavior. It has also allowed it to be classified, defined and included as a new member of the already known virus families, baptizing it as SARS-CoV-2. In addition, it has made it possible to find out its origin, know how it is transmitted, investigate its capacity for diffusion and contagion, and obtain the necessary information for the future development of drugs and vaccines.

Currently, research centers are capable of genetic sequencing. There are different technologies to carry it out. Sanger sequencing was one of the first to be developed and to automate the sequencing process that is known today, it remains a reference. Over the years, new technologies have emerged that allow more information to be obtained from the sequenced organism more quickly. These include, among others, technologies such as Illumina and IonTorrent, considered part of the second generation of genomic sequencing, and Pacific Bioscience and Oxford Nanopore, which are part of a third generation.

Genomic sequencing has starred in one of the great scientific milestones of the 21st century, since the presentation of the Human Genome Project, which unveiled our genetic code and which has revolutionized the study of our biological characteristics and the fight against different diseases.

Among the applications of sequencing are the greater knowledge of the origins of the species, the early detection of syndromes and genes associated with diseases and the identification of people in forensic science, among others.

Several months after the SARS-CoV-2 genome was sequenced, the Covid-19 vaccines began to be distributed and deployed. On November 5, 2020, there were several dozen vaccines against the virus that were in phases I, II and III of clinical trials, respectively. On the other hand, six from Russia and China which apply in more restricted situations [14,15].

The technological platforms and strategies that were put in place have been very different. Some fall within the so-called traditional ones, which are the inactivated and attenuated, recently commercialized recombinants and vectors; and others that have never massively used DNA and RNA.

Of the ten ongoing vaccines, four use a platform of non-replicating adenovirus vectors, four use the classic technology of viral inactivation, two messenger RNA wrapped in a lipid coating and one is based on protein subunits in the form of a recombinant nanoparticle. with saponin as adjuvant [16].

Four of them belong to the People's Republic of China, CanSino Biological of non-replicating vectors and Sinovac and Sinopharm of inactivated vaccines, one to the Russian Federation, Gamaleya Research Institute of adenovirus Ad26 and Ad5 in heterologous prime-boost scheme, another to the United Kingdom, formed by chimpanzee adenovirus from the Oxford Vaccine Group/AstraZeneca, three from the USA Moderna, Inc from messenger RNA, Johnson & Johnson and Novavax from recombinant nanoparticle, one from India, Bharat Biotech, inactivated vaccine and finally the vaccine from Germany and the USA (Pfizer / BioNTech of messenger RNA. Protein subunit vaccines (virus like particles) are found in previous phases [17,18]. In these, both humoral and cellular immunity have been measured.

For the first, binding antibodies of the IgG, IgM and IgA type are used, which bind to purified proteins of the SARS-CoV-2 virus (RBD and/or Spike) and are measured by ELISA technique. Neutralizing IgG antibodies are also detected, which determine their functional ability to prevent virus infection in vitro. Cellular responses are analyzed by evaluating CD4 + and CD8 + T lymphocytes with the expression of cytokines that can condition Th1 responses, such as IL-2, INF- γ and TNF-2 or Th2 responses, that is, IL-4, IL-5 or IL-17, associated with immunopathogenicity phenomena [19,20].

3.1. Vaccine from Pfizer /BioNTech, Comirnaty

The Pfizer/BioNTech Vaccine. BNT162b2 is a messenger RNA vaccine that encodes the spike surface glycoprotein encapsulated in lipid nanoparticles, with a vaccination schedule of two doses separated by 21 days. It has a systemic reactogenicity of moderate intensity after the second dose, which is lower in those over 65 years of age. It induces good humoral immune responses that improve after the second dose, including those over 65 years of age. Cellular responses are from CD4 + and CD8 + lymphocytes with a polarized profile towards Th1 lymphocytes.

The upper and lower respiratory tract of vaccinated non-human primates were protected after intratracheal and intranasal virus inoculation. Storage must be done at very low temperatures (-20°C) and it is very heat sensitive once

defrosted, since it can only be kept refrigerated for 5 days. Phase III has included 44,000 participants aged 18 or over [21-23].

3.2. Modern vaccine

The Moderna Vaccine, Inc. mRNA-1273 vaccine is an mRNA vaccine that encodes the Spike surface glycoprotein encapsulated in lipid nanoparticles, with a two-dose vaccination schedule on days 0 and 29. The vaccine produces systemic effects on a high proportion of vaccinated that increase after the second dose. They are less frequent in those over 55 years of age.

It induces the production of antibodies against the surface glycoprotein S, after the first dose and neutralizing antibodies after the second in children under and over 55 years of age, even against the clade 614G of the virus. Induce CD4 + cellular immune responses with Th1 cytokine profile.

In vaccinated non-human primates, it prevents replication in the upper and lower respiratory tract after virus inoculation, without Th2 responses that could suggest the appearance of Vaccine Associated Enhanced Respiratory Disease (VAERD).

Storage of this vaccine must be done at very low temperatures (-80°C) and it is very heat sensitive once thawed and can be kept refrigerated for 28-30 days. And in its development phase, 30,000 individuals over 18 years of age [24-27] have participated.

3.3. Oxford Vaccine Group / AstraZeneca. ChAdOx1 nCoV-19. AZD1222

It is a vaccine in which glycoprotein S is carried in a non-replicating chimpanzee adenovirus with a vaccination scheme of two doses of 5x10¹⁰ virus particles at 0 and 28 days in volunteers aged 18 to 55 years. Reactogenicity is slightly higher than that of the MenACYW-TT vaccine used as placebo, improving with prophylactic paracetamol, but without reducing immunogenicity.

This vaccine produces antibodies against protein S and neutralizing antibodies in all participants after the second dose, and no interference has been found between previous anti-vector immunity and the immune response to the first and second doses. It also generates cellular immune responses.

The antibodies against the vector generated after the first dose do not seem to influence the humoral response to the homologous booster, but they do influence the cellular response. In nonhuman primates, the vaccine prevents or reduces viral replication in the lower respiratory tract. The storage conditions are the usual ones for routine vaccination programs. Phase III has included 30,000 participants [28].

3.4. Vaccine from Janssen Vaccines & Prevention B.V./Johnson & Johnson

The vaccine from Janssen Vaccines & Prevention B.V./Johnson & Johnson. Ad26.COV2.S, is a vaccine in which the surface glycoprotein S is carried in a non-replicating human adenovirus 26, with a vaccination scheme with a dose of 5x10¹⁰ virus particles.

The safety profile is acceptable, with less reactogenicity in people over 65 years of age. One dose of vaccine elicits neutralizing antibody responses in all ages, including individuals over 65 years of age.

It also induces responses against CD4 + Th1 and CD8 + T lymphocytes, without Th2 responses and in vaccinated animals, after virus inoculation, an expansion of neutralizing and T-cell responses is not observed, which suggests a minimal or viral replication absent in upper and lower respiratory tract. The storage conditions are the usual ones. Phase III of the clinical trial consists of 60,000 participants [29,30].

3.5. Vaccine Novavax

The Novavax Vaccine. NVX-CoV2373, is a nanoparticle vaccine that has been constructed with the integral protein S obtained by recombinant techniques in infecting baculovirus of insect cells *Spodoptera frugiperda*. It includes a Matrix-M1 saponin as an adjuvant, with a vaccination schedule of two doses separated by three weeks.

The vaccine has a good safety profile and generates neutralizing antibody responses superior to those exhibited by convalescents from COVID-19. Furthermore, it additionally induces cellular responses with a Th1 cytokine profile. And observe if, after a test of virus inoculation in non-human primates, the presence of replicating virus in the lower respiratory tract is very scarce and null in the upper one. Furthermore, the preservation conditions of the vaccine are the usual ones for vaccines in population programs (2-8°C) [31,32].

4. Interchangeability of vaccines

Currently, researchers are carrying out different studies and trials to have sufficient evidence to support the use of different types of vaccines against coronavirus. So far there is not enough scientific evidence to determine the interchangeability of the different types of doses of the Covid-19 vaccines.

For example, the English government has warned that a situation of imminent risk, of the use of a second dose of another vaccine, if the first one was not available for the second administration. But it is not recommended to do this, since so far there is no evidence to confirm this alternative, although studies are being carried out.

The United Kingdom authorized the emergency use of the Pfizer/BioNTech and the University of Oxford/AstraZeneca vaccines 28 days apart.

The evidence to date, as in any type of vaccine when it is started, it is recommended to start with a certain brand and end with the same brand, until there are no more studies that support the interchangeability of vaccines regardless of their origin. Already, the immune response is not studied when different commercial brands are exchanged, as in the case of all vaccines against SARS-CoV-2. When that is proven, there will be scientific evidence that you can start with one and end with another trademark. It would not be the adverse effects that contraindicate interchangeability, but rather the power of the immune response.

The British government only supported the use of differently designed doses of vaccines in a situation of very high risk. Because, the body that works on vaccines (Vaccine Taskforce) and that depends on the UK government, indicates that they would try to give people a dose of one type of vaccine and then a booster with a different type; since all approved vaccines need two doses each to be most effective in preventing the new coronavirus. Because vaccines work in different ways, receiving doses of different brands could maximize the immune response and provide better and longer-lasting protection, through the method known as heterologous prime-boost.

On the other hand, it is not advisable to exchange or change vaccines, mainly because their manufacturing design is very different. Due, for example, to the fact that the English and the Russian are developed with vectors, in which the intention is to deceive the organism, with an adenovirus that enters with a protein inside and that is the one that will produce the antibodies.

The two North American vaccines are different, since they have a small portion of the nanoglycoprotein of the RNA helix and what is injected with the vaccine is what causes antibodies to begin to be produced.

With the Chinese vaccine, which uses the traditional vaccine manufacturing system, where the viruses are attenuated, it cannot be exchanged. Whoever gets the first dose of a vaccine must complete it with the scientific arguments of the second dose of the same vaccine, since it can even cause certain damage to the immune system.

Vaccine specialists, for now, only recommend the use of a single type of vaccine to avoid any type of damage that may be generated in the autoimmune system. In all the vaccines on the calendar there are not always the same brands of vaccines and there is no problem with interchangeability, therefore, surely in the not too distant future, if the evidence supports it there will be information for interchangeability with respect to these vaccines, since in all the vaccines of the vaccination calendar, different commercial brands are used to know if they are interchangeable.

It should be remembered that the technology used by Pfizer is that of RNA, which is introduced into the body a sequence that contains genetic instructions for the person's own cells to produce antigens and generate an immune response. While the Oxford gene inoculates the coronavirus gene into human cells to produce the unique COVID-19 spicula protein, to which the immune system develops a response if the real virus enters the body.

4.1. Strategies in vaccination

Different strategies are being followed during the Covid19 vaccination. There are countries, including ours and also some autonomous communities, that before the arrival of the vaccine doses, some opt to vaccinate with half the doses and reserve the following for the second dose. While in others, they opt to vaccinate with all the doses that arrive and vaccinate as many people as possible and wait for the second dose with the arrival of new dose shipments. But we do not know what would happen to a logistical problem and distribution of new doses.

In the Pfizer/BioNTech vaccine, it is recommended that the second dose must be given at 21 days, but in the event of any problem that may exist in the delivery delays of these vaccines, the second dose must be given no later than 42 days after the first dose, and thus the laboratory would avoid problems of later claims.

By verifying whether for some variants of SARS-CoV-2, the vaccines in use may be affected in the protection they confer. A working group in Texas had previously proposed the results of an mRNA vaccine that encodes glycoprotein S and that induced the production of neutralizing antibodies in concentrations similar to those of a serum panel of Covid-19 convalescent people. This vaccine, BNT162b2, in a phase II / III clinical trial showed 95% protection against Covid-19 in volunteers over 16 years of age who received both doses of the vaccine. And the way they have carried out their study was by generating an isogenic strain Y501 of the SARS-CoV-2 virus with the backbone of N501, which is the source of the S glycoprotein of the BNT162b2 vaccine. They confronted her with the serum of 20 participants, drawn two to four weeks after receiving two doses of the vaccine separated by three weeks using the plaque reduction neutralization test (PRNT50). And it is stated that there is no reduction in the neutralization activity against the virus carrying the Y501 mutation. The Y501 virus, does not include the entire set of mutations of the current strains of the United Kingdom and South Africa, the authors think that the neutralization of this virus by human serum is consistent with the neutralization of a panel of fifteen pseudoviruses carrying glycoproteins with mutations found in other circulating strains of SARS-CoV-2.

With the appearance of these new variants of SARS-CoV-2 in the United Kingdom, South Africa, Brazil, India, etc., which share multiple mutations in the spike surface glycoprotein through N501Y substitutions, concern has increased since it is located in the "Receptor binding domain", which is the element through which the virus enters the cell and where neutralizing antibodies are directed. This variant enhances the binding of the SARS-CoV-2 virus to the cellular receptor ACE2 and is spreading rapidly worldwide.

Thus, the permanent evolution of the virus requires a continuous evolutionary monitoring of the changes in order to protect the vaccine well. This surveillance must be accompanied by the pertinent preparation in case a change in the composition of the vaccine is necessary, which would be facilitated by the flexibility of the messenger RNA technology.

In our country, the Spanish Vaccination Association has prepared a document with a series of arguments in favor of vaccination against Covid-19, which is a decalogue to argue the much-needed vaccine, which is the only preventive tool that has to try to end the pandemic.

5. Conclusion

Thus, the different vaccines are being supplied and gradually arriving in all countries, as they are approved by the different international and national regulatory agencies. As we can see, there are still many unknowns to solve regarding SARS-COV-2, but I am sure that the scientific advances that are taking place worldwide by all the research teams that are working, all these answers will go away. clarifying.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

References

- [1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med.* 2020; 382: 727-733.

- [2] Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol Biol.* 2015; 1282: 1-23.
- [3] Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020; 579: 270–273.
- [4] Walls et al. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein, *Cell.* 2020; 180: 1-12.
- [5] Grifoni et al. *Cell Host & Microbe.* 2020; 27: 671–680.
- [6] Lee CH, Koohy H. In silico identification of vaccine targets for 2019-nCoV. *F1000 Research.* 2020; 9: 145.
- [7] Amanat and Krammer, SARS-CoV-2 Vaccines: Status Report, *Immunity.* 2020.
- [8] Callaway A, Spencer N. The race for Coronavirus vaccines. *Nature.* 2020; 580: 576-577.
- [9] COVID-19 shot protects monkeys. Cohen. *J. Science* 2020; 368: 456.
- [10] Enjuanes L, et al. Molecular Basis of Coronavirus Virulence and Vaccine Development. *Advances in Virus Research.* 2016; 96: 245-286.
- [11] Lurie N, et al. Developing Covid-19 Vaccines at Pandemic Speed. *New Eng J Med.* 30 Mar 2020.
- [12] Relevant WHO documents for SARS-CoV-2 vaccines and other biologicals.
- [13] Corey L, Mascola J, Fauci AS, Collins FS. A Strategic Approach to COVID-19 Vaccine R&D. *Science.* 2020.
- [14] Corum J, Wee S-L, Zimmer C. Coronavirus Vaccine Tracker. *The New York Times [Internet].* 2020.
- [15] Krammer F. SARS-CoV-2 vaccines in development. *Nature [Internet].* octubre de. 2020; 586(7830): 516.
- [16] Draft landscape of COVID-19 candidate vaccines_3nov2020 [Internet].
- [17] Mullard A. COVID-19 vaccine development pipeline gears up. *The Lancet [Internet].* 2020; 395(10239): 1751-2.
- [18] Amanat F, Krammer F. SARS-CoV-2 Vaccines: Status Report. *Immunity [Internet].* 14 de abril de 2020; 52(4): 583-9.
- [19] Sekine T, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin J-B, Olsson A, et al. Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19. *Cell [Internet].* 1 2020; 183(1): 158-168.
- [20] Coronavirus: the Commission approves third contract to ensure access to a potential vaccine [Internet]. European Commission. 2020. Available in: [https://www.who.int/news-room/q-a-detail/coronavirus-disease-\(covid-19\)-vaccines?adgroupsurvey={adgroupsurvey}&gclid=CjwKCAjw3riIBhAwEiwAzD3TiTqGDtZzRZBu6amqis5ZJMK60H0eiTv8nCsIeydheA3tweR2dMN4TRoCo-4QAvD_BwE](https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-vaccines?adgroupsurvey={adgroupsurvey}&gclid=CjwKCAjw3riIBhAwEiwAzD3TiTqGDtZzRZBu6amqis5ZJMK60H0eiTv8nCsIeydheA3tweR2dMN4TRoCo-4QAvD_BwE)
- [21] Walsh EE, Frenck RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N Engl J Med [Internet].* 14 de octubre de. 2020.
- [22] Concurrent human antibody and TH1 type T-cell responses elicited by a COVID-19 RNA vaccine. *medRxiv [Internet].* 2020.
- [23] Van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. *Nature [Internet].* 30 de julio de 2020; 1-8.

- [24] Anderson EJ, Roupael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. *N Engl J Med* [Internet]. 29 de septiembre de 2020 [citado 6 de noviembre de. 2020].
- [25] Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature* [Internet]. 12 de agosto de. 2020; 1-8.
- [26] Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. *N Engl J Med* [Internet]. 15 October 2020; 383(16): 1544-55.
- [27] ACIP August 2020 Presentation Slides. Immunization Practices. CDC [Internet]. 2020.
- [28] Sadoff J, Gars ML, Shukarev G, Heerwegh D, Truyers C, Groot AM de, et al. Safety and immunogenicity of the Ad26.COV2.S COVID-19 vaccine candidate: interim results of a phase 1/2a, double-blind, randomized, placebo-controlled trial. *medRxiv* [Internet]. 25 September 2020.
- [29] Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. *N Engl J Med* [Internet]. 2 September 2020.
- [30] Mercado N. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques [Internet]. *Nature*. 2020.
- [31] Guebre-Xabier M, Patel N, Tian J-H, Zhou B, Maciejewski S, Lam K, et al. NVX-CoV2373 vaccine protects cynomolgus macaque upper and lower airways against SARS-CoV-2 challenge. *bioRxiv* [Internet]. 2020.
- [32] Bangaru S, Ozorowski G, Turner HL, Antanasijevic A, Huang D, Wang X, et al. Structural analysis of full-length SARS-CoV-2 spike protein from an advanced vaccine candidate. *bioRxiv* [Internet]. 2020.