ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

COVID-19 vaccines and immunological implications: a literature review

Vacinas COVID-19 e suas implicações imunológicas: uma revisão de literatura

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ABSTRACT

COVID-19 and immunological mechanisms currently are topics of great worldwide relevance. Clinical manifestations and the dangerous complications resulting from a cytokine storm motivated the creation of vaccines against SARS-CoV-2 at an accelerated pace, generating suspicions and different levels of efficacy and safety. This is a review article addressing research published in 2020 and 2021. The electronic libraries SciELO (Scientific Electronic Library Online), PubMed, LILACS (Latin American and Caribbean Literature in Health Sciences), and MEDLINE were used for specific screening with the following descriptors: COVID-19 vaccines, SARS-CoV-2, immunology of COVID-19. Issues such as the immunological mechanism, efficacy, and adverse effects of vaccines currently available on the world market are widely discussed.

Keywords: Coronavirus infections, vaccines, betacoronavirus.

RESUMO

A COVID-19 e seus mecanismos imunológicos são, atualmente, temas de grande relevância mundial. Suas manifestações clínicas e as perigosas complicações decorrentes da tempestade de citocinas motivaram a criação de vacinas contra o SARS-CoV-2 em um ritmo acelerado, gerando desconfianças e diferentes níveis de eficácia e segurança. Este estudo trata-se de um artigo de revisão que abordou pesquisas publicadas no período de 2020 e 2021, utilizando as bibliotecas eletrônicas SciELO (*Scientific Electronic Library Online*), PubMed, LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde) e MEDLINE com o rastreamento específico por meio dos seguintes descritores: vacinas COVID-19, SARS-CoV-2, imunologia do COVID-19. Questões como o mecanismo imunológico, eficácia e efeitos adversos das vacinas disponíveis no mercado mundial atual foram amplamente discutidas.

Descritores: Infecções por coronavírus, vacinas, betacoronavírus.

Introduction

Reviewing immunology concepts

The defense against microorganisms, whether intracellular (such as viruses) or extracellular (such as bacteria and protozoa), occurs through reactions of innate immunity initially, followed by late responses of acquired immunity.[1]

Innate immunity (also called natural or native immunity) provides the first line of defense. The main components are physical and chemical barriers (epithelium and antimicrobial agents produced on epithelial surfaces); phagocytic cells (such as neutrophils, macrophages), dendritic cells (antigen-presenting cells) and natural killer (NK) cells; and blood proteins, including members of the complement

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Submitted: 05/20/2021, accepted: 08/19/2021.

Arq Asma Alerg Imunol. 2021;5(4):346-56.

http://dx.doi.org/10.5935/2526-5393.20210054

system and other mediators of inflammation. These cells react to the products of microorganisms and injured cells, always responding in the same way to repeated exposures and not distinguishing the differences between them.[1]

In contrast to innate immunity, there is another immune mechanism that tends to respond and adapt to infection in a specific way: acquired immunity (also called adaptive or specific). The adaptive immune system recognizes and reacts to a large number of molecules. Its defining characteristics are the ability to distinguish between different substances (specificity) and the ability to respond more vigorously to repeated exposures to the same microorganism (memory). The unique components of adaptive immunity are cells called lymphocytes and their secreted products, such as antibodies. Foreign substances that induce specific immune responses or are recognized by lymphocytes or antibodies are called antigens.[2]

Acquired immunity is also divided into two forms of defense: represented by T lymphocytes (CD4, CD8, regulator) and known as cellular immunity; and by the response through antibodies (immunoglobulins) produced by B lymphocytes, called humoral immunity.[2]

By specifying the immune response to intracellular pathogens (such as viruses), after the antigen-presenting cells carry some viral protein to the CD4 T lymphocytes, these cells will secrete interleukin (IL)-2, which is a growth factor for the proliferation of antigen-specific T cells (clonal expansion). They aid in the recruitment and differentiation into effector T cells, which aid in the elimination of the pathogen. CD4 T cells also stimulate CD8 T cells and these also proliferate, differentiate, and kill infected cells, being very active in viral infections.[2]

As for humoral immunity, helper T cells stimulate B lymphocytes to differentiate into plasma cells, and, depending on the antigen, specific antibodies will be formed. The main antibodies or immunoglobulins formed are of the IgA class (found mainly in mucous membranes, acting on protein antigens), IgE (present mainly in allergic reactions and parasitic infections, acting on protein antigens), IgM, and IgG (acting in responses against infections; IgM acts in the active phase of the disease, that is, the individual is infected in the acute phase, and IgG means that the organism is in the chronic phase of the disease or has already been in contact with the antigen at some point in life). Antibodies act through opsonization by binding to the pathogen to phagocytosis occur.[3]

COVID-19 disease and its relation to immunity

COVID-19, caused by the SARS-CoV-2 virus, a single-stranded RNA virus, of the *Coronaviridae* family, is a new respiratory pathology, originating in China, which through rapid transmission caused a pandemic and has shown important clinical repercussions, due to its complex immunopathological mechanisms.[4] Infection by SARS-CoV-2 causes from a common cold to systemic conditions characterized by severe acute respiratory syndrome; there are also coagulopathies, neurological disorders, in addition to a severe systemic inflammatory state, in which a "cytokine storm" may occur, immunopathologically. The magnitude of clinical manifestations is related to the systemic conditions of infected individuals. SARS-CoV-2 infects cells through a structural peak protein called protein S.[5]

There are three stages of the disease:[6]

– *Viral replication phase:* occurs in the first seven days of infection; during this period, the innate immunity will act through the release of interferon (IFN) alpha and beta and stimulus of cell lessons NK, as a way to prevent the spread of the virus. The main clinical manifestations of this phase are dry cough, fever, adynamia, anosmia, and even the absence of symptoms.
– *Pulmonary phaser:* with an average duration from the seventh to the tenth day (D7-D10). At this stage, the end of the viral replication status and the start of hyperinflammation. The virus has a predilection for pneumocytes II that contain ACE receptors, preventing the action of IFN and causing an inflammatory environment, with the destruction of the basement membrane surfactant and macrophages releasing free radicals, increaseI walk to vascular permeability and predisposing to pneumonia. The destruction of alveolar surfactant with the formation of the hyaline membrane in the alveoli causes difficulty in gas exchange, inflammation, increased vascular permeability, and, consequently, a hypoxemic state, which contributes to a diffuse alveolar damage and evolution clinic for Ang's syndrome acute respiratory disease (ARDS).
– *Systemic inflammatory response syndrome phase:* observed after the D10. Initially, it is

verified the macrophage activation syndrome (MAS); and, right away, an antigenic alteration that stimulates the excessive production of IL-6, causing dysregulation of the immune response. A tumor necrosis factor (tumor necrosis factor – TNF) alpha is another cytokine that contributes to this immune dysregulation, because, in addition to not helping to fight the virus, it stimulates a systemic hyperinflammatory response, causes walk tissue damage throughout the body, and causes a reduction of TCD4 and NK lymphocytes. Nessand period, B lymphocytes stimulate the production of antibodies (mainly IgM). Another important mechanism is The HIF1-alpha synthesis, stimulated by the hypoxemic state itself, which inhibits fibrinolysis and activates tissue factors (extrinsic). Oinflammatory state (TNF-alpha, IL-6) increases platelet aggregation, stimulating prothrombotic events (coagulability), which may progress to disseminated vascular coagulation. The two main clinical manifestations are ARDS and coagulopathy (pulmonary thromboembolism, deep vein thrombosis). The cytokines involved include interleukin-1beta (IL-B), IL-1RA, IL-7, IL-8, IL-9, IL-10, granulocyte, and macrophage colony-stimulating factor (GM-CSF), IFN-gamma, IP10 (interferon y-inducible protein), TNF-α, and vascular endothelial growth factor (VEGF).

Methodology

This is a review study that addressed research published between 2020 and 2021. Only original articles that investigated the topics: immunology and pathophysiology of COVID-19, vaccination, adverse effects of vaccines were selected for this review. To guide this review, the following question was elaborated: "How will the various types of vaccines help the body's immunity, as a form of defense against the SARS-CoV-2 virus?"

For the selection of articles in this review, a survey was carried out in the database of the electronic libraries SciELO (Scientific Electronic Library Online), PubMed, LILACS (Latin American and Caribbean Literature in Health Sciences), and MEDLINE between the months of January to April 2021 with specific screening using the following descriptors: COVID-19 vaccines, SARS-CoV-2, COVID-19 immunology. A total of 57 articles were selected and, among these, 30 were used to prepare the review.

Inclusion criteria for eligibility were original articles and randomized double-blind studies, which clearly described the protocols used in vaccination trials, vaccine side effects, and the trial phases each vaccine is in. Repeated articles and articles that did not fully describe the protocols used were excluded from the study.

Development of COVID-19 vaccines

The development of a new vaccine, under appropriate circumstances, is carried out by a long process that lasts from 10 to 15 years, on average.[7] In a pandemic situation, the urgency led to an overlapping of the phases, with the challenge of developing a vaccine against COVID-19 in a period of 12 to 24 months, while respecting safety standards.[8]

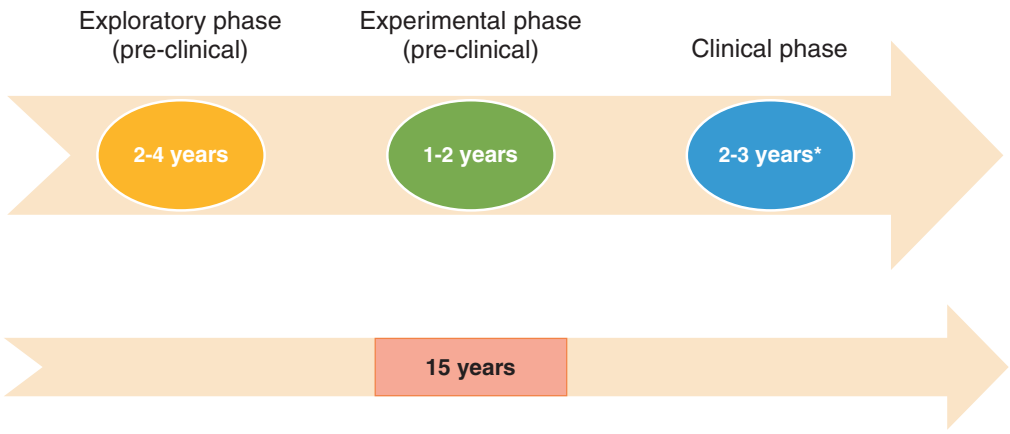
The phases are divided into pre-clinical and clinical, with their respective steps (Figure 1). The first stage of the pre-clinical phase consists of the exploratory phase, which usually lasts two to four years; it involves basic laboratory research and computer modeling to identify natural or synthetic antigens that can be used as vaccine candidates against the disease in question.[8]

The second stage (lasting from one to two years) comprises pre-clinical studies involving cell culture or tissue culture systems and tests on animals, such as mice, to assess the safety of the candidate vaccine and its immunogenicity - ability to provoke an immune response.[7,8] The study guides researchers towards an idea of the cellular responses that can be expected in humans, as well as the safest and most effective starting dose and method of application.[8]

Given the good results in animals with the issue of safety, efficacy, and immunogenicity, the process moves to the clinical phase in humans, testing in small groups and, later, in large groups, divided into three trials.[7]

Phase 1 - Safety: the vaccine is administered to a small group of healthy and immunocompetent individuals, to mainly assess safety, adequate initial dosage, and immunogenic response, as a secondary effect. The durability of 2-3 years.[7]

Phase 2 - Expanded safety: the vaccine is now administered to hundreds of participants in different age groups, re-testing safety, appropriate dosage, adverse events, the interval between doses, as well as the ability of the vaccine to stimulate the immune system.[7,8] The durability of 2-3 years.[7]



* Duration of each stage of the clinical phase.

Figure 1
The new vaccine development process.

Phase 3 - Efficacy: large-scale clinical trials begin, comprising thousands of participants, to prove safety and mainly evaluating efficacy;[8] defined as the percentage by which the disease incidence rate is reduced in the vaccinated groups compared to the placebo group,[7] obtaining more data on immunogenicity and adverse reactions.[8] The durability of 2-3 years.[7]

Phase 4 - Pharmacovigilance: monitoring of vaccine side effects with additional safety and efficacy data over time.[8] Performed after the registration of the vaccine by administrative bodies such as the FDA (Food and Drug Administration), ANVISA (National Health Surveillance Agency), and EMA (European Medicines Agency). Durability 1-2 years.[7]

The viral sequence allowed work to develop a vaccine to continue weeks after China's initial notification to the World Health Organization (WHO) on December 31, 2019, of the outbreak.[9] Coalition for Epidemic Preparedness Innovations (CEPI) funding of grants for vaccine development, announced in January 2020, along with additional funding provided by national and multinational research funders, has driven safe and effective vaccines to be developed. with a term of six to 18 months.[9] As well as the viral similarity of SARS-CoV-2 with SARS-CoV, in which there are previous studies, it contributed to the immediate search for a protective immune response.[8]

Studies have shown that protein S (spike) is the main target for the design and development of these vaccines, as it is responsible for binding the virus to the host cell surface receptor (ACE2, most likely).[10] Candidate vaccines against SARS-CoV-2 being developed around the world and currently under evaluation are based on different platforms, four of which stand out: RNA base, inactivated virus, non-replicating viral vector, and in protein subunit.[10,11]

RNA vaccines

RNA vaccines consist of messenger RNAs (mRNA) that encode viral antigens, which can be translated by human cells to produce antigenic proteins and stimulate the immune system.[12] In other words, in laboratories, vaccines use fragments of genetic material, which encode a part of the virus, such as the Spike protein (in the case of SARS-CoV-2) and, when injected into the hosts, they use the RNA instructions to make copies and trigger an immune response.[8]

The obstacle in the development of this vaccine has been the propensity of the mRNA to degrade, as stability and proper intracellular translation are necessary for the success of the vaccine. As a strategy developed to solve this problem, RNA vaccines are administered in complex with additional agents, such as protamine or nanoparticles based on lipids and polymers, aiming to increase their effectiveness.[13]

mRNA vaccines are advantageous in being safe compared to DNA vaccines as the mRNA does not integrate into the host genome, thus minimizing genotoxicity. Compared to inactivated virus vaccines or live vector vaccines, synthetic mRNA vaccine production is quality-controlled with a reduced chance of biological contamination during production.[11]

They are highly adaptable to new pathogens and capable of recapitulating the native conformation and modifications of antigenic proteins.[12] Lipid-based mRNA transporters are biodegradable. Furthermore, they demonstrate efficacy in inducing a strong humoral and cellular immune response, and their manufacture is fast and on a large scale, meeting the needs of a pandemic.[11]

However, RNA vaccines have some disadvantages, as mRNA without a proper formulation is unstable and rapidly degraded. mRNA is impermeable to cell membranes and cannot be efficiently internalized into the cytosol for translation. It can also activate the innate immune system and potentially induce inflammation and toxicity. These vaccines also require a strict cold chain condition for storage and distribution.[11]

The two main developers of SARS-CoV-2 RNA vaccines are Moderna and BioNTech / Pfizer.[12]

Both vaccines are remarkably effective, involving large randomized, placebo-controlled clinical trials with several individuals. They have evidence of some immune response 10 to 14 days after the application of the first dose of the vaccine and prevention of the severe form of the disease.[14] They require booster doses to ensure a high neutralizing antibody titer and long-term immunogenicity.[13] Overall, these impressive results place the two mRNA vaccines at the top of the most effective vaccines to date.[14]

Pfizer Inc./BionNTech SE

BioNTech (German company) together with Pfizer (an American company) developed vaccines based on mRNA. BioNTech and Pfizer's mRNA vaccine had four candidates: BNT162b1, BNT162b2, BNT162a1, and BNT162c2, of which only two advanced to the next phases.[12,13]

The nucleoside-modified mRNA vaccines are BNT162b1 and BNT162b2. BNT162b1 encodes a trimerized receptor-binding domain (RBD) of the Spike protein, while BNT162b2 encodes a full-length spike protein.[12]

After studies conducted in Germany and the USA in phase I/II, demonstrating that BNT162b1 induced neutralizing and RBD-binding antibodies with titers above that of convalescent human serum, another trial was coordinated comparing the responses to vaccination between BNT162b1 and BNT162b2.[13]

BNT162b1 and BNT162b2 have been shown to induce similar neutralizing titers in young and elderly adults. However, BNT162b2 had fewer systemic adverse reactions in older adults. In light of this, BNT162b2 was advanced instead of BNT162b1 in phase III clinical trial.[13]

On November 18, 2020, Pfizer and BioNTech announced the efficacy analysis of their Phase III clinical trial, whose evaluation showed that BNT162b2 is 95% effective against COVID-19.[13] The results of 95% of vaccine efficacy occur after the second dose, which increases the immune response and probably makes it more durable. The second dose must be administered after 21 days and is authorized for patients 16 years of age and older; there is no maximum age restriction.[14]

For now, in the United States, the Centers for Disease Control and Prevention (CDC) and the FDA recommend proceeding with the two-dose regimen whenever possible.[14]

No serious safety concerns were noted among the 43,000 enrolled participants. These data indicated that BNT162b2 is another well-tolerated and effective COVID-19 vaccine.[13]

Modern (Modern/NIAID)

Moderna is an American company based in Cambridge, Massachusetts. The Modern mRNA vaccine, mRNA-1273, encodes the spike protein so that when the vaccine is injected into the body, the immune cells that process the mRNA and the protein manufactured will subsequently be targeted for destruction.[7]

A specific antibody response appeared on the fifteenth day after the first dose, showing better efficacy in the need for a two-dose regimen.[7]

On November 16, 2020, Moderna unveiled the first interim analysis of its phase III trial, showing an estimated efficacy of 94.5% after the second dose of the vaccine, which was administered after 28 days for those over 18 and no maximum age restriction.[12,14]

His simultaneous security review also didn't notice any significant concerns. Therefore, its promising result suggested that the mRNA-1273 vaccine is safe and effective in preventing symptomatic COVID-19.[12]

Curevac

German biopharmaceutical company CureVac NV announced a clinical development collaboration for its vaccine against SARS-CoV-2 with pharmaceutical company Bayer. An mRNA-based technology platform, RNActive®, was applied to develop the vaccine, called CVnCoV.[15]

In line with pioneering work using mRNA formulated with protamine to target tumors, CureVac has established that mRNA elicits immune responses against target antigens as a prophylactic vaccine. CureVac's proprietary mRNA technology is designed to rapidly identify, produce and test stable and immunogenic mRNA molecules.[16]

CVnCoV is composed of sequence-engineered mRNA formulated with lipid nanoparticles (LNP), not chemically modified, which encodes the full-length S protein with two proline mutations (S2P). These mutations stabilize the protein's conformation, preventing the virus from binding to it and starting the viral replication process.[15,16]

In a provisional analysis, it was shown that two doses of CVnCoV ranging from 2 µg to 12 µg per dose, administered 28 days apart, are safe. Seroconversion (defined as a 4-fold increase from baseline) of virus-neutralizing antibodies two weeks after the second vaccination occurred in all participants who received doses of 12 µg.[15]

No serious vaccine-related adverse events were reported. There were dose-dependent increases in the frequency and severity of solicited systemic adverse events and, to a lesser extent, in local reactions, but most were mild or moderate and of transient duration.[15]

Non-replicating viral vector vaccine

In this type of vaccine, the antigen is cloned into a viral vector that cannot reproduce itself, that is, another known and safe virus is used, to carry specific proteins that can trigger an immune response without causing the disease.[8]

The viral vector mimics natural infection and therefore can produce stronger specific cellular and humoral immune responses compared to the recombinant protein vaccine. Furthermore, viral vectors can accept large insertions into their genome, providing a flexible platform for antigen design.[12]

Common vectors include human adenoviruses (especially, 5 and 26) or chimpanzee (ChAd), parainfluenza virus, measles virus, rabies virus, vesicular stomatitis virus, modified Vaccinia Ankara virus (MVA), and adeno-associated virus (AAV).[8,12]

Disadvantages include that the manufacturing process requires care with the optimization of cell systems and the exclusion of contaminants, which can affect the efficiency of viral vectors.[12] Finally, pre-existing immunity to the viral vector can reduce the effectiveness of the immune response.[8]

The top three candidates for this platform are AstraZeneca/ Oxford University (AZD1222), Gamaleya Research Institute (Gram-COVID-Vac), and Janssen Pharmaceutical Companies/ Johnson & Johnson (Ad26COVS2).[12]

AstraZeneca/Oxford University

AstraZeneca is an Anglo-Swedish pharmaceutical conglomerate and, in partnership with the University of Oxford, the laboratory was one of the pioneers in developing a vaccine against COVID-19, called AZD1222.[17]

The vaccine uses a viral vector of a non-replicating simian adenovirus (chimpanzee), which presents a genomic segment of the virus that expresses the

glycoprotein SARS-CoV-2 spike (S).[17] The dose of the AZD1222 vaccine was based on the previous experience of the Oxford group, which developed a similar type of vaccine for MERS-CoV using chimpanzee adenovirus (ChAdOx1).[12]

The vaccine has been shown to trigger specific antibodies to protein S and T cell responses and to induce neutralizing antibodies after the initial regimen and booster, certifying that it is well tolerated and immunogenic.[12]

The mean total efficacy evaluated, considering the joint studies of the United Kingdom, Brazil, and South Africa was 70.42% (95%CI: 54.84% - 80.63%). Administration of the second dose is indicated after four to twelve weeks, as a greater level of efficacy was observed when there was a longer interval between the first and second dose.[17]

Initially, no serious adverse effects were observed in clinical trials, demonstrating an adequate safety profile similar to other vaccines regularly used.[17] However, in March 2020, the Ministries of Health of several European countries suspended the application of the immunizing agent due to the high risk of thrombosis in vaccinated patients. According to a study carried out in Germany, among the 1.6 million doses applied, 13 demonstrated an association with thrombosis of the cavernous sinuses or cerebral veins.[18]

The Gamaleya National Center of Epidemiology and Microbiology

The COVID-19 vaccine was developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia, called Sputnik V, and registered on August 11, 2020, by the Russian Ministry of Health as Gam-COVID-Vac, is a viral vector vaccine of adenovirus.[12]

The vaccine uses a heterologous recombinant adenovirus approach in two vectors, adenovirus 26 (Ad26) and adenovirus 5 (Ad5) for peak expression of the SARS-CoV-2 protein.[19] We opted for two different adenovirus vectors administered separately in a first and second dose, 21 days apart, as using the same adenovirus for both doses can lead the body to develop an immune response against the vector and destroy it when the second dose is administered.[20] Two different vectors reduce the chance of decreasing its effectiveness.[20] That said, the use of two different serotypes, administered 21 days apart, is intended to overcome any pre-existing adenovirus immunity in the population.[19]

Results showed that Gam-COVID-Vac has an efficacy of 91.4% after the first dose. An efficacy above 95% was also verified when the interval established between the first and the second dose was 21 days.[12]

There was no unexpected adverse effect documented during the clinical trial and the promising results suggest that Gam-COVID-Vac is safe and effective in preventing COVID-19.[12]

Janssen Pharmaceutical Companies/Johnson & Johnson

Johnson & Johnson's vaccine is based on technology that involves a virus, in this case, adenovirus 26 (Ad26) as a viral vector, in which the spike protein gene SARS-CoV-2 is added to its DNA. The adenovirus is modified so that it does not multiply and, therefore, does not cause the disease.[21]

After administration of a modified adenovirus vaccine, Ad26 enters cells and releases its viral DNA. The cells use the viral DNA to produce the spike protein and thereby activate the body's immune system to produce antibodies that recognize the spike protein. If further exposure of the vaccinated person to SARS-CoV-2 occurs, the immune system initiates the recognition of the virus and prevents infection.[21]

The Johnson & Johnson vaccine initially showed the ability to produce antibodies against SARS-CoV-2 in 90% of people who received it after the first dose. Data presented by Johnson & Johnson suggest that one dose of the vaccine was 66% effective in preventing moderate to severe disease and 100% effective in preventing COVID-19-related hospitalization and death.[21]

Inactivated virus vaccine

Inactivated whole vaccines are composed of virions inactivated by heat, radiation, or chemicals so that they cannot replicate. Despite being safer than live attenuated vaccines, immunogenic epitopes of inactivated viruses can be structurally deformed during the inactivation process, impairing the protective immune response.[8,12] They tend to produce a weaker immune response than live attenuated vaccines; therefore, adjuvants are needed to enhance the immune response.[10]

SinovacBiotech Ltd.

Sinovac is a biopharmaceutical company headquartered in Beijing (China), which developed a vaccine in partnership with the Butantan Institute (Brazil), called CoronaVac.[12,17]

Coronavac is composed of the attenuated whole virus of SARS-CoV-2, originated from a strain derived from a patient, cultivated in a Vero cell line (epithelial cells extracted from a primate of the genus *Chlorocebus*, known as African green monkey), inactivated with β-propionolactone, purified and adsorbed with aluminum hydroxide.[17]

The phase III clinical trial was initiated in Brazil, Indonesia, and Turkey.[12] In Brazil, the study was conducted by the Butantan Institute in 17 research centers with about 12,000 volunteers. Regarding the efficacy of CoronaVac, in the trials in Brazil, it was shown a mean total efficacy of 50.39% (95% CI: 35.36-61.98) and, concerning the prevention of mild forms, the efficacy was 77.96% (95% CI: 46.15-90.44). Thus, for the Coronavac vaccine to achieve such efficacy, it is recommended that the second dose be administered within an interval of two to four weeks after the first dose.[17]

BharatBiotech

BharatBiotech is an Indian pharmaceutical company that, in collaboration with the Indian Council of Medical Research and the National Institute of Virology, formulated its vaccine, Covaxin, based on an inactivated live virus platform. This vaccine requires two doses given intramuscularly 28 days apart.[22,23]

Live attenuated vaccines

Live attenuated vaccines involve live pathogens weakened manually by the deletion or mutation of the pathogenic component of the viral genome, not being able to induce infection, but able to stimulate humoral and cellular immune responses and, therefore, mimic characteristics of natural infection.[10,12] As a result, they are often immunogenic with a single administration without an adjuvant.[24]

This type of vaccine presents a higher risk than other technologies, especially in immunocompromised patients, as it includes the possibility of reversion to a virulent state and danger of infection. The biosafety of live attenuated vaccines needs to be carefully evaluated before proceeding to clinical use.[12]

Codagenix and the Serum Institute of India are developing a live attenuated vaccine against SARS-CoV-2, using codon deoptimization technology, based on previous experience with the respiratory syncytial virus (RSV) and influenza.[24]

Subunit protein-based vaccine

Vaccines are produced from purified pieces of the virus.[8] Antigenic fragments of a microorganism that best stimulate an immune response require multiple dosing regimens with adjuvants to achieve strong immune responses.[11]

Subunit vaccines produced by genetic engineering techniques, in which other microorganisms are programmed to produce the desired antigenic fraction, are called recombinant vaccines.[10,12] Furthermore, they are considered safe and can be used in immunocompromised patients.[8]

Novavax Inc.

Novavax is a North American company that also entered the race to develop a vaccine against SARS-CoV-2, called NVX-CoV2373.[11] Funded by CEPI and US Operation Warp Speed, it has developed a recombinant nanoparticle vaccine that exhibits the peak protein SARS-CoV-2, being genetically modified to obtain greater structural stability. Their production used baculoviruses designed to infect Sf9 insect cells.[11,24]

The use of an adjuvant to increase the effectiveness of seroconversion is warranted, so Novavax is using its saponin-based Matrix-M adjuvant.[24] In addition to the humoral response, strong cellular responses are observed after the administration of two doses.[11,24]

Preliminary clinical trial data showed that the NVX-CoV2373 vaccine was 95.6% effective against the original SARS-CoV-2 variant, while also protecting against the newer B.1.1.7 (85.6%) and variants B.1,351 (60%).[25]

The NVX-CoV2373 vaccine can be stored at 2°C to 8°C and is safe. An interim data analysis reported that serious adverse events occurred in small numbers.[25]

Vaccines based on virus-like particles

Virus-like particles (VLPs) represent an interesting approach for vaccine development, being an alternative technology as it seeks to mimic the viral structure.[8,10]

VLPs can be designed to express the surface proteins or nucleic acid sequences of the original virus without the risk of replication or infection as they lack the core genetic material. Its advantage is that, although it is categorized as a recombinant protein vaccine, it still maintains the native conformation of viral proteins, being advantageous over other subunit protein vaccines in terms of immunogenicity and antigenicity.[11]

Medicago

It is a Canadian pharmaceutical company that generated a virus-like particle vaccine (VLP) using a plant-based method – a synthetic gene containing a part of the SARS-CoV-2 genes is transferred into a tobacco species, *Nicotianabenthamiana*, using a bacterial vector. These plants then express VLPs that can be purified.[11,24]

Adverse effects of vaccines

Although there is still a need for more studies, according to Sax PE, it can already be said that, at present, there is no 100% safe vaccine.[14] However, it is worth noting that such effects have become minimal concerning the damage that SARS-CoV-2 can do to the human body. It is also known that there are three ways to guarantee the safety of a vaccine: computer simulation, animal experiments, and human trials. It is the safest method when it is replicated in humans due to its greater proximity to reality.[26]

Comparing the techniques used in the manufacture of vaccines against COVID-19, mRNA vaccines have greater safety, such as those developed by "Pfizer/BioNTech" (BNT162b2) and "Modern" (mRNA-1273), even though we know that both will cause side effects in the majority of the population that receives it, due to their exaggeratedly fast immunological response, characterizing this group as reactogenic vaccines.[27]

As for the effects, pain at the injection site of the dose can be cited as the most common, which lasts from 12 to 14 hours after administration, being characterized as severe intensity by 1% of the population. Symptoms such as headache and fatigue are also recurrent but are clinically treated with a good response to analgesics and anti-inflammatory drugs.[28]

Due to the occurrence of hypersensitivity reactions in some rare patients, including anaphylaxis, which is estimated to occur in approximately 1 in 100,000 doses, a 15-minute observation period after dose administration was determined, and for those with a previous history of severe allergies, the observation time should double to 30 minutes.[14]

There were no reports of cases of Guillain-Barré syndrome or transverse myelitis. Long-term side effects could not be studied in detail, as they were only months after the vaccine was released. However, it is worth noting that such events are commonly very rare.[14]

According to Jackson LAet al., in one of the RNAm vaccine trials, there was a report of effects with varying degrees of severity, even though the test group was mostly young and healthy.[29] Young patients had more side effects than elderly patients, and the second dose caused more effects than the first.[14]

Vaccines that use a non-replicating viral vector (Sputnik V and Johnson&Jonhson) also proved to be tolerable, in addition to a good immune response.[27] This group caused small local reactions with signs of phlogosis, headache, fever, malaise, and fatigue, which should disappear within 96 hours after administration of the dose.[30]

As for the inactivated SARS-CoV-2 viral antigen vaccine (Coronavac), a remarkable reduction in adverse effects when compared to the existing ones has already been proven. Most effects tend to disappear 72 hours after administration of the dose and are characterized by being nonspecific systemic symptoms, which, on a severity scale during phase II of the study, were classified as moderate. There were no reports of serious adverse reactions. The major effect on patients was redness and pain at the vaccine site.[30]

Novavax, produced in the United States, a vaccine based on protein subunit (NVX-CoV2373), only produced mild effects: arthralgia, fatigue, headache, myalgia, nausea, and malaise after at least 72 hours. yet there were no serious adverse effects in the study population. As previously mentioned in other vaccines, signs of redness and pain were also presented at the injection site.[13]

AstraZeneca (AZD1222), in turn, as mentioned above, after approval of its use, demonstrated a dangerous thrombotic potential that motivated the health authorities to decree its suspension. The reports of thrombosis started 4 to 16 days after the application of the dose, being 12 female patients and

1 male, aged 20-63 years. According to the explained pathological mechanism, with vaccination, there is the formation of antibodies against platelet antigens motivated by the immunological reaction. These produced antibodies will bind to the Fc receptor which causes massive platelet activation. It is noteworthy that the reason why it occurs with greater prevalence in cerebral vessels is not known.[18]

Despite not having full knowledge of the long-term effects, the application of vaccines in the vulnerable population is justified and necessary, since the effects of the disease are more devastating in certain groups.[26]

Conclusion

Following what has been described, the prerogative that not all vaccines are safe and have already been properly tested is notorious. However, due to the short period and the urgency in which the world lives due to the disease pandemic, it is essential that the population can adhere to the vaccines that have been nationally approved, as COVID-19 can bring even more damage to the population than the possible side effects. Furthermore, it is concluded that RNA vaccines have better efficacy; however, they are dangerously more associated with side effects, which, in contrast, are scarce in vaccines made from the attenuated virus.

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No conflicts of interest declared concerning the publication of this article.

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