



## CHAPTER 3

# COVID-19 Vaccines: A Literature Review

  10.56238/pacfdnsv1-003

### Alexander de Sa Vilela Filho

E-mail: alexander.vilela@sempreceub.com

### Breno Menegale Bianchetti

E-mail: breno.mb@sempreceub.com

### Carolina Malard Peixer

E-mail: carolina.malard@sempreceub.com

### Matheus Santos Cordón

E-mail: matheus.santosc@sempreceub.com

### Mayara de Oliveira Felipe Rocha

E-mail: mayara.rocha@sempreceub.com

### Vinicius Cardoso Ribeiro Vasconcelos

E-mail: vinicius.cardoso@sempreceub.com

### ABSTRACT

**Introduction:** In 2019, the SARS-Cov-2 virus emerged in Wuhan province, China, causing the pandemic of COVID-19 (R. MOJICA-CRESPO et al, 2020). In Brazil, the first confirmed case of COVID-19 was recorded on February 26, 2020 (MINISTÉRIO DA SAÚDE, 2020). In an effort to reduce the spread of this virus and end the pandemic, scientists around the world have worked to develop efficient and safe vaccines in record time to combat the pathogen. At the time of writing, 104 vaccines are under development, 8 approved by the World Health Organization (WHO, 2020) (KNOLL M D ET AL, 2020) and 4 approved by

Brazil's National Health Surveillance Agency (ANVISA, 2020).

**Objective:** To determine the difference in susceptibility to develop the severe form of the disease in people who had Covid and were vaccinated, compared to those who were not vaccinated in Brazil. **Material and Methods:** The review was based on articles published in national and international databases, such as Scielo and PubMed, as well as websites of the World Health Organization, Pan American Health Organization, Ministry of Health, National Health Surveillance Agency, among others. **Final Considerations:** The present literature review concluded that the four vaccines approved by ANVISA have proven efficacy in fighting the development, but mainly in aggravating the clinical picture of the new coronavirus disease, with certain exceptions of some vaccines in pregnant women and children due to the lack of data collected from these two specific groups. Thus, besides all the biosafety protocols recommended by the health agencies during the pandemic scenario, it can be seen that vaccination was responsible for controlling the number of new cases of the disease in Brazil and that it brought significant improvement in the lives of those infected by the new coronavirus, avoiding the worsening of the clinical picture and reducing the mortality rate.

**Keywords:** vaccines, COVID-19, Astrazeneca, CoronaVac, Janssen, Pfizer,

## 1 INTRODUCTION

### HISTORY OF THE PANDEMIC

In 2019, the SARS-Cov-2 virus emerged in Wuhan province, China, causing the pandemic of COVID-19. Such a virus had zoonotic origin, from wild animals and spread rapidly by direct route through contact with the viral particles present in saliva droplets or in aerosol suspension (R. MOJICA-CRESPO et al, 2020).

When these viral particles are able to bind, via the spike protein, to cells (Hosseini et al, 2020), the body can react causing mild symptoms such as body aches, nasal congestion, headache, conjunctivitis, sore throat, diarrhea, loss of taste or smell, skin rash, or discoloration of fingers or toes (PAHO, 2020). In

addition to these mild symptoms COVID-19 can cause more severe symptoms such as Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV) (PAHO, 2020).

In Brazil, the first confirmed case of COVID-19 was recorded on February 26, 2020 (MINISTÉRIO DA SAÚDE, 2020). However, on November 15, 2021, at 17:20, there were already 21,960,766 confirmed cases and 611,346 deaths from infection with the new coronavirus (PAINEL CORONAVÍRUS, 2021). This rapid dissemination not only caused damage to the health of the population, but also socioeconomic problems such as: difficulty in the economic support of the financial system and the population; mental illness of people in times of confinement and fear for the risk of infection and death; and obstacles in access to essential goods such as food, medicines, transportation, among others (PORTAL FIOCRUZ, 2020).

In the quest to reduce the spread of this virus and stop the pandemic, scientists around the world have worked to develop efficient and safe vaccines in record time to combat the pathogen. At the time of writing, 104 vaccines are under development, 8 approved by the World Health Organization (WHO, 2020) (Knoll M D et al, 2020) and 4 have been approved by Brazil's National Health Surveillance Agency (ANVISA, 2021). These are the Oxford/Astrazeneca, Janssen, CoronaVac and Pfizer vaccines, each with a specific mode of action, efficacy and different costs.

## **2 HISTORY OF VACCINES**

The history of vaccines began in the late 18th century, with the idea of attenuation of virulent infections, developed by physician Edward Jenner, to combat smallpox. It is worth mentioning that, by the end of the 1800s, Europe was living with frequent episodes of smallpox outbreaks. At that time, therefore, the medical class was already mobilized to combat this recurring pathology. However, it was only when English doctors realized that patients affected by the human variant of smallpox, who had already been infected by the bovine variant (cowpox), presented clinical pictures that were notoriously more attenuated and much less aggressive, that a great leap forward in smallpox control was effectively taken. It should be noted that the disease in bovine hosts was called vaccinia, which directly influenced the nomenclature of the new discovery (LARROCA, 2000).

Jenner's conclusion allowed the understanding of two fundamental points: not only an animal variation of the pathology was able to protect humans from severe infections of the human variation, but also the deliberate inoculation of the attenuated pathogen in healthy human individuals could induce future protection without severe manifestation of the disease (CONTI, 2021); this last conclusion was derived from the process called variolization. Variolization consisted in collecting secretion from the skin wounds of patients infected with a mild variation of the disease and infecting healthy humans, with the aim of activating the protective response (known today as immune response). Soon after, it was concluded that this process was analogous to using small amounts of poison to make a person immune to the toxic effects, since the results of the experiments proved to be very efficient and promising. The development of this technique was crucial for the evolution of vaccines, but when Jenner published "An Inquiry into the Causes

and Effects of the Variolae Vaccinae", the work suffered strong criticism and discredit from the medical academy, but undeniably, when it proved effective, about two years after its publication, it became one of the greatest references on the study of immunization at the time.

Therefore, Jenner realized that the use of an animal virus (probably smallpox) could prevent the disease, based on the idea that a virulent agent external to the healthy individual could be inoculated in an attenuated form in humans (PLOTKIN ET AL, 2014) in order to generate a protective response against the aggravation and classic manifestation of the disease. Therefore, a technique that would revolutionize health practices, epidemic control and collective health in Europe and, later, in the world, was born.

Still in the late 18th century and early 19th century, Pasteur had an important contribution to the development of new vaccine techniques, especially in the field of developing the understanding of the protection process against external agents. In fact, the author Tania M. Fernandes (2010) argues that lies, in this specific point, the big difference between the understanding of Jenner and Pasteur:

The central idea, introduced by Jenner, that the smallpox vaccine produced a disease was, as we have already pointed out, accepted by Pasteur. According to this idea, it was not the smallpox virus that was present in the vaccine, but a similar virus modified by dissemination in cattle. Although supporters of the same understanding of the vaccine - as a disease -, there are quite profound differences in the understanding that both assumed about this process, which, for Pasteur, was justified by the presence of a specific etiological agent, whose action was controllable.

That is, in the 19th century, with the advance of technology, but especially the development of microbiology headed by Pasteur, vaccines started to be developed in laboratories and this allowed discovering that immunogenicity could be maintained if bacteria, in particular, were carefully killed by heat or chemical treatment. Importantly, Pasteur's work on pathogen attenuation paved the way for the creation of the first vaccine with live attenuated organisms and inactivated vaccines. Inactivation was first applied to pathogens that cause diseases such as typhoid fever, plague, and cholera bacilli (PLOTKIN ET AL, 2014).

In the early 20th century, the contribution of Pasteur's legacy unfolded further with the work of his pupils Albert Calmette and Camille Guérin, who together were responsible for producing the Bacillus Calmette-Guerin Vaccine, better known as BCG, which was decisive in controlling and combating the dreaded tuberculosis infection.

Already in the first half of the 20th century, there was a major revolution with the discovery that cells could be grown in vitro and used as substrates for viral growth. Enders, Weller and Robbins were responsible for showing that several viruses could be grown in cell cultures. Then, through the selection of clones by passage in cell cultures in vitro, it was possible to create the vaccines against measles, rubella, mumps and varicella. Furthermore, in this period, with the beginning of bacteriology, it was discovered that many of these pathogens were surrounded by a polysaccharide capsule and that antibodies against the capsule were able to promote phagocytosis. Using this information it was possible to develop the

meningococcal polysaccharide vaccine by Artenstein, Gottschlich and collaborators (PLOTKIN ET AL, 2014).

In addition, in the late 20th century, the genetic engineering revolution had a major impact on vaccine development. The first fruit of this revolution was the hepatitis B vaccine (PLOTKIN ET AL, 2014). Furthermore, this revolution gave rise to new techniques, which are much more efficient in production and economical in manufacturing, such as split product, subunit, isolated protein, peptide, marker vaccine, live vector, and nucleic acid approaches (FRANCIS MJ ET AL, 2018). Soon, one can see how the evolution of genetic engineering and vaccines has been crucial for the development of mankind, especially in the field of fighting and preventing infectious diseases, since the principle of vaccination is to induce protection against a pathogen by mimicking its natural interaction with the human immune system (CANOUI ET AL, 2019).

Currently, in the middle of the new coronavirus pandemic, the world and the scientific community have been striving, through vaccines, to minimize the impacts of the virus on individuals and try to re-establish a minimally normal life, as in the pre-pandemic scenario.

### **3 ASTRAZENECA**

#### **3.1 VACCINE PRESENTATION**

The ChAdOx nCoV-19 vaccine, better known by the name of its developers and producers: the University of Oxford and the pharmaceutical company AstraZeneca (Oxford-AstraZeneca), is produced using the viral vector model. In Brazil, there is a production partnership with the FioCruz Institute (KNOLL et al, 2021).

#### **3.2 MEANS OF ACTION - OPERATION**

The Oxford-AstraZeneca vaccine comprises a single replication-deficient recombinant chimpanzee adenovirus vector expressing the S glycoprotein of SARS CoV-2. After administration, this glycoprotein is expressed on site, stimulating neutralizing antibodies and the cellular immune response (Vaccine Bulletin).

#### **3.3 RESEARCH**

Initially, 4 randomized clinical trials were done in 3 different countries: UK, South Africa and Brazil. These studies reported on the safety and efficacy of this vaccine in adults 18 years of age and older. After the results of phase 1 it was concluded that a booster dose would be required 28 days after the first dose.(Knoll et al, 2021). But due to logistical constraints, the interval between dose 1 and dose 2 ranged from 3 to 28 weeks (VACCINE BULLETIN).

### 3.4 EFFICIENCY

Interim results from the studies that took place in the UK and Brazil showed that in approximately 4 months of follow-up of 11,636 participants (18-55 years old) no hospital admissions for COVID occurred in the participants who received this vaccine, while in the control group 10 participants went to hospital because of the virus (KNOLL et al, 2021).

### 3.5 COST

According to the TCU (Federal Audit Court) the unit price of the Oxford-AstraZeneca vaccine produced by Fiocruz is R\$19.87.

### 3.6 TRANSPORTATION

This vaccine must be conserved under refrigeration (2 to 8°C), it must not be frozen and it must be kept in its original package in order to protect from light. After the withdrawal of the first dose, keep the vial at room temperature (up to 30°C), and use it within 6 hours or, store it under refrigeration (2 to 8°C) and use it within 48 hours (VACCINE BULLETIN).

### 3.7 CONTRAINDICATIONS AND ADVERSE REACTIONS

Contraindications are: hypersensitivity to the active ingredient or to any of the excipients of the covid-19 (recombinant) vaccine, patients who have suffered significant venous and/or arterial thrombosis in combination with thrombocytopenia after vaccination with any covid-19 vaccine, and individuals who have had previous episodes of Capillary Extravasation Syndrome (see the Warnings and Precautions section) (VACCINE BULLETIN).

Adverse reactions of vaccination can be divided by frequency: **Very common** as headache, nausea, myalgia, arthralgia, injection site tenderness, injection site pain, injection site heat sensation, injection site pruritus, injection site ecchymosis, fatigue, malaise, fever, chills; **Common:** Vomiting, diarrhea, pain in extremities, swelling at injection site, erythema at injection site, induration at injection site, pyrexia, influenza-like symptoms; **Uncommon:** Hyperhidrosis, pruritus, rash, urticaria, abdominal pain, dizziness, drowsiness, decreased appetite, lymphadenopathy. In the elderly ( $\geq 65$  years of age), these reactions were generally milder and less frequently reported (Vaccine Bulletin).

### 3.8 PEDIATRIC, ADOLESCENT AND PREGNANT USE

The use of AstraZeneca vaccine in pregnant women has not been extensively researched; animal studies have not indicated any direct or indirect harmful effects on pregnancy, embryofetal development, parturition or postnatal development. Therefore, as a precautionary measure, vaccination with AstraZeneca vaccine is not recommended during pregnancy (VACCINE BULLETIN).

The safety and effectiveness of covid-19 (recombinant) vaccine in children and adolescents (less than 18 years of age) have not been established.

## **4 CORONAVAC**

### **4.1 VACCINE PRESENTATION**

CoronaVac (developed by Sinovac Life Sciences, Beijing, China) is presented as an injectable suspension, and can be monodose or multidose (with two or ten doses). One dose is composed of 0.5 mL containing 600 SU of inactivated SARS-CoV-2 virus antigen each and should be administered intramuscularly.

Excipients: aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride and water for injections.

### **4.2 MEANS OF ACTION - OPERATION**

CoronaVac is a vaccine that works with inactivated, i.e. killed, virus. In immunizers of this type, the virus reaches this state through the use of chemicals (those used in CoronaVac are formaldehyde - which prevents the growth of microorganisms in various products - and beta-propiolactone. These compounds lead the virus to death), which make up the method used in the production of CoronaVac, although there are other means, such as irradiation or heat (BUTANTAN, 2021).

Inactivated virus vaccines are more stable, easy to transport and store, and because the virus is dead, they produce few adverse events, as opposed to attenuated virus vaccines, in which the virus remains alive (BUTANTAN, 2021).

### **4.3 RESEARCH**

CoronaVac, an inactivated whole virus SARS-CoV-2 candidate vaccine developed by Sinovac Life Sciences (Beijing, China), has been in phase 3 trials since mid-2020 in Brazil, Indonesia, Chile, and Turkey. On April 28, 2021, it was approved in 22 countries for emergency use.(TANRIOVER, MINE DURUSU et al, 2021)

### **4.4 EFFICIENCY**

A large phase 3 study in Brazil showed that two doses, given 14 days apart, had efficacy of 51% [95% confidence interval (CI): 36%-62%] against symptomatic SARS-CoV-2 infection, 100% (95% CI: 17%-100%) against severe COVID-19, and 100% (95% CI: 56%-100%) against hospitalization, starting 14 days after the second dose of vaccination. No COVID-19-related deaths occurred in the vaccinated group; there was one COVID-19-related death in the placebo group. Vaccine efficacy was maintained in groups with and without comorbidities and regardless of prior SARS-CoV-2 infection. The mean duration of follow-up was 73 days (PAHO, 2021).

#### 4.5 COST

According to the TCU (Tribunal de Contas da União), the unit cost of the CoronaVac vaccine is R\$58.20.

#### 4.6 TRANSPORTATION

The vaccine must be stored and transported under refrigeration, between +2°C and +8°C, protected from light and must not be frozen. If kept under appropriate conditions, the vaccine is valid for 12 months from the date of manufacture (Vaccine Bulletin).

#### 4.7 CONTRAINDICATIONS AND ADVERSE REACTIONS

The vaccine is contraindicated for people allergic to any components of the product, described in item 4.1, besides individuals with fever, acute illness and acute onset of chronic diseases (VACCINE BULLETIN).

Adverse reactions are divided according to age (adults and elderly), frequency of cases, and whether it is a local or systemic symptom.

In adults (18-59 years old), up to 7 days after the administration of the second dose, it is **very common to have**, as systemic adverse reactions, headache and fatigue; and locally, pain. Moreover, it is **common to have** as systemic reactions: nausea, diarrhea, myalgia, chills, loss of appetite, cough, arthralgia, pruritus, rhinorrhea, and nasal congestion; and locally: erythema, swelling, induration, and pruritus. Finally, it is **uncommon to have** systemic reactions such as vomiting, fever, exanthema, allergic reaction, oropharyngeal pain, odynophagia, sneezing, asthenia, dizziness, abdominal pain, somnolence, malaise, flushing, pain in the extremities, upper abdominal pain, back pain, vertigo, dyspnea, and edema; as well as hematoma locally.

In the elderly (over 60 years old), up to 7 days after the administration of the second dose, it is **very common to have** local pain. It is also **common to have**, as systemic reactions, nausea, diarrhea, headache, fatigue, myalgia, cough, arthralgia, pruritus, rhinorrhea, odynophagia, and nasal congestion; and, as local reactions, pruritus, erythema, local edema, and induration. Finally, it is **uncommon to have** systemic reactions such as vomiting, chills, decreased appetite, allergic reaction, asthenia, dizziness, ecchymosis, hypothermia and discomfort in the limbs, and hematoma as a local reaction (Vaccine Bulletin).

#### 4.8 PEDIATRIC, ADOLESCENT AND PREGNANT USE

There are no results from studies conducted with covid-19 (inactivated) adsorbed vaccine in the pediatric population.

CoronaVac has been shown to be well tolerated with a good safety profile in subjects 18 years and older in phase 1/2 trials, and provided a good humoral response against SARS-CoV -2 (TANRIOVER, MINE DURUSU et al, 2021).

The WHO recommends the use of the Sinovac-CoronaVac vaccine in pregnant women when the benefits of vaccination for pregnant women outweigh the potential risks (PAHO, 2021).

## **5 JANSSEN**

### **5.1 VACCINE PRESENTATION**

Johnson & Johnson pharmaceuticals' Ad26.COVS vaccine, known as Janssen, is produced using a recombinant adenovirus vector and was derived from the first clinical isolate of the Wuhan strain in China. (SADOFF et al, 2021)

### **5.2 MEANS OF ACTION - OPERATION**

The vaccine produced by Johnson & Johnson uses the technique of introducing a recombinant adenovirus. According to Freire (2020), the adenovirus has specific programming for human cellular infection and, precisely for this reason, works as a kind of carrier of genetic material external to the individual to be infected. Thus, the technique is effective by removing adenoviral genes, which attribute infectious and harmful characteristics to humans, and replace them by known viral genes. In the case of the Janssen vaccine, the removed gene prevents the adenovirus from replicating itself and any pathological manifestations of the virus from developing. The gene allocated in the adenovirus, on the other hand, belongs to Sars-CoV2 and is responsible for encoding the full length stabilized SPIKE proteins, of the new coronavirus (SADOFF, 2021).

In this way, the technique creates an adenovirus vector that will be deployed in the healthy human organism. The vector then delivers the adenovirus, loaded with the gene that produces the SPIKE protein, to the antigen-presenting cells, which, by means of their own cellular machinery, will produce messenger RNA (mRNA) for translation of the proteins (antigens). Already metabolized, the antigens will be directed to the lymphatic system, to be exposed to the auxiliary T cells. This process triggers the neutralizing humoral immunity in an extremely potent way and cellular immunity, which was polarized towards the Th1 subpopulation, producer of IFN- $\gamma$  (BOS et al, 2020).

### **5.3 RESEARCH**

The randomized clinical trials started on July 22, 2020, at 12 centers in Belgium and the United States. Randomization was performed via an interactive web response system and stratified according to site with the use of randomly permuted blocks. Participants and investigators remained unaware of trial group assignments throughout the trial. Trial participants included healthy adults aged 18 to 55 years and those aged 65 years and older, with the trial divided into three groups, the youngest in cohort 1a with a target recruitment of 375 participants and cohort 1b an exploratory cohort for in-depth immunogenicity analysis with a target recruitment of 25 participants. The oldest age group was included in cohort 3, with a



target enrollment of 375 participants. Cohort 2 was responsible for collecting long-term data, comparing a single-dose regimen with a two-dose regimen (SADOFF et al, 2021).

#### 5.4 EFFICIENCY

Results showed that neutralizing antibodies against wild-type virus were detected in 90% or more of all participants on day 29 after the first dose of vaccine, regardless of vaccine dose or age group, and reached 96% on day 57 with a further increase in titers in cohort 1a. Titers remained stable until at least day 71. A second dose provided an increase in titer by a factor of 2.6 to 2.9. On day 15, CD4 + T cell responses were detected in 76 to 83% of participants in cohort 1 and in 60 to 67% of those in cohort 3, with a clear bias toward type 1 helper T cells. CD8 + T cell responses were robust overall, but lower in cohort 3 (SADOFF et al, 2021).

No participant stopped the study because of an adverse event. Five serious adverse events occurred: one case of hypotension that was considered by the investigator to be unrelated to the vaccine due to a history of recurrent hypotension; one case of bilateral nephrolithiasis in a participant with a history of kidney stones (unrelated); one case of legionella pneumonia (unrelated); one worsening of multiple sclerosis, which remained undiagnosed for approximately 8 to 10 years based on MRI findings (unrelated); and one case of fever that resulted in hospitalization for suspected Covid-19. In the latter case, the participant recovered within 12 hours and the fever was subsequently considered by the investigator to be vaccine related (SADOFF et al, 2021).

#### 5.5 COST

According to the TCU (Tribunal de Contas da União), the unitary price of the Janssen vaccine is R\$56.30.

#### 5.6 TRANSPORTATION

The conservation of this vaccine must be done as follows: before the first puncture of the vial-ampoule it must be conserved between 2 °C and 8 °C and protected from light. And, after the first puncture of the vial-ampoule, you must use the doses of the vial immediately or keep the vial-ampoule between 2 °C and 8 °C for up to 6 hours.

#### 5.7 CONTRAINDICATIONS AND ADVERSE REACTIONS

The contraindication for this vaccine is only for patients with a history of hypersensitivity to the active substance or to any of the excipients that are part of the formulation.

The **most common** adverse reactions of this vaccine are pain at the injection site (48.6%), headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%). Cough, arthralgia, and pyrexia are

**common** (<10%). Tremor, sneezing, skin irritation, hyperhidrosis, muscle weakness, back pain, asthenia, and malaise are **uncommon** (<1%) (Vaccine package insert).

## 5.8 PEDIATRIC, ADOLESCENT AND PREGNANT USE

The use of this vaccine in pregnancy is not fully evidenced. In animal studies, there is no indication of any direct or indirect harmful effects related to pregnancy. Therefore, the researchers and doctors who developed the vaccine do not advise giving it to pregnant women. Unless indicated by a doctor or dentist.

The safety and effectiveness of Janssen vaccine in children and adolescents (less than 18 years of age) have not been established.

## 6 PFIZER

### 6.1 VACCINE PRESENTATION

Produced by the US laboratory Pfizer, in partnership with the German laboratory BioNTech, the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) is a formulated, lipid nanoparticle of nucleoside-modified mRNA encoding the pre-fusion peak glycoprotein of the SARS-CoV-2 causing disease COVID-19. Vaccination consists of 2 doses (30 µg, 0.3 mL each) administered intramuscularly, 3 weeks apart (OLIVER, SARA et al. 2020).

### 6.2 MEANS OF ACTION - OPERATION

The nucleoside-modified messenger RNA is formulated in lipid nanoparticles, allowing the non-replicating RNA to enter host cells to allow transient expression of the SARS-CoV-2 virus S antigen. The mRNA encodes the integral membrane-bound S protein, with two point mutations in the central helix. Mutation of these two amino acids to proline locks the S protein into an antigenically preferred pre-fusion conformation. The vaccine induces cellular immunity and production of neutralizing antibodies against the spike (S) antigen, which may contribute to protection against COVID-19. (VACCINE GUIDE)

### 6.3 RESEARCH

A total of 43,548 participants underwent randomization, of which 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19, with onset at least 7 days after the second dose, among participants assigned to receive BNT162b2 and 162 cases among those assigned to receive placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credibility interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed in subgroups defined by age, sex, race, ethnicity, baseline body mass index, and presence of coexisting diseases. Among the 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by mild to moderate short-term

injection site pain, fatigue, and headache. The incidence of serious adverse events was low and similar in the vaccine and placebo groups (POLACK et al., 2020)

#### 6.4 EFFICIENCY

Pfizer-BioNTech 2-dose COVID-19 vaccination performed 21 days apart showed 95% efficacy with respect to symptomatic disease prevention and was measured 7 days after the second dose. In addition, the vaccine was shown to be effective in all age, racial and ethnic groups.(BANERJI, ALEENA et al.2021).

People previously infected with COVID-19 exhibited robust immune response with the presence of SARS-CoV-2 specific antibodies after one dose of the vaccine, while individuals who had not had the infection before showed similar levels of SARS-CoV-2 specific antibodies to previously infected individuals after the second dose of the vaccine. Possibly this is due to previously infected individuals having acquired natural immunity and the first vaccination acting as a recall injection to their immune system (KHEHRA, NIMRAT et al. 2021).

Since Pfizer began global distribution of the BNT162b2 vaccine in December 2020, the UK was the first to delay the second dose to the maximum 12-week interval in order to conduct research on the efficacy of a single dose of the BNT162b2 vaccine. While a single dose may be effective within 21 days, a second dose within the maximum 12-week interval is still highly recommended and necessary to provide more durable / long-lasting protection (KHEHRA, NIMRAT et al. 2021).

#### 6.5 COST

According to the TCU's (Federal Audit Court) Monitoring Report, the unit cost of the CORMINATY vaccine<sup>®</sup>, produced by the American laboratory Pfizer, in partnership with the German laboratory BioNTech is R\$56.30.

#### 6.6 TRANSPORTATION

Tozinameran vaccine is transported in dry ice containers and stored at approximately -70°C. The vaccine is distributed as a frozen suspension in a 0.45 ml volume, preservative-free, multi-dose vial. After dilution with 1.8 ml of 0.9% sodium chloride injection, each vial contains up to 6 dosages of 0.3 ml. Once thawed, the vaccine should not be frozen again (PADDA, INDERBIR S. et al. 2021).

#### 6.7 CONTRAINDICATIONS AND ADVERSE REACTIONS

The adverse effects reported were Injection site tenderness/pain, Injection site swelling, Injection site redness, Fever, Fatigue, Headache, Muscle pain, Chills, Joint pain, Nausea, Malaise, Lymphadenopathy, Severe allergic reaction (rare) and Temporary unilateral facial tilt (rare) (PADDA, INDERBIR S. et al. 2021).

Allergic reactions to vaccines are attributed to the inactive ingredients or excipients. They are necessary and added for specific purposes, and represent the main contributor to immediate and specific IgE-mediated reactions associated with vaccines. Patients who have an immediate or severe allergic reaction to the vaccine should not receive a second dose (BANERJI, ALEENA et al.2021).

## 6.8 PEDIATRIC, ADOLESCENT AND PREGNANT USE

### 6.8.1 Use for pregnant women

Pfizer's vaccine received final registration from Anvisa on February 23, 2021 (ANVISA, 2021).

Studies indicate that the two doses of the BNT162b2 vaccine produced satisfactory immune response against SARS-CoV-2 virus although SARS-CoV-2 IgG levels are lower in pregnant women than those observed in non-pregnant women. The results of adverse reactions in the population vaccinated with the two doses of this vaccine do not indicate any safety concerns (BOOKSTEIN PERETZ, S. et al. 2021).

### 6.8.2 Use for adolescents aged 12 to 15 years

Anvisa authorized the application of the vaccine for people over 12 years old on June 11, 2021 (ANVISA, 2021).

Studies indicate that the BNT162b2 vaccine has a favorable safety profile and produced a more efficient immune response in this age group than the immune response produced by this same vaccine in young adults, 16 to 25 years of age (FRENCK, JR. RW et al ).

### 6.8.3 Use for children from 5 to 11 years old

To date, Anvisa has not authorized application of the vaccine for children under 12 years old in Brazil, but the laboratory requested on 11/12 that the agency include this age group in the vaccination campaign. At the production date of this article, the request is still under analysis (ANVISA, 2021). By way of comparison, in some countries, such as the USA, the use for children between 5 and 11 years of age is permitted.

For this age group, the vaccine is supplied in a vial with an orange cap and an orange border label. This vial should not be used in individuals 12 years of age and older. When preparing the multiple-dose vial as described, the content should be diluted with a sterile 0.9% sodium chloride injection (Health Care Provider Information Sheet, 2021).

## 7 FINAL CONSIDERATIONS

The present literature review concluded that the four vaccines approved by ANVISA have proven efficacy in fighting the development, but especially in worsening the clinical picture of the new coronavirus disease, with certain exceptions of some vaccines in pregnant women and children due to the lack of data collected from these two specific groups. Thus, besides all the biosafety protocols recommended by the

health agencies during the pandemic scenario, it can be seen that vaccination was responsible for controlling the number of new cases of the disease in Brazil.

However, it should be noted that at the time of writing, the Covid-19 Pandemic has not yet ended, so much of the fundamental data for a more in-depth and robust analysis has yet to be generated, collected, and analyzed. Despite this academically unfavorable scenario for definitive conclusions, this work is in line with the view of author Gordon Ada (2007), of the Immunology and Genetics division at the Australian National University, who has analyzed an extensive list of infectious diseases and how the number of cases of infected people increased or decreased after the use of vaccines. In his work, he compares data from past epidemics, before and after vaccines were developed. The result, according to the author himself, in his quantitative tables and graphs, demonstrates the effectiveness of immunizers in effectively decreasing the number of infected people, at a rate of over 99%, with *outcomes* ranging from encouraging to extraordinarily good.

Therefore, anchored in the solid literature review on vaccines and the pathologies they control throughout the research process, this paper, although it still needs more concrete data that have not yet been fully processed around the world, tends to affirm that mass vaccination has brought significant improvement in the lives of those infected by the new coronavirus, avoiding the worsening of the clinical picture and reducing the mortality rate.

It is also noteworthy that, for the sake of this necessary search for a better understanding of the virus, the Ministry of Health started in May 2021 a survey on the prevalence of infection by SARS-COV-2 in Brazil (PrevCOV). This survey will be the most comprehensive on the subject in the world, as it will involve 27 capital cities and their metropolitan regions and 62,097 households in 274 municipalities, the equivalent of 211,129 people. The objective of this study is to show the magnitude of virus circulation in Brazil and how and in which states, capitals and metropolitan regions SARS-CoV-2 infection has been more intense. With this study, the Ministry of Health will be able to monitor vaccination data, indicating whether the population has taken the first and second dose of vaccines offered (PAHO, 2021). This research is still in progress, but it will be important to provide subsidies to improve public policies to confront the pandemic by health authorities (PAHO, 2021).

Moreover, additional information has been gathered on the effectiveness of the vaccines, such as the mechanism of action, the process until the proof of effectiveness, the cost, transportation, contraindications, adverse reactions, and specificities of the use of each one in children and pregnant women, in order for the reader to have a more comprehensive notion of each immunizer.

Finally, the low number of studies on the use of vaccines in pregnant women and children was verified as a limitation of the research.

## REFERENCES

- Ada G. The importance of vaccination. *Front Biosci* 2007; 12: 1278-90.
- National Health Surveillance Agency. Anvisa Note: Anvisa grants first definitive registration for Covid-19 vaccine in the Americas. National Health Surveillance Agency, 2021. Available at: <https://www.gov.br/pt-br/noticias/saude-e-vigilancia-sanitaria/2021/02/anvisa-concede-primeiro-registro-definitivo-para-vacina-contr-a-covid-19-nas-americas>. Accessed November 9, 2021.
- Banerji, A., Wickner, PG, Saff, R., Stone, CA, Jr, Robinson, LB, Long, AA, Wolfson, AR, Williams, P., Khan, DA, Phillips, E., & Blumenthal, KG (2021). mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. *The journal of clinical allergy and immunology. In practice* , 9 (4), 1423-1437. <https://doi.org/10.1016/j.jaip.2020.12.047>
- Bookstein Peretz, S., Regev, N., Novick, L., Nachshol, M., Goffer, E., Ben-David, A., Asraf, K., Doolman, R., Levin, E.G., Regev Yochay, G. and Yinon, Y. (2021), Short-term outcome of pregnant women vaccinated with BNT162b2 mRNA COVID-19 vaccine. *Ultrasound Obstet Gynecol*, 58: 450-456. <https://doi.org/10.1002/uog.23729>.
- Bos R, Rutten L, van der Lubbe JEM, Bakkers MJG, Hardenberg G, Wegmann F, Zuijdgeest D, de Wilde AH, Koornneef A, Verwilligen A, van Manen D, Kwaks T, Vogels R, Dalebout TJ, Myeni SK, Kikkert M, Snijder EJ, Li Z, Barouch DH, Vellinga J, Langedijk JPM, Zahn RC, Custers J, Schuitemaker H. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. *NPJ Vaccines* . 2020;5:91.
- Covid-19 (recombinant) vaccine package insert, healthcare professional, version 009. 2021. Available at: [https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=VACINA%20COVID-19%20\(RECOMBINANT\)](https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=VACINA%20COVID-19%20(RECOMBINANT))
- Vaccine Bulletin. Available at: [https://vacinacovid.butantan.gov.br/assets/arquivos/Bulas\\_Anvisa/20210806profissional.pdf](https://vacinacovid.butantan.gov.br/assets/arquivos/Bulas_Anvisa/20210806profissional.pdf) Accessed on 06/10/2021.
- Janssen vaccine package insert. Available at: <https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/bulas-e-rotulos/bulas-uso-emergencial/vacinas/vacina-covid-19-janssen.pdf>
- Package insert for health professionals. Available at: [https://www.pfizer.com.br/sites/default/files/inline-files/Comirnaty\\_Profissional\\_de\\_Saude\\_21.pdf](https://www.pfizer.com.br/sites/default/files/inline-files/Comirnaty_Profissional_de_Saude_21.pdf). Accessed on 05/10/2021.
- Canouï E, Launay O. Histoire et principes de la vaccination. *Rev Mal Respir*. 2019;36:74-81. doi: 10.1016/j.rmr.2018.02.015.
- New cases of COVID-19 by reporting date. Coronavirus Brazil, 2021. Available at: <https://covid.saude.gov.br/>
- CONTI, A. A. Vaccination through time: from the first smallpox vaccine to current vaccination campaigns against the COVID-19 pandemic. *Acta Biomedica Atenei Parmensis*, [S. l.], v. 92, n. S6, p. e2021453, 2021. DOI: 10.23750/abm.v92iS6.12211. Available at: <https://mattioli1885journals.com/index.php/actabiomedica/article/view/12211>. Accessed: 9 Nov. 2021.
- Fact sheet for healthcare providers administering vaccine (vaccination providers): Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). Revised October 2021. Accessed November 6, 2021. Available at: <https://www.fda.gov/media/153714/download>.
- FERNANDES, T.M. *Vaccina Antivariólíca: ciência, técnica e o poder dos homens, 1808-1920* [online]. 2nd ed. rev. Rio de Janeiro: Editora FIOCRUZ, 2010, 144 p. ISBN: 978-65-5708-095-5. <https://doi.org/10.7476/9786557080955>

Francis MJ (2018) Recent advances in vaccine technologies. *Vet Clin North Am Small Anim Pract* 48:231-241. <https://doi.org/10.1016/j.cvsm.2017.10.002>

FREIRE, M. G. Oxford vaccine: passport to life in freedom? *ISECENSA Research and Development Bulletin*, V. 3, N. 7. 2020.

Frenck, Jr. RW et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *NEJM* DOI: 10.1056/NEJMoa2107456, published on May 27, 2021. Available at: [https://www.nejm.org/doi/full/10.1056/NEJMoa2107456#article\\_citing\\_articles](https://www.nejm.org/doi/full/10.1056/NEJMoa2107456#article_citing_articles).

Butantan Institute. Understand how the inactivated virus technology used in CoronaVac works. Instituto Butantan, 2021. Available at: <https://butantan.gov.br/covid/butantan-tira-duvida/tira-duvida-noticias/entenda-como-funciona-a-tecnologia-de-virus-inativado-usada-na-coronavac>. Accessed on November 08, 2021.

Khehra, N., Padda, I., Jaferi, U., Atwal, H., Narain, S., & Parmar, MS (2021). Tozinameran vaccine (BNT162b2): The journey from preclinical research to clinical trials and authorization. *AAPS PharmSciTech*, 22 (5), 172. <https://doi.org/10.1208/s12249-021-02058-y>

Knoll M D, Wonodi C. Oxford-AstraZeneca COVID-19 vaccine efficacy. Elsevier . 2020. DOI:[https://doi.org/10.1016/S0140-6736\(20\)32623-4](https://doi.org/10.1016/S0140-6736(20)32623-4) . available at: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)32623-4/fulltext#figures](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32623-4/fulltext#figures) .

LAROCCA, Liliana Muller; CARRARO, Telma Elisa. THE WORLD OF VACCINES - (UN)KNOWN PATHS. *Cogitare Enfermagem*, [S.l.], v. 5, n. 2, 2000. ISSN 2176-9133. Available at: <<https://revistas.ufpr.br/cogitare/article/view/44884/27311>>. Accessed on: 09 Nov. 2021. doi:<http://dx.doi.org/10.5380/ce.v5i2.44884>.

Mojica-Crespo R, Morales-Crespo MM. Pandemic COVID-19, the new health emergency of international concern: a review. *Semergen*. 2020;PMCID: PMC7229959. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7229959/> .

Anvisa Note: Anvisa analyzes Pfizer's request to include children in Covid vaccine. Agência Nacional de Vigilância Sanitária. 2021. Available at: <https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2021/anvisa-analisa-pedido-da-pfizer-para-incluir-criancas-em-vacina-contracovid>.

Anvisa Note: Anvisa authorizes Pfizer vaccine for children older than 12 years. National Health Surveillance Agency. 2021. Available at: <https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2021/anvisa-autoriza-vacina-da-pfizer-para-criancas-com-mais-de-12-anos>.

Oliver, SE, Gargano, JW, Marin, M., Wallace, M., Curran, KG, Chamberland, M., McClung, N., Campos-Outcalt, D., Morgan, RL, Mbaeyi, S., Romero, JR, Talbot, HK, Lee, GM, Bell, BP, & Dooling, K. (2020). The interim recommendation of the Advisory Committee on Immunization Practices for the use of the Pfizer-BioNTech COVID-19 vaccine - United States, December 2020. *MMWR. Weekly morbidity and mortality report*, 69 (50), 1922-1924. <https://doi.org/10.15585/mmwr.mm6950e2>

Pan American Health Organization (PAHO) Available at: <https://www.paho.org/pt/topics>. Ministry of Health.

Padda IS, Parmar M. COVID vaccine (SARS-COV-2). [Updated June 15, 2021]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK567793/>

Coronavirus Brazil panel. 2021. Available at: <https://covid.saude.gov.br/>

Plotkin S. History of vaccination. *Proc Natl Acad Sci U S A*. [Internet]. 2014 August 18. 2014;111:12283-12287.

Polack et al, 2020 F.P. Polack, S.J. Thomas, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, et al. Safety and efficacy of the BNT161b2 mRNA covid-19 vaccine, *New England Journal of Medicine*, 383 (27) (2020), pp. 2603-2615, 10.1056/NEJMoa2034577

Fiocruz Portal. Available at:<https://portal.fiocruz.br/> .

Interim recommendations for the use of the inactivated COVID-19 vaccine, Coronavac, developed by Sinovac. Interim guidance, May 24, 2021. Available at: [https://iris.paho.org/bitstream/handle/10665.2/54598/OPASWB RAPHECOVID19210060\\_por.pdf?sequence=1&isAllowed=y](https://iris.paho.org/bitstream/handle/10665.2/54598/OPASWB RAPHECOVID19210060_por.pdf?sequence=1&isAllowed=y) . Accessed on: 06/10/2021.

Seyed Hosseini E, Riahi Kashani N, Nikzad H, Azadbakht J, Hassani Bafrani H, Haddad Kashani H. The novel coronavirus Disease-2019 (COVID-19): Mechanism of action, detection and recent therapeutic strategies. *Virology*. 2020;PMCID: PMC7513802. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7513802/> .

Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1-2a trial of Ad26. COV2. S Covid-19 vaccine. *N Engl J Med*. 2021;384(19):1824-1835.

Tribunal de contas da união (TCU).2021. Available at: <https://portal.tcu.gov.br/inicio/>.

Tanriover, Mine Durusu et al. "Efficacy and safety of an inactivated whole-virus SARS-CoV-2 vaccine (CoronaVac): interim results from a double-blind, randomized, placebo-controlled, phase 3 clinical trial in Turkey." *Lancet* (London, England) vol. 398,10296 (2021): 213-222. doi: 10.1016 / S0140-6736 (21) 01429-X Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8266301/> Accessed: 06/10/2021.

Voysey M, Clemens S, Madhi S, Weckx L, Folegatti P, Aley P, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Elsevier* .2020. DOI:[https://doi.org/10.1016/S0140-6736\(20\)32661-1](https://doi.org/10.1016/S0140-6736(20)32661-1) . Available at: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)32661-1/fulltext#articleInformation](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext#articleInformation)