VACCINES against SARS. Cov.2

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Since the World Health Organization first alerted the world to the existence of a mysterious group of pneumonia cases in Wuhan, China, researchers have already developed more than two hundred vaccine candidates to combat the expansion of the coronavirus SARS.CoV.2. At the end of November 2020, there were 237 SARS-CoV-2 vaccine projects worldwide. Most are still in the preclinical stage, tested on animals, but 48 are already tested on humans. Several of these 48 have already reached the end of the clinical trial stage and have yielded promising results. According to the World Health Organization (WHO) count, of the 48 vaccines that have reached the human testing stage, 11 have reached Phase 3, during which the product is tested on a large number of volunteers to confirm its efficacy and detect possible side effects. Three vaccines have successfully passed this Phase III of clinical assessment and are ready to use in the public. These are the cavvines developed by Pfizer-BioNTech, Moderna and AstraZemeca. The public vaccination developed by Pfizer-Biotech has already started in UK ans United States without incident. Thus, after ten months of speedy development, the competition between the various laboratories for producoing an efficacious and safe vaccine against the new coronavirus has taken a decisive turn and has resulted in a promising result.

A - THE VARIOUS TYPES OF VACCINES

Hopes for an effective and safe vaccine are based in part on the wide variety of techniques used in the multiple projects launched.
The methods differ, but all vaccines have the same goal: to teach the body's immune system to recognize and manufacture its defenses - antibodies - specifically against Sars-CoV-2. These defenses will be able to quickly neutralize the virus when they cross it.
There are several ways to present the body with the "identity card" of the virus from which the body can build its immune defenses:

1) - Attenuated or inactivated virus vaccines,

These are the more conventional vaccines, the historical vaccines, Pasteur's and Jenner's. They are themselves divided into two categories: live attenuated vaccines, which contain the entire pathogen but weakened by chemical or physical treatment, and inactivated vaccines that contain a version of the pathogen unable to multiply.

Attenuated virus vaccine
Examples: MMR (measles-mumps-rubella) vaccines, chickenpox vaccine, oral polio vaccine, shingles vaccine (herpes zooster), yellow fever.
This technic is used by 4 vaccines in development against SARS-CoV-2
The aim here is to inject the person with a weakened version of the virus that causes the disease. This attenuated virus is "alive" but no longer has pathogenic power. Most of the time, the virus may continue to replicate, but not enough to be a threat and make the body sick. Attenuated live virus has the advantage of causing a complete and robust immune response as well as lasting immunity,

without the need for adjuvants (products stimulating the body's defenses). It is also an inexpensive method. However, it can have some risks to people with fragile immune systems that are less able to fight a virus, even if weakened, so it is not recommended for these persons. This type of vaccine also presents the risk of worsening Sars-CoV-2 infection instead of helping the body fight it. This phenomenon, known as *Antibody-dependent enhancement* (ADE) was at the origin of the fiasco of the dengue vaccine designed by Sanofi-Pasteur, which had caused the death of several children between 2016 and 2017 in the Philippines. Attenuated virus vaccines also require refrigering and light protection, which can complicate their transport and retention.

Inactivated virus vaccine
Examples: influenza, polio, hepatitis A, rabies vaccines.
This technique is used by 18 vaccines in development against SARS-CoV-2
The injected virus has been killed (by heat, radiation or exposure to chemical agents) and has lost its ability to replicate in the body. But it retaines enough of its physical integrity to be recognized by the immune system. While this method is safer than attenuated viruses - especially for fragile people - the immune protection it confers is less durable and less complete, as physical treatment of viruses can damage one or more of its antigen proteins. It needs both adjuvants and multiple doses to create an effective protection.

2) - Viral vector vaccines :

Replicating viral vector vaccine
Examples: the vaccine developed against Ebola (2016).
This technique is used by 20 vaccines in development against SARS-CoV-2.
This type of vaccine uses a viral vector to carry some of the SARS-Cov-2 virus genes into the body, causing antibodies to form in the body. The vector virus, such as an adenovirus, has been genetically manipulated to make it lose all pathogenicity, and genetic material from the SARS-Cov-2 virus, such as genes encoding the spike protein, has been inserted into its genome. Once the virus "vehicles" have entered a human cell, its genetic material (modified to encode the spicule protein) is released and then "read" to produce both the coronavirus spicule protein and copies of itself that will infect new cells.
This technique provides a strong immune response (which is positive), as well as long-lasting protection. But it is expensive and complex, and its effectiveness can be compromised if the person has already been in contact with the virus chosen to deliver the antigen. The latter must not trigger the reaction of antibodies against its "original" version, at the risk of being eliminated withour succeeding in provoking an immune reaction against the antigen it carries.

Non-replicating viral vector vaccine
No vaccine using this technique has ever been commercialized
This technique is used by 28 vaccines in development against SARS-Cov.2
The functioning of these vaccines is similar to those that use replicating viral vectors, with the difference that once entered the cell, the virus will only make the chosen antigen and not copies of itself. This technique, used in gene therapy for a long time (adenovirus in particular), is considered very safe. Adenoviruses are particularly used by researchers. This family of viruses, known to cause mostly common respiratory infections, offers good stability, great safety and an advantageous ease of handling.

However this complex technique, long to develop, is expensive, and there may be immunological reactions of the body to the viral vector.

3) - Protein vaccines

This type of vaccine uses a newer technology. It involves injecting proteins from SARS-Cov-2, which will be recognized by the body.

Protein sub-unit vaccines
Examples: Hepatitis B or pertussis vaccines
This technique is used by 77 vaccines in development against SARS-CoV-2
These vaccines are quite simple. They contain only coronavirus proteins, which will be directly injected into the body and recognized as antigens.
Since no "living" components are injected, the method is considered particularly safe. But because these proteins are injected alone, they do not cause a very important immune response. They are often accompanied by adjuvant products, which stimulate the immune response. This method can also have a significant cost and development time.

Pseudoviral particle vaccines
Examples: Vaccines against human papillomavirus or hepatitis C
This technique is used by 20 vaccines in development against SARS-CoV-2.
They contain proteins that come together to form a structure and on the surface of which is the coronavirus antigen (its spicule protein). This structure, called "recombinant," is not infectious, since it is empty, but it mimics the shape of the virus quite well.
This type of vaccine has very good results in the immune response, but it is technically very difficult to manufacture and requires a lot of investment.

4) - Genetic vaccines,

This is the most innovative technique. These vaccines do not contain any material of the virus but only its genetic material, DNA or RNA. Introduced into the body by a vector, it migrates into human cells to synthesize the proteins of the virus - the "identity card" of the virus - against which the body can develop antibodies.

DNA vaccines
No DNA vaccine for humans has been marketed to date
This technique is used by 20 vaccines in development against SARS-Cov-2
These vaccines contain DNA from the virus. The injected DNA strands carry the genes of the virus responsible for the synthesis of its antigens (e.g. spicule protein, spike). Needles planted in the skin generate an electric micro-field, which causes the strands to migrate into the surrounding human cells and allows them to penetrate their nucleus. (Electroporation technique). Once in the nucleus, the genes are "read" by the cellular machinery, which makes the corresponding protein: the Spike protein, from the SARS-CoV-2 spicule. The viral proteins thus manufactured (in many copies within human cells) are detected in the intracellular medium, triggering the immune response from the organism.

Although new, this technology is considered safe. On the other hand, it usually causes a moderate immune response and requires the use of adjuvants, or even several doses administered a few weeks apart, in order to provide lasting protection.

RNA vaccines
No RNA vaccine for humans has been commercialized to date
Technique used by 29 vaccines in development against SARS-CoV-2. See the next paragraph.
These vaccines work similarly to DNA vaccines, but use messenger RNA instead of DNA. Messenger RNA is a temporary copy of a DNA fragment, intended to be read in the receiving cell to make a protein in its ribosomes. This messenger RNA is encapsulated in a lipid envelope to be injected into the body to be immunized. Once injected, messenger RNA enters human cells through its lipid envelope that fuses with the cell membrane. The messenger RNA will then directly synthesize the viral protein by the ribosomes without having to pass through the nucleus of the cell, which greatly decreases the risk of genotoxicity (modification of the DNA of our cells).
the Spike proteins of SARS-CoV-2 produced in the cells are detected and trigger the desired immune response.
The risks and benefits associated with this technique are similar to those of DNA vaccines. However, the messenger RNA technique avoids having to bring viral DNA host cells into the genome, a potential source of subsequent problems, and a potential source of strong reactions of genotoxicity in the host. It is therefore much safer. On the other hand, mRNA is less stable than DNA and requires much colder storage conditions. Such vaccines can be produced with unprecedented speed (as evidenced by the fact that the first two SARS-CoV-2 vaccines that were able to pass successfully all control barriers and be ready today for clinical use are messenger RNA vaccines).

<u>B - VACCINES THAT HAVE REACHED PHASE III OF CLINICAL EXPERIMENTATION, READY FOR PUBLIC APPLICATION</u>

Eleven vaccines with different characteristics have reached Phase 3, the last stage of pre-market testing.

Pfizer, BioNTech and Fosun Pharma, RNA Vaccine, approved for clinical use in the UK and US (December 2020). Efficiency 95%. FDA-approved. Public use started.

Moderna and Niaid, RNA Vaccine, Phase III Clinical Experiment completed. Ready for clinical use, 94.5% announced efficacy. Signed up by the FDA, Public Use Started.

CanSino Biologics Inc. and Beijing Institute of Biotechnology, Viral Vector, Licensed since June for Military Use for One Year, Unsused Effectiveness

Gamaleya Research Institute, Viral Vector, "Sputnik V," Authorized on August 11 as part of the Emergency Use Authorization Mechanism, Efficiency Declared 95%

AstraZeneca and University of Oxford, Viral Vector, Phase III Trials Completed, Efficiency Announced at 70%

Janssen, a subsidiary of Johnson and Johnson, Viral Vector, Planned Marketing in the First Quarter of 2021, Unsurlected Efficiency

Sinopharm and Beijing Institute of Biological Products, Inactivated Vaccine, Marketable since late July for limited use (especially for health workers), unsurpassed efficacy

Sinovac and Instituto Butantan, Inactivated Vaccine, licensed since July for limited use, unknown efficacy

Sinopharm and Wuhan Institute of Biological Products, Inactivated Vaccine, Licensed Marketing since late July for limited use (especially for medical workers). Also authorized on 14 September in the United Arab Emirates. Efficiency not known

Novavax, Protein Sub-Unit, Planned Marketing in The First Quarter of 2021, Unsured Efficiency

Bharat and Indian Council of Medical Research - National Institute of Virology, Inactivated Vaccine, Planned Marketing in Q2 2021, Efficiency Not Known

Other laboratories are less advanced: the vaccines they are developing are still in phase 1, including the safety of the product and its ability to trigger an immune response; phase 2, during which the vaccine study continues and the appropriate dose is determined.

C - ARN VACCINES

1) History

Since its discovery in 1961, messenger RNA has been the subject of extensive applied research for its use for the treatment of various pathologies (Ugur Sahin, 2014) [1]. The concept of the use of nucleic acid-coded drugs was developed in the 1990s following the demonstration by Wolff and collaborators[2] that direct injection of messenger RNA transcribed in vitro - (IVT)mRNA - or a DNA-containing plasmid (plasmid DNA) into the mouse skeletal muscle led to the expression of the nucleic acid-coded protein in the injected muscle.

This research was continued, but with DNA rather than messenger RNA because of the instability of it, and research focused on technologies based on the use of DNA plasmid or viral DNA. In the 1990s exploration of the use of transscribed messenger RNA in vitro was developed for a variety of uses, including protein substitution and vaccination for cancer and infectious diseases. The first applications of this technique were for cancer[3]. In 1995 Conry RM et al[4] demonstrated that intramuscular injections of naked RNA encoding the carcinoembryonaire antigen elicited a response with specific antibody formation of antigens. In 1996 Boczkowski D et al[5].showed that dendritic cells exposed to mRNA encoding for a specific antigen or a total mRNA extracted from tumor cells and administered sub-skin in a tumor-affected mouse induce an immune response of T cells and inhibited the growth of tumors already developed Since, many clinical trials using vaccines based on ex vivo transfected dendritic cells with IVT mRNA have been conducted in cancer patients and have established the possible and safe nature of this approach[6].

Attempts to apply these mRNA vaccines against infectious diseases came later. In 1993 it was shown that IVTmRNA carried in a liposome and encoding a nucleoprotein of the influenza virus induces a specific response of the virus in the T cells of mice[7]. It was not until 2012 that the first preclinical mRNA trials were conducted on infectious agents. Geall AJ et al. (2012) [8] showed that intramuscular injections of self-amplifying IVTmRNA coated in lipid nanoparticles induce a protective antibody response against RSV, respiratory syncitial virus and influenza virus in mice. The concept of messenger RNA vaccination against infectious diseases had proven its validity[9]. However, the clinical applications of this concept have so far been limited by the instability and inefficiency of the intake of mRNA *in vivo*[10].

2) How it works

Messenger RNA vaccines are therefore based on the injection of synthetic messenger RNA. This includes the sequence of the protein of interest, as well as other non-structural proteins that will facilitate its translation by cellular machinery. This sequence is surrounded by a cap at the 5' end and a poly-A tail at the 3' end. The antigen encoded by Pfizer and BioNTech's BNT162b2 vaccine is an S-protein optimized for SARS-CoV-2 .

There is also a second construction in which a replicase is added (after the 5'UTR). These RNAs are called *self-replicating (amplify selfing)*. The latter allows for more antigens because the replicase will independently amplify the mRNA.

One factor that has long limited the use of messenger RNAs in the field of infectious disease vaccines. It is the weakness of the immune response obtained from the body receiving these RNAs. To obtain a strong adaptive immune response to mRNA intake encoding SARS-CoV-2 proteins, the innate immunity receptors would have to be activated in order to trigger a "danger signal" in the cells. This "innate effect" is an essential step in creating a local environment containing pro-inflammatory cytokines and interferons, conducive to the recruitment and proper activation of immune cells against pathogens. A nucleic acid vaccine should not only deliver nucleic acid encoding the target antigen but should also sufficiently activate the hazard sensors expressed by the cells. The "danger sensors" for mature mRNA molecules that synthesize proteins are located in the cell cytoplasm and the hazard sensors for the detection of exogenous mRNAs are mainly located in endosomes (TLR7/8, Toll-like receptors 7 and 8). The mRNA molecules used as a vaccine should therefore be transported in endosomes. This can be done using a lipid nanovector[11].

It appears that many cell types are able to internalize these RNAs which are then translated into protein. This process mimics what happens in a natural infection. The cell "infected" with antigens from mRNA presents them *via* its Major Histocompatibility Complex(MHC) toimmunity cells. Messenger RNA vaccines have been shown to stimulate both the cellular immune response (CD4-Tcells and CD8) and the humoral immune response (activation of B lymphocytes and production of antigen-specific antibodies).

mRNA can also trigger innate immunity. Dendritic cells, monocytes and B cells strongly express TLR 7, a non-specific intracellular recognition system of pathogens (PAMPs-PRR system) specific to single-brin RNA. When TLR7 recognizes single-stranded RNA, cells secrete IFN-alpha and other chemokines. These cells, all of which are antigen-presenting cells, also activate T cells via their TLR 7. Here, it is the RNA molecule itself that activates these mechanisms and not the translated protein antigen.

3) Benefits

If messenger RNA vaccines are now attracting a lot of attention from experts this is because they offer significant benefits.
First, their *large-scale, low-cost* production is not a problem with current technology. [12] They can be manufactured more easily and faster than traditional vaccines that require the growth and then inactivation of pathogens or their proteins.
They may also have a *more lasting effect* against pathogens that tend to mutate, such as coronaviruses and influenza viruses.
Each vaccine dose is *extremely pure* and contains *only RNA of interest encapsulated* in its lipid carrier and nothing else. So they're safe.
As mentioned above, adjuvants do not appear to be necessary to obtain a satisfactory response, and a simple lipid capsule potentiates the immunogenic properties of RNA.
mRNAs have a *very short half-life and are easily degraded*.
They *do not interact with the genome.* Their support by the cellular machinery takes place exclusively in the *cytoplasm* unlike DNA vaccines.

Reading the literature on the subject, it seems that mARN vaccines give high hopes for treating infectious diseases for which there is still no vaccine, such as SARS-Cov.2..

4) Limits and questions

However, this new technology has limitations or drawbacks
First, mNRAs can cause adverse reactions in the body where they are injected.
Some clinical studies have reported grade 3 adverse events, that is adverse events, that completely invalidate or threaten the patient's life, for two mNRA vaccines to fight rabies and H10N8 and H7N9 viruses while they were in Phase 1 trial in humans.
Then this type of vaccine is unstable. mRNAs tend to degrade rapidly, which may limit their effectiveness, and the strength of immunity they generate. [13]
This fragility of messenger RNAs is a handicap. Pfizer has announced that its vaccine will have to be kept at - 80 degrees C. This poses obvious logistical problems. It will then be impossible to buy the vaccine in advance and store it in the refrigerator before vaccination. It is conceivable that people will have to go to vaccination centres that are able to store large quantities of vaccine units in liquid nitrogen, and to carry out the injection in a relatively short period of time.

The questions that arise about these vaccines are mainly related to a lack of scientific hindsight in their use. As explained above, messenger RNA vaccination activates both adaptive and innate immune response. But the high production of interferons, as a result of the activation of TLR7, would also increase the activity of ribonucleases, enzymes that cut RNA. Vaccine messenger RNAs that lose their lipid capsule or are not encapsulated at the time of injection would therefore be more likely to be destroyed before they even enter the cells.

5) Pfizer-Biotech's BNT162b1 vaccine

The BNT162b1 vaccine developed by Pfizer and the German biotechnology company BioNTech is a messenger RNA carried in lipid *nanoparticle-formulated nucleoside-modified mRNA* that encodes

the receptor binding domain (RBD) of the SARS-CoV-2 spike protein. The version of this spicule protein contains mutations that enclose it in a conformation such that it induces at best a response with the formation of neutralizing antibodies in the body that receives it. The mRNA encoding the spike protein's RBD is wrapped in a lipid nanoparticle that stabilizes it and allows it easier access to cell endosomes. It is given in two successive doses separated by a 21-day interval.

An initial report on the results of the Phase 1 clinical review of the BNT162b1 vaccine was published by Pfizer and BioNTech on October 14,2020 in the New England Journal of Medicine (Walsh EE, Oct 14, 2020). 195 people took part in the event, divided into 13 groups of 15 participants. In each group 12 participants received the vaccine and three received a placebo. BNT162b2 caused fewer systemic reactions than BNT162b1, particularly in older adults. The examination proved the safety of the vaccine and its immunogenicity.

According to the results of Phases 1 and 2 of the experiment published on October 22, 2020 in the journal Nature[15], Pfizer's vaccine caused no serious adverse effects and led to a strong immunological response, the study involved 45 patients who had received one of the three doses of either the candidate vaccine or a placebo. None of these patients had any adverse serious effects. Some developed side effects such as fever (75% in the group that received the highest dose), fatigue, headache, chills, muscle pain and joint pain. The researchers found that the vaccine caused the body's immune system to produce neutralizing antibodies at levels 1.8 to 2.8 higher than those found in patients who had cured the infection. The vaccine also led the body to produce T cells and other molecules to fight the virus, according to the results of another phase 1/phase 2 clinical trial published in Nature in late September 2020[16]

Pfizer and BioNTech began the Phase III clinical trial in July 2020, recruiting 44,000 people in the United States, Brazil and Argentina. Half of the volunteers received the vaccine, the other half received a placebo. [17]
Pfizer and BioNTech received FDA approval in October to begin enrolling children 12 years of age and older in clinical trials.
On November 9, 2020 Pfizer and BioNTech made their first announcement on the results already achieved in Phase 3. They informed that their vaccine could prevent more than 90% of Covid-9 symptomatic infections[18]. The Pfizer vaccine's clinical efficacy study involved the enrollment of 45,538 participants, 42% of whom were of diverse origin. No serious incidents were noted, and there were no safety concerns in the study. The first analysis of the results covered 62 cases, and showed preventive efficacy in vaccinated patients greater than 90%, seven days after the injection of the second dose. This meant that protection is provided 28 days after the start of vaccination.

On November 18, the two companies released the main analysis of the first results of the Phase III clinical trial of theirvaccine. Of the 44,000 people in the trial, 170 cases of symptomatic Covid-19 were identified, of which 162 were in the placebo group, and only eight were in the vaccine group. This meant that the vaccine reduced the risk of infection by 95%.

On 2 December 2020, the UK's national health agency for drug control, the *Medicines and Healthcare products Regulatory Agency* (MHRA), the UK's drug agency, recognised Pfizer/ BioNTech's vaccine as safe for use, giving the go-ahead for the start of vaccine vaccinations in the UK[20]just seven months after the start of clinical trials of the vaccine. China and Russia have already approved the use of vaccines developed in their countries, but have not completed testing of

participants in clinical trials. The United Kingdom became the first country to allow a vaccine against SARS-Cov-2. On December 8, 2020 at 6:31 a.m. Margaret Keenan, 91, became the first person in the world to receive the SARS-CoV-2 vaccine from Pfizer-BioNtech [21]
Health Canada gave the go-ahead for approval of the Pfizer/BioNTech vaccine, and on December 9 became the second country to open up to the use of the vaccine. Canada ordered 76 million doses from Pfizer. [22]

The results of the Pfizer Vaccine Phase 3 clinical trial were reviewed by the FDA in the United States for vaccine acceptance in that country. The FDA released a paper on this vaccine on December 10,2020. This 100-page document includes all analyses from the agency and Pfizer on the vaccine. Pfizer had announced that the two-dose vaccine was 95% effective, which is verified. But the report goes further by showing that the protection afforded by the vaccine already begins ten days after the first dose of vaccine, with an efficacy of 52%. During the same period, the number of cases of Covid-19 increased steadily in the placebo group. The effectiveness reaches 95% after the second dose. The FDA report shows that the vaccine is effective at the same level regardless of age, race or weight. The vaccine protects people aged 65 and over with the same effectiveness it shows in young people, a reassuring finding. The robust response to the vaccine in elderly and obese individuals is important news.
The FDA report takes up the results of previous Pfizer reports, going into much more detail on adverse side effects and events. The report notes that many participants suffered pain, fever and other side effects after vaccination, which is normal for a vaccine. Reactions to injection sites occurred in 84% of participants, fatigue in 62.9%, headaches in 55.1%, chills in 31.9% and fever in 14.2% of cases. Severe reactions were observed in 2.8% of volunteers over the age of 55 and in 4.6% of volunteers under the age of 55. Younger participants often had stronger reactions related to their more robust immune systems. Severe adverse events, more severe than the only strong reaction, were observed with the same low rate (0.5%) vaccinated subjects as well as those who received placebo. There were four cases of Bell's palsy (facial paralysis), paralysis or temporary weakness in the arm injected by the vaccine (none in the placebo group). There were also 64 cases of lymphadenopathy, with swollen lymph nodes in the vaccinated group compared to six cases in the placebo group. It can be said that no serious adverse events were observed in the participants in the clinical trial, which could have been caused directly by the vaccine.
The paper shows that scientists at the FDA have recognized the efficacy and safety of the Pfizer/ BioNTech vaccine. The document describes the vaccine as "highly effective" with "a favorable safety profile."

These Phase 3 results of Pfizer/BioNTech's BNT162b2mRNA vaccine were included in a summary paper published on December 10, 2020 in the New England Journal of Medicine (Polak et al.) [24]It states that the study involved 43,548 participants, over 16 years of age, of whom 21,720 received the vaccine, according to a randomized award, and 21,728 a placebo. People who were obese, or with previously established pathological conditions, were well represented among the participants and 40% of them were over the age of 55. Secondary incidents included moderate pain at the injection site, fatigue and headaches, which is common to any vaccination. The incidence of serious events was low, and was similarly common in both groups, whether the vaccine was received or a placebo received. There were only 8 cases of Covid-19 among the 21,720 participants who received the vaccine, with the disease beginning 7 days after the second dose of the vaccine, while 162 cases of the condition were reported among participants who received only placebo. Of the 10 cases of

severe Covid-19 that began after the first dose of injected product, 9 occurred in subjects who received placebo and only one in a subject who had received BNT162b2
So the results are impressive. It can be concluded that the injection regimen for the BNT162b2 vaccine in two successive doses, 21 days apart, provides 95% protection in people over 16 years of age.. This efficacy has been similarly observed in the various subgroups defined by age, sex, ethnicity, body mass index, and pre-existence of pathological conditions. Safety over an average of two months of observation appeared similar to that noted with other antiviral vaccinations. There are certainly limits to the scope of these early results. The number of cases of severe covid-19 reported after vaccination (one in the vaccinated group, eight in the placebo group) is too low to draw conclusions, particularly on the occurrence of a severe case despite vaccination. Furthermore, the report does not provide data on the number of asymptomatic cases detected by seroconversion to a nucleoprotein of the virus that is not included in the vaccine composition. Finally there were only 20,000 people vaccinated in this series. What will happen to the millions - in fact billions - to come? Can't severe incidents appear in the course of this massive immunization? How long will the vaccine remain effective? These are questions that cannot be answered today. In addition, the requirement to keep the vaccine cold (-70 degrees) places limits on its use in developing countries and poor regions of the world.

But the results themselves are impressive enough to rule out any objection to the immediate implementation of vaccination. On December 11, 2020, the FDA granted Pfizer/BioNTech approval for emergency use of the vaccine in the United States. As NEJM columnist Eric J.Rubin writes, *"This is a triumph."* It must be recognized that this success is due in part to the very rapid communication of the virus sequence, made to scientists around the world, by the Chinese Centers for Disease Control. It was the case for the rapid development of the mRNA vaccine, combined with recent experience with messenger RNA vaccines, particularly in the field of cancer.

Pfizer announced that phase three of its clinical trial, which began in July 2020, will continue for another two years, during which data on the safety and efficacy of the vaccine will continue to be collected. The company encourages volunteers to stay in the research as long as possible so that they can clarify the effectiveness of the vaccine.
Pfizer and BioNTech plan to manufacture 50 million doses of their vaccine by the end of December 2020, enough for 25 million people. The Center for Disease Control and Prevention expects 40 million doses of vaccine to be available in the United States by 2020, with 25 million coming from Pfizer and 15 million coming from Moderna if the latter vaccine is accepted by the FDA in December. The U.S. government has agreed to acquire 100 million doses of each vaccine, with the option to purchase an additional 900 million doses of each of the two vaccines. Pfizer and BioNTech hope to produce up to 1.3 trillion doses in 202 to serve the world. Moderna expects to produce 500 million to a trillion doses of its vaccine in 2021.
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<u>6) Moderna's mRNA 1273 vaccine</u>

The mRNA 1273 candidate vaccine developed by the American firm Moderna and the National Institute of Allergy and Infectious Diseases (NIAID) is a messenger RNA vaccine very close in its design and operation of Pfizer/BioNTech's BNT 162 b2 mRNA vaccine. It also uses messenger RNAs encoding the spike protein. The vaccine codes for the S-2P antigen, which consists of the SARS-CoV-2 glycoprotein membrane with a transmembrnaire anchor and an intact S1-S2 cleavage

site. [25] S2P is stabilized in its conformation by two substitutions of proline in amino acid positions 986 and 987 at the top of the central propeller in sub-unit S2. [26]

On July 14, 2020 Moderna published the first promising results of a Phase I clinical trial involving 45 participants aged 18 to 55. [27] Participants received the two successive dosses of the vaccine 28 days apart. They were divided into three groups based on the low, medium or high dose of vaccine administered. After receiving both doses of the vaccine, all participants developed neutralizing antibodies at levels higher than those found in convalescents of SaRS-CoV-2 infection. The vaccine developed by Moderna therefore appeared safe and well tolerated. However, more than half of the participants experienced some side adverse effects, similar to those observed after influenza vaccination, including fatigue, chills, muscle aches, and pain at the injection site. Some of the participants in the medium-dose and high dose of vaccine groups developed fever after the second injection. A person who received the highest dose experienced a "severe" fever, with nausea, a feeling of lightness in the head and an episode of syncope. This participant recovered after a day and a half of discomfort. Such doses will not be delivered in Phase 3 clinical trials.

On July 28, 2020, the Moderna team published a new study in the New England Journal of Medicine, showing how Moderna's vaccine induces a strong immune response in macaques. After receiving a dose of 10 or 100 grams of vaccine and a second dose two weeks later, the monkeys were exposed to coronavirus at the eighth week. The researchers found that monkeys developed a strong immune response against the virus. Their immune system produced both neutralizing antibodies and T cells. Two days after their re-exposure to the virus, no viral replication could be found in the nose and lungs, suggesting that the vaccine had protected the monkeys from early infection.
The government organization Warp Speed has allocated $955 million to Moderna for research and development of this vaccine.
It should be noted about this Moderna vaccine that scientists used the heK-293 cell line from the tissues of an aborted fetus in Holland in the 1970s. However, this lineage was only used by Moderna to test the spike protein which was then used to build the vaccine. HEK-293 cells were not used in the construction of the vaccine itself but to increase the knowledge needed to design the vaccine. [29]

On November 16, 2020, the company announced the first results of the Phase 3 clinical trial of its vaccine. This study, called the COVE study, enrolled more than 30,000 participants in the United States. 95 cases of COVID-19 were observed in this series, including 90 cases in the placebo group and 5 cases in the mRNA-1273 vaccine group. The 95 cases included 15 adults over the age of 65 and 20 participants from various communities. This gave 94.5% efficacy of the m-RNA 1273 vaccine in protecting against the SARS-CoV-19 virus. [30] 11 cases of severe COVID-19 were observed in the placebo group, none in the vaccine group. The vaccine had been generally well tolerated, with the majority of adverse effects being of moderate or moderate severity. Severe degree 3 reactions were observed in 2% of cases. It involved pain at the injection site in 2.7% of cases after the injection of the first dose of vaccine, and fatigue (9.7%), arthralgias (5.2%), headache (4.5%) varied pain (4.1%) redness at the injection site (2%) after the second injection. These events were short-lived. Overall, these data showed that the vaccine was safe and effective in the same way in all subgroups. Based on these results, Moderna planned, within a week of this declaration, to submit an authorization for the vaccine to the FDA as a matter of urgency.
The company hopes to produce 500 million to 1 trillion doses by 2021.

Clinical phase 3 of the Clinical Trial of the Moderna Vaccine continues. Moderna plans to continue its placebo-controlled trial until 151 cases of symptomatic disease are identified. Given the current transmission rates, this could take only a few weeks.

The vaccine prepared by Moderna is very similar to the vaccine produced by Pfizer/BioNTech and has similar characteristics in terms of efficacy and possible side effects. However, it could have an advantage over the Pfizer/BioTech vaccine: it is indeed more stable and this stability has been proven for long periods of time at -20°C, which corresponds to the temperatures of freezers in pharmacies. However even -20 °c is problematic, because this temperature requires transport in very specific thermos, model of those used in Africa for the transport of the Ebola vaccine[32].

D - THE VACCINE ChAdOx1nCoV-19 OF OXFORD /ASTRAZENECA

The ChAdOx1 nCoV-19 vaccine, commonly referred to as the Oxford vaccine, was developed by researchers at the University of Oxford and AstraZeneca. It is a vaccine based on the use of an adenovirus vector that codes for the spike protein. (adenovirus-vector-based vaccine). The vaccine uses an adenovirus vector genetically modified so that it cannot replicate in humans - the replication-deficient simian adenovirus vector ChAdOx1 - and has inserted genes into the adenovirus genome to code for the spike proteins - full- length structural surface glycoprotein or "spike" protein - This is the sequence encoding amino acids 2-1273 of CoV-2-SARS synthesized with the tPA leader of the 5' end (tissue plasminogen activator) cloned into a shuttle plasmid. The vaccine "teaches" the body to recognize these antigens, so that when a vaccinated person is exposed to the CoV-2-SARS virus their immune system can eliminate it. The vaccine is given in two doses, 28 days apart.

In a press statement issued on 23 November 2020[34] Oxford University has teported the first results of his Phase 3 clinical study of the vaccine. It said that the candidate vaccine was 70% effective in preventing COVID-19 and could be 90% effective when administered at the correct dose. The first analysis of these late-stage trials was based on 131 participants who developed COVID-19 after receiving either the vaccine or placebo. In those who received two full doses, the vaccine was about 62 percent effective in preventing COVID-19, but in those who received first a half-dose and then a full dose (this was not deliberate, but the result of a dosing error in the early trials), the vaccine was 90 percent effective. No serious safety problems were found, and none of the participants who developed an infection after receiving the vaccine required hospitalization or had severe disease. The trials had to be stopped twice after two different participants developed neurological symptoms, but were resumed when researchers found no link between the vaccine and the symptoms, according to Vox. Another trial participant, a 28-year-old Brazilian doctor, had died from complications related to COVID-19, but he had received only the placebo and not the vaccine itself.
Commentators found these results curious if not disorienting. How could immunization be more effective in those who received a lower dose of vaccine? [3]. There seemed to have been an error somewhere, probably in the group for which AstraZeneca claimed 90% effectiveness of the vaccine. [4]. The impression of the commentators is that the vaccine has an efficacy of 62%, therefore moderate, and that other data are needed to understand the 90% posted after a more fabled dose of vaccine, which seems amazing. [5]

However, the technique used to produce the ChAdOx1nCOV-19 vaccine raises an ethical challenge. Indeed, the adenovirus ChAdOIx1, which researchers use as a carrier of the sequence comprising the genes of the spike protein, is obtained and propagated in particular cells, T-RexHEK293 (Invitrogen)[6]. This lineage comes from the heK293 cell line. This HEK 293 lineage was generated in 1973 from fetal human kidney cells, extracted from the remains of a deliberately aborted fetus in Holland. The identity of the parents of the aborted fetus is unknown, as is the reason for the abortion[7]. Would there not be genuine cooperation in the evil of abortion, even if this evil was perpetrated forty years ago?

The discussion on this subject is facilitated by the reflection that was made in 2005 by the Pontifical Academy for Life regarding the use of the rubella vaccine prepared with human cells RA 2//3 from an abortion[40]. On December 21, 2020 Cardinal Luis Ladaria, Prefect of the Congregation for the Doctrine of the Faith, issued a note on the morality of the use of certain vaccines against COVID-19. This note echoes the conclusions of the Academy's statement, simplifying them, to apply them to the case of COVID-19 infection. Among other things, it encourages producers and distributors of SARS vaccines. Cov.2 to ensure the ethical nature of the vaccine they have chosen to produce and disseminate. It also states that the pharmaceutical industry, governments and international institutions have a moral imperative to ensure the ethical nature of SARS-CoV vaccines.2 which they intend to produce, authorize or disseminate in their respective sectors.

The first care of *the Pontifical Academy for Fan Life* his 2005 declaration was to pinpoint the various forms of cooperation with evil.
A first distinction is made between *active* (or positive) cooperation with evil and *passive* (or negative) cooperation with evil, the first referring to the performance of an act of cooperation in a bad action that is performed by another person, while the second refers to the omission of an act of denunciation or obstruction of evil action, when there was a moral duty to preventthe evil inquestion. It is clear that any kind of formal passive cooperation must be considered illegal, but even passive material cooperation must be avoided.

Formal cooperation is when the moral officer cooperates in the immoral action of another person, sharing the wrong intention of the latter. Formal cooperation is always fully guilty and morally illegal.
Material cooperation is when the moral agent contributes materially to the carrying out of the evil act, without sharing the evil intent of the act. In other words, that person finds himself physically associated in some way with the evil act, without having intended it, and without approving that act. This material cooperation can be divided into two categories: immediate and mediated.
In *immediate material (direct) cooperation* the subject directly cooperates with the wrong act (for example the nurse assisting a doctor performing an abortion). In *mediated (indirect) material cooperation* the subject does not participate in the immoral act but his action indirectly facilitates its execution - for example, providing sterile compresses to a clinic performing abortions. This material cooperation can be further divided into proximate mediated material cooperation and remote mediated material cooperation, according to the chronological or spatial "distance" that exists between the act of cooperation and the evil act perpetrated by the principal agent. When the immediate material cooperation concerns a serious matter, such as an attack on human life, it must always be considered illicit, even if the collaborators do not share the intention of the person committing the bad act. In the case of mediate material cooperation and if the collaboration is indirect, the moral seriousness of the cooperation, and therefore its imputability, diminishes with the increase in the distance (temporal or material) between the act of cooperation and the bad action. However, even with an important distance

(forty years) and an imputability that has become negligible, the fact of cooperation remains because abortion cannot be erased from history and memory.

How does this teaching apply to the issue of vaccines?
- First, any form of formal cooperation in an abortion should be considered morally wrong. Therefore, anyone who - regardless of the category to which he or she belongs - cooperates in one way or another, sharing the intention to do so, in carrying out a voluntary abortion for the purpose of producing the above-mentioned vaccines, is, in reality, participating in the same moral evil as the person who performed the abortion. This participation would also occur in the case where a person sharing the intention of the abortion refrains from denouncing or criticizing this illicit action, although he or she has a moral duty to do so (passive formal cooperation). It follows that persons who, knowing the origin of the human cells used to prepare the vaccine, do not protest against the use of these vaccines and do nothing against their use are guilty of passive cooperation, and therefore attributable
- Cooperation with the wrong of the initial abortion to which the production of the vaccine is linked reaches its highest level when it is carried out by national and international authorities when these authorities, although aware of the ethical problem carried by the vaccine, do not take it into account and authorize or even impose the use of the said vaccine in their area of governance. The preparation, distribution, and marketing of vaccines produced using biological material whose origin is linked to cells from a voluntarily aborted fetus is morally reprehensible. However, it must be recognized that, in the production-distribution-market chain, different cooperating agents may have very different moral responsibilities depending on their position in the chain.
- Medical doctors who prescribe the use of the vaccine, and vaccine users, for themselves or their children, engage in a very distant form of mediated material cooperation, with no consequences for responsibility and accountability.
-On the other hand, if these same physicians or vaccine users approve the act of voluntary abortion that led to the development of the vaccine, they enter into a formal cooperation, and their accountability is complete.

In conclusion:
Ethically problematic vaccines should not be used if they can be used without endangering human health. Otherwise, an alternative vaccine should be used.
If the infectious agent against which the vaccine is directed is highly invasive, causes serious disease, has significant lethality, and if there is no alternative vaccine available, the ethically problematic vaccine will be used, but it must be made clear that acceptance does not mean approval, but choosing the lesser evil for the common good.

How does this general thinking about vaccines apply to the specific case of the AstraZeneka SARS vaccine.2 ?
This vaccine unquestionably uses T-RexHEK293 cells in the preparation of the viral vector used as a "carrier" of genetic information. The origin of this cell line is a voluntarily aborted human fetus. There is therefore cooperation to the evil of this abortion on the part of all those involved in the development of the vaccine and authorize it. This cooperation is both formal and material, which implies total responsibility. On the other hand, this cooperation is material, indirect, mediated and remote for the doctors who prescribe the vaccine and for those who use it, which greatly reduces their responsibility.

There are, however, a number of factors, specific to the manufacture of AstraZeneca's SARS.CoV.2 vaccine, that appear to reduce the seriousness of the moral responsibility of the producers and users of this vaccine.
(1)- The human fetus from which the kidney cells for the HEK293 lineage were derived was not aborted for use of its cells in the laboratory. The abortion came only secondarily, after the abortion, and there was apparently no direct causal link between the abortion and the preparation of the human kidney cells from the aborted fetal tissue. An attempt has been made to use this argument to justify the extraction of human cells for laboratory purposes from the remains of voluntarily aborted fetuses, citing a double effect. The proper purpose would be the collection of human cells for vaccine research and development. The negative effect would be the death of the fetus that was not sought for its own sake. But this cannot apply because the good effect (collection of human cells for vaccines) goes through the bad effect (abortion).
2)- The two successive transfections to which the kidney cells of the aborted fetus were subjected to give the T-RexHEK293 line introduced a transformation in the genome of the cells, which made them different from the initial kidney cells, and it is this difference that makes them useful in biology. This is true, but the difference is minimal, of the order of a mutation. The T-RexHEK293 line is not a "cousin" of the human kidney cells derived from the aborted fetus but is a direct descendant of these cells.
3)- T-RexHEK293 cells are not involved in the vaccine's mode of action, which is genetic. They allow the production of a transport adenovirus modified to host additional genes in its genome, so the use of these cells could be considered an accessory, complementary fact to the development of the vaccine. This perspective is not correct because the quality of the vaccine depends on the quality of the vector and therefore on the cell lines that allow its development. The use of T-RexHEK293 cells is an integral part of vaccine development .

These circumstances, which could be considered mitigating, cannot override the fact that in the development of AstraZeneca's vaccine, use is made of a cell line derived from a voluntary abortion. It is therefore ethically appropriate not to use this vaccine, but to use alternative vaccines.

However, the December 21, 2020 note from the Congregation for the Doctrine of the Faith authorizes the use of these vaccines in the fight against SARS.CoV.2, "using cell lines from aborted fetuses in their preparation" in the event that no alternative vaccine is available. But it is unclear where and when such a vaccine shortage situation could occur. There are currently 48 vaccines against SARS.Cov.2, which do not pose an ethical problem, and have now reached the stage of clinical use. Among these 48, the messenger RNA vaccines Pfizer/BioNTech and Moderna, stand out for their high efficacy (95%) and safety. The Astra Zeneca vaccine (whose efficacy is relatively low, 70%) can therefore be dispensed with without problems,

The note from the Congregation for the Doctrine of the Faith still indicates that the use of unethical vaccines, which have historically been linked to voluntary abortion, would be possible in those countries where the distribution of ethical vaccines would be "more difficult due to *special storage and transport conditions"*. The paper alludes to the special storage requirements of messenger RNA vaccines that require low temperatures and therefore special equipment to remain stable (-70C and -20C). In fact, Pfizer/BioNTech brings its own storage containers where it operates, and this would be true for African countries as well as for Latin American or Pacific countries. Keeping the Moderna vaccine at 20 degrees Celsius is even easier technically. Moreover, China is making a very large international effort to offer its SARS vaccines at low prices for poor countries. Cov.2, (Sinopharm, Sinovac), which are conventional, attenuated virus vaccines, effective, meeting ethical

demands. Even in poorer countries, alternative vaccines to the AstraZeneca vaccine will be available in the near future. It should also be remembered that to remain silent about the unethical nature of the AstraZeneca vaccine would be to cooperate with the evil of abortion and to encourage other companies to also use cell lines from human fetuses who are deliberately aborted. We do not want this moral regression.

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[40] Pontifical Academy for Life, Declarartion, *Moral Reflections on Vaccines Prepared from Cells Derived from Aborted Human Fetuses,* Vatican, 5 june 2005. Le document se trouve en ligne dans le The National Catholic Bioethics Quarterly, Autumn 2006, vol.6, n°3, pp.541-550.
[41] Congregation for the Doctrine of the Faith, Note on the morality of using some anti-Covid vaccines, Rome,. December 21 2020., n°2: "*In this sense, when ethically irreproachable Covid-19 vaccines are not available (e.g. in countries where vaccines without ethical problems are not made available to physicians and patients, or where their distribution is more difficult due to special storage and transport conditions, or when various types of vaccines are distributed in the same country but health authorities do not allow citizens to choose the vaccine with which to be*

inoculated) it is morally acceptable to receive Covid-19 vaccines that have used cell lines from aborted fetuses in their research and production process". « En ce sens, lorsque des vaccins Covid-19 éthiquement irréprochables ne sont pas disponibles (par exemple dans les pays où des vaccins sans problèmes éthiques ne sont pas mis à la disposition des médecins et des patients, ou lorsque leur distribution est plus difficile en raison de conditions de stockage et de transport particulières, ou lorsque différents types de vaccins sont distribués dans un même pays mais que les autorités sanitaires ne permettent pas aux citoyens de choisir le vaccin avec lequel ils seront inoculés), il est moralement acceptable de recevoir des vaccins Covid-19 qui ont utilisé des lignées cellulaires provenant de fœtus avortés dans leur processus de recherche et de production. *»*