MINISTRY OF ECONOMY
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OBSERVATORY OF TECHNOLOGIES RELATED TO COVID-19

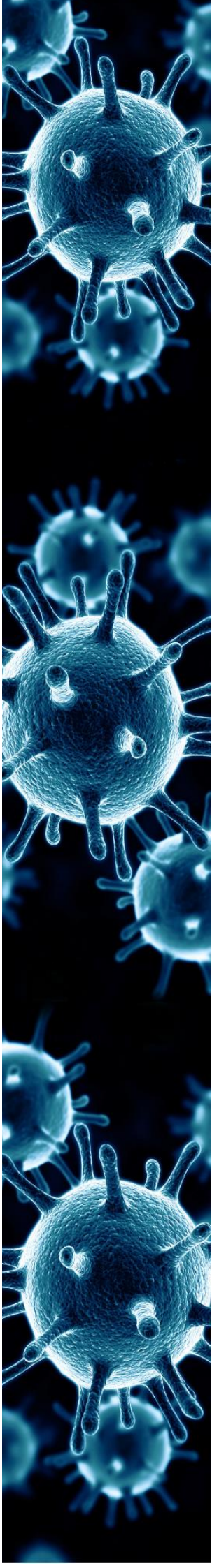
Overview of the patent documents related to RNA-based vaccines in clinical trials for prevention of COVID-19

Author: Irene von der Weid

Collaborators: Cristina d'Urso de Souza Mendes
Leticia Galeazzi Ferraz
Núbia Gabriela Benício Chedid

COVID-19 Observatory Team

Alexandre Lopes Lourenço
Cristina d'Urso de Souza Mendes
Irene von der Weid
Leticia Galeazzi Ferraz
Núbia Gabriela Benício Chedid
Tatiana Carestiato



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1. SARS-CoV-2 AND COVID-19

COVID-19 is an infectious disease caused by the coronavirus SARS-COV-2, which can lead to severe acute respiratory syndrome. Coronaviruses are a group of enveloped viruses with a single-stranded RNA genome, responsible for usually mild to moderate and short-term respiratory infections. However, some types, such as MERS-CoV, SARS-CoV, and SARS-COV-2 itself, can cause more severe infections.

The first respiratory conditions caused by the new coronavirus and observed in COVID-19 have been reported to the international authorities on December 31, 2019. The World Health Organization (WHO) declared the pandemic on March 11 and, until December 14, 2020, more than 70,8 million cases and more than 1.6 deaths have been reported in all continents ().

Despite the fact that 80% of the confirmed cases of COVID-19 had mild symptoms or were asymptomatic, 15% of the people infected had severe symptoms, and 5% are patients with extremely severe symptoms in need of assisted ventilation, which can evolve to severe pneumonia and even multiple organ failure and death (Iser, *et al*., 2020). To date, there is no specific antiviral treatment for the disease, and only recently one of the potential vaccines was approved for emergency use during the pandemic in some countries.

Considering the severity of the pandemic, the need to find a vaccine capable of inducing immunity, controlling the pandemic and thus, preventing new COVID-19 waves around the world, becomes evident.

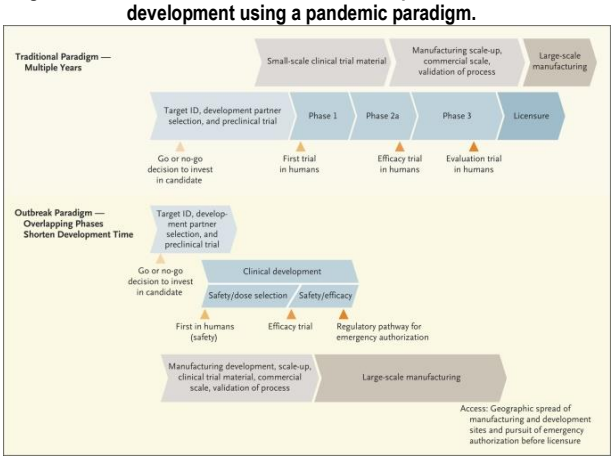
2. DEVELOPMENT OF VACCINES

The development of vaccines is a slow, expensive process, because the vaccine is a product that could potentially damage the population, as it will be applied to a great number of people of probably several age groups. The investment is high and usually involves several potential vaccines and several years until it is possible to produce a licensed vaccine. Due to the cost and the high failure rates, developers generally follow a linear sequence of stages, with several pauses for data analysis or manufacturing process checks.

The scenario of the COVID-19 pandemic imposed the challenge of a very quick development of a vaccine, which requires a new paradigm (Figure 1), with a quick start and several stages developed at the same time before confirming the successful result of previous stage, which involves high financial risk for the developers (Lurie, *et al.,* 2020).

Considering the critical situation over the world with the dissemination of COVID-19, this new paradigm of vaccines development has been used by several companies and research institutes seeking a quicker and more efficient solution to control the pandemic.

Figure 1. Difference between traditional development of vaccines and development using a pandemic paradigm.



Source: Lurie, *et al*., 2020

In addition to the shift in the paradigm for the stages of vaccines development, especially the overlapping of stages during clinical trials, another essential factor that contributed to the quick development of potential vaccines for prevention of COVID-19 was the use of existing platforms being tested for other viruses, such as SARS-CoV and MERS-CoV, for example.

The term "vaccine platform technology" refers to a system that uses the same basic components, such as a base technology (backbone), which can easily be adapted to the use against different pathogens due to the insertion of new sequences.

It is remarkable the efforts around the world in order to develop vaccines against COVID-19, evidencing that, the first ones to reach clinical trials came from existing platforms and from the quick adaptation based on research aimed at other viruses (Mukherjee, 2020).

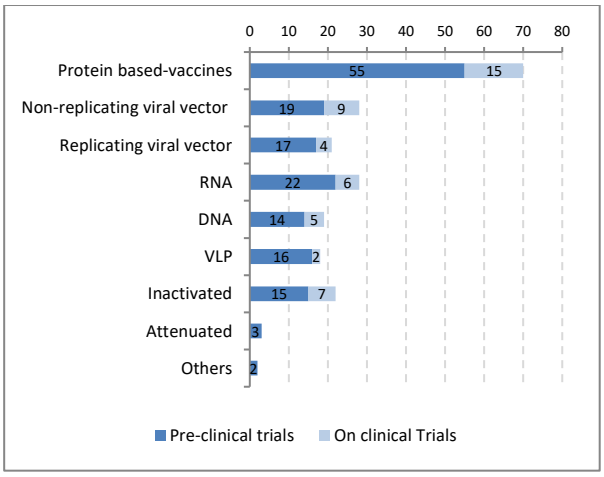
Studies show that the RNA-based vaccines enable a quick adaptation of research and production. As an example, it is possible to mention the mRNA-based vaccine from the American company Moderna, which was developed from an adaptation of research aimed at the Nipah virus, which also causes Respiratory Syndrome. Based on the draft genome for SARS-CoV-2, shared online on January 11, 2020, Moderna replaced the Nipah RNA for the SARS-CoV-2 RNA and started sending a potential vaccine to the National Institute of Allergy and Infectious Diseases of the National Institute of Health (NIAID/NIH) for clinical trials. This process only took six weeks – the quickest return in medical history – from the beginning of the project to the potential vaccine (Dance, 2020).

Although SARS-CoV-2 is a new virus, researchers already knew a great deal about coronavirus in general and learned a great deal from studies of vaccines initiated during the SARS and MERS outbreaks in 2003 and 2012, respectively. A promising potential antigen for the SARS-CoV-2 vaccine is known as the spike protein, which stands out on the virus's surface to create the "crown"-like appearance after which the coronavirus was named (Dance, 2020).

The main technologies involved in developing the potential COVID-19 vaccines are: (i) protein-based vaccines (protein sub-units or virus-like particles (VLP)); (ii) viral vectors (replicating or non-replicating); (iii) nucleic acid vaccines (DNA or RNA); and (iv) virus vaccines (attenuated or inactivated).

According to the "Landscape of COVID-19 candidate vaccines" published in the WHO's website and accessed on November 12, 2020, there were 163 potential vaccines for COVID-19 in pre-clinical trial stages and 48 in clinical trials[1]. The number of vaccines under development with each of these technologies is presented in Figure 2.

Figure 2. Number of vaccines in pre-clinical and clinical trials separated according to the development platform



Source: Based on data from WHO.

Several vaccine platforms are under development for COVID-19. Among those with greater potential are the genetic platforms, based on DNA and RNA, followed by the platforms for the development of vaccines with recombinant sub-units. The RNA and DNA vaccines can be quickly obtained because they are derived from synthetic processes and, therefore, do not require cell culture or fermentation. The experience of developers and regulators with these platforms for cancer vaccines can facilitate the trials and the quick release of new vaccines. However, it is worth mentioning that there are no vaccines using a DNA or RNA platform that have been approved so far for commercial use, which makes the development and feasibility of these types of vaccine an even bigger challenge (Lurie, *et al*., 2020; Krammer, 2020).

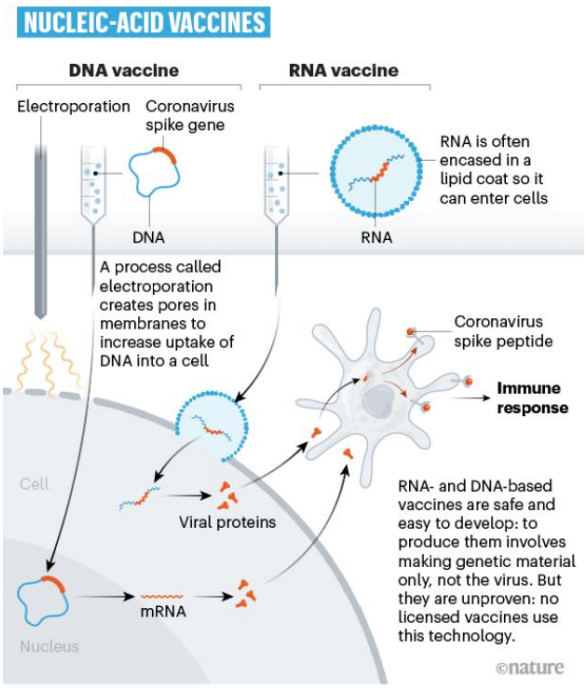
3. NUCLEIC ACID VACCINES

Nucleic acid vaccines (DNA or RNA) have the same objective as traditional vaccines, but they work slightly differently. Instead of injecting an attenuated virus or bacteria into the body as a traditional vaccine, DNA and RNA vaccines use a portion of the genetic code of the virus itself to stimulate an immune response. In other words, they carry the genetic instructions so the host's cells can produce antigens (Abbasi, 2020).

The main differences between DNA and RNA vaccines can be identified in Figure 3 (Callaway, 2020b) and include the form of entry of the nucleic acid (vaccine) into the host cell. For the DNA vaccine, the fragment is inserted into the cells through a little electrical pulse. Additionally, the DNA needs to penetrate the cell nucleus and transcribe the DNA into RNA, so the host cell can start the effective production of viral proteins – the antigens that must activate the individual's immune system. On its turn, by penetrating the host cell, the RNA has the potential to cause the production of antigens without the initial stages required when DNA fragments are injected.

Both vaccines seem to induce a good immune response in the host. Despite the advantage of the DNA vaccine as to the molecule's stability under high temperatures, there is a disadvantage of the requirement of a special device to cause the electrical pulse needed for penetration into the cell. With respect to the RNA vaccine, the advantage is the safety of the nucleic acid as it remains in the cytoplasm, outside the cell nucleus; therefore there is no chance of integration into the host's genome.

Figure 3. Mechanism of action of nucleic acid vaccines



Source: Callaway, 2020b

3.1. RNA Vaccines

As mentioned, among the major advantages of nucleic acid vaccines (DNA or RNA), there is the possibility of quick and large-scale production at a lower cost, considering that there is no need to cultivate micro-organisms, as in the case of attenuated and inactivated vaccines, requiring a smaller laboratory structure. Additionally, the RNA vaccine platform is flexible, which enables the quick adaptation of the vaccine for new virus variants, which is common for respiratory viruses, reducing the time for the eventual need to develop new vaccines.

The gene vaccines also eliminate the risk for a person to become sick after vaccination, which can occur if the attenuated viruses are used.

[1] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

The mRNA is the intermediate stage between the translation of the DNA that encodes the protein and the production of these proteins by the ribosomes in the cytoplasm. Two main types of RNA are currently studied as vaccine: non-replicating mRNA and self-amplifying RNA (saRNA) derived from viruses. The conventional mRNA-based vaccines encode the antigen of interest and include untranslated regions (UTRs) in ends 5' and 3', while saRNA encodes not only the antigen, but also the viral replication machinery that allows the amplification of intracellular RNA and the abundant expression of proteins (Geall, *et al*., 2012; Pardi, *et al*., 2018). It is possible to identify the type of technology for the RNA vaccine adopted by each of the six vaccines analyzed in this study in Table 1.

Several techniques have been developed to enhance the platforms for RNA vaccines, such as the optimization of the flanking UTRs regions 5' cap and the poly A tail, so that the mRNA becomes similar to the mature mRNA molecules that naturally occur in the cytoplasm of eukaryotic cells. Additionally, the naked mRNA is quickly degraded by extracellular RNAses and is not internalized efficiently. Therefore, a wide variety of *in vitro* and *in vivo* transfection reagents have been developed to facilitate the cell's uptake of mRNA and protect it from degradation (Pardi, *et al.*, 2018).

Despite the quick, unprecedented development, RNA vaccines are not clinically proven. None of the commercially available vaccines use this platform and, up to the COVID-19 pandemic, it had not been tested in humans in large scale. However, experts affirm that, if it is possible to expand the technology, the pandemic can help introduce a new plug-and-play approach for vaccinology (Abbasi, 2020).

3.2. Mechanism of action of the RNA vaccines

The mRNA vaccines are emerging as a promising alternative to the traditional vaccine platforms, since they can be manufactured quickly and adapted to a wide range of conditions. In clinical trials, mRNA vaccines intended for several infectious diseases and cancer are usually safe and well-tolerated. Over the last few years, several mRNA vaccines have been optimized and validated in immunogenicity and efficacy studies (Martin & Lowery 2020). Six of the potential vaccines currently in clinical trials to prevent COVID-19 are RNA-based (Table 1), namely: mRNA-1273 (Moderna/NIAID), BNT-162b2 (BioNTech/Pfizer), CVnCoV (CureVac), LNP-nCoVsaRNA (Imperial College London), ARCT-021 (Arcturus /Duke-NUS), and ARCov (Walvax Biotechnology/Academy of Military Medical Sciences).

Table 1. RNA-based vaccines for COVID-19 in clinical trials

Potential vaccine	Developer	Country	Current stage of clinical trial	Platform used
LNP- mRNA-1273	Moderna/NIAID	**US**	**Phase 3**	mRNA
mRNA BNT-162b2	BioNTech/ /Pfizer	**DE/US**	**Phase 3**	mRNA
CVnCoV	Curevac	**DE**	**Phase 2**	mRNA
ARCT-021	Arcturus/Duke-NUS	**US/SG**	**Phase ½ (combined)**	saRNA
LNP-nCoVsaRNA	Imperial College London	**UK**	**Phase 1**	saRNA
ARCoV	Walvax Biotechnology / Academy of Military Medical Sciences	**China**	**Phase 1**	mRNA

Source: This study.

The classic potential RNA-based vaccine uses the mRNA delivery method in a host cell, instructing it to produce a specific protein or antigen (i.e., a foreign substance that induces an immune response). The induced immune response is directed against the antigen encoded by the mRNA. In order to prevent the degradation of the mRNA and enhance the vaccine's efficacy, the mRNA is also encapsulated in a protective envelope[2].

The recent interest in mRNA vaccines has been fostered by methods that increase mRNA stability and production of the antigen protein, in addition to methods to enhance the delivery systems in the host's body. These methods include the use of modified nucleosides, as well as the development of nanoparticle delivery technologies that stabilize mRNA, increase cell uptake, and enhance mRNA bioavailability. Avoiding the risk of integration into the host's genome is considered a comparative advantage of mRNA vaccines (compared to the DNA vaccines), since, unlike DNA vaccines, they do not need to reach the nucleus to express the antigen.

Another technology of interest with respect to the platforms of RNA-based vaccine is related to saRNA vaccines, which have higher performance of the antigen expressed by the mRNA. The capacity of saRNA vaccines to provide a wide, long-term *in vivo* production of antigens, together with potent immunostimulant properties, allows the same immune responses with lower doses of vaccine, which will likely be needed to meet the global demands of the COVID-19 pandemic (Fuller & Berglund, 2020).

3.3. mRNA-1273 Vaccine (Moderna/NIAID)

The mRNA-1273 vaccine was developed by scientists from the biotechnology company Moderna, based in Cambridge, and associates researchers from the NIAD (NIH), Massachusetts. The quick development of this potential vaccine was only possible because it was based on previous studies that used the same platform for other viruses, such as the Nipah (Dance, 2020) and other related coronaviruses that cause the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) (Humphreys & Sebastian, 2018). Therefore, the vaccine combines Moderna's mRNA delivery platform and the stabilized SARS-CoV-2 S protein immunogen (S-2P) developed by NIAID scientists[3].

The experimental vaccine was developed using the genetic mRNA platform that directs the body's cells to express a viral protein that is expected to cause a strong immune response. The vaccine mRNA-1273 is manufactured in a dispersion of ionizable lipid nanoparticles (SM-102) and 3 commercially available lipids[4].

[2] https://www.curevac.com/

[3] https://www.niaid.nih.gov/news-events/atomic-structure-novel-coronavirus-protein

[4] https://clinicaltrials.gov/ct2/show/NCT04283461

The S protein, also known as *spike*, is present on the surface of coronaviruses and is responsible for the connection between the viral particle and the human cells, enabling the entry of the virus into the host's cells. The scientists at NAID and Moderna has already been working on a vaccine for the MERS-CoV coronavirus, targeting the S protein, which enabled the quick progress in developing a potential vaccine against COVID-19. As soon as the genetic information for SARS-CoV-2 became available, the scientists quickly selected a sequence to express the stabilized protein of the new virus in the existing mRNA platform (NIAID/NIH, March 2020).

With the positive results obtained in studies using monkeys (Corbett, *et al*., 2020) in March 2020, the company began the trials for the first vaccine against COVID-19 in humans. Therefore, the pharmaceutical company Moderna began the clinical trials for its vaccine mRNA-1273 only 2 months after the identification of the genetic sequencing of SARS-CoV-2, on March 16, 2020 (NCT04283461). The phase I clinical trials showed that the vaccine was considered safe and well-tolerated, with a safety profile that is consistent with other modern vaccines against infectious diseases (Jackson, *et al.,* 2020). The phase II clinical trial (NCT04405076) included 600 individuals. Additionally, a study involving 40 patients over the age of 56 suggested that a second dose would be necessary to ensure immunity in elderly patients (Anderson, *et al.*, 2020).

In July 2020, a phase 3 study (NCT04470427) was initiated with 30,000 healthy individuals in about 89 centers over the United States (NIH, July 27, 2020)[5], which preliminary results showed that the vaccine had a 94.1% efficacy (Callaway, 2020a). The phase 3 COVE study exceeded 2 months of average monitoring post-vaccination, as required by the US agency FDA, for Emergency Use Authorization[6].

Still in July, Moderna lost a patent dispute for a portion of its vaccine technology in the United States, with respect to the formulation of lipid nanoparticles (LNP), used to direct and deliver mRNA into human cells (Nature Biotechnology, September/2020). However, the company affirmed that it would not affect the development of the vaccine for COVID-19[7].

3.4. BNT162b2 vaccine – BioNTech, Pfizer, and Fosun Pharma

For most of its history, the German biotechnology company BioNTech has focused exclusively on cancer drugs. Its first major foray into infectious diseases came in August 2018, when it signed an agreement with Pfizer to work on a seasonal flu vaccine. The idea was to use BioNTech's customization process to develop a better vaccine against the flu pathogen, which mutates every winter season.[8]

According to the BioNTech portal, the pipeline of vaccines using the company's mRNA platform addresses different therapeutic areas applicable to the treatment of many diseases, including cancer, infectious diseases, and rare diseases. Considering that the structural elements of mRNA have an impact on its performance, such as potential immunogenicity, translation efficiency, and stability of the molecule: the company has vast experience in designing, synthesizing, manufacturing, and formulating therapeutic mRNA and adapting its composition to suit the desired application. Among the different mRNA produced by BioNTech we cite uRNA (optimized unmodified mRNA), modRNA (modified RNA), saRNA (self-amplifying mRNA), and taRNA (trans-amplifying mRNA). Among the mRNA delivery formulations, the company has 3 different types of formulations, depending on the application and delivery route of the vaccine, namely Lipoplex, Lipid Nanoparticles (LNPs), and polyplexes. More information about these technologies is available on the company's website.[9]

BioNTech has partnered with Pfizer, a multinational pharmaceutical company based in New York, and the Chinese pharmaceutical company Fosun Pharma to develop and produce a COVID-19 mRNA vaccine. In May, a phase 1/2 clinical trial with two versions of the vaccine was launched. The analysis of results from this first phase of clinical trials in humans showed that both versions stimulated the production of antibodies against SARS-CoV-2 (Mulligan, et at., 2020; Walsh, et al., 2020), as well as immune cells called T cells, which respond to the virus (Sahin, et al., 2020). It was then verified that one of the versions, called BNT162b2, produced significantly fewer side effects, such as fever and fatigue, and, thus, this one was selected to integrate the phase 2/3 tests. On July 27, 2020, the companies announced the launch of a clinical trial phase 2/3 with 44,000 volunteers in the United States and other countries, including Argentina, Brazil, and Germany (Coronavirus Vaccine Tracker, NYT).

On November 9, 2020, Pfizer and BioNTech made history by presenting preliminary data indicating that their coronavirus vaccine was over 90% effective. It was the first time that a group evidenced the production of antibodies against COVID-19 induced by a vaccine, with a 90% efficacy. A week later, Moderna reported similar results for its vaccine.

The results from phase 3 clinical trials of the potential vaccine BNT162b2, involving 43,548 participants, demonstrated that Pfizer's vaccine is 95% effective in preventing COVID-19 and has no serious side effects. Similar efficacy (usually 90 to 100%) was observed in all subgroups defined by age, sex, race, ethnicity, baseline body mass index, and the presence of coexisting conditions. (Polack, et al., 2020)

On December 2, 2020, the UK authorized in an emergency manner the Pfizer/BioNTech vaccine, becoming the first western country to approve a vaccine against the SARS-CoV-2 coronavirus. Vaccination in the UK began on December 8, 2020, and, on December 10, 2020, the members of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) of the US Food and Drug Administration (FDA) recommended authorization of the application of emergency use of the vaccine against COVID-19 in the United States, starting vaccination in the second half of December.

[5] https://www.nih.gov/news-events/news-releases/phase-3-clinical-trial-investigational-vaccine-covid-19-begins
[6] https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-primary-efficacy-analysis-phase-3-cove-study
[7] https://www.reuters.com/article/us-moderna-patent-vaccine-idUSKCN24P2LJ
[8] https://www.bloomberg.com/features/2020-moderna-biontech-covid-shot/
[9] https://biontech.de/how-we-translate/mrna-therapeutics

Canada, Mexico, Saudi Arabia, and Bahrain have also authorized the emergency use of the vaccine, so that 6 countries will soon be vaccinating at least part of their population with this vaccine.

3.5. CureVac vaccine

The vaccine developed by the German company CureVac (CVnCoV) consists of an optimized mRNA, not chemically modified, which encodes the entire S-glycoprotein (*spike*) of SARS-CoV-2, encapsulated in lipid nanoparticles (NPL), acting by inducing immunity to SARS-CoV-2 (Integrity/Clarivate). The company has been involved in the vaccine area since 2007, having already worked with MERS coronavirus in 2017. The project to develop an mRNA vaccine against SARS-CoV-2 began in January 2020, as soon as the virus sequence was published. In May, preclinical results with low doses of the vaccine indicated the production of high titers of neutralizing antibodies (Rauch, et al., 2020), so the company received approval from regulatory authorities in Germany and Belgium to initiate phase I clinical trials in Europe, in July 2020 (NCT04449276).

In August, the company registered a phase 2 clinical trial (NCT04449276). In November, the company reported the positive results of phase 1 clinical trial with strong induction of neutralizing antibody production, in addition to the indication of T-cell activation and the beginning of phase 2b/3, before the end of 2020.[10]

3.6. Arcturus Therapeutics/Duke-NUS Medical School' vaccine

The company Arcturus Therapeutics, based in California and founded in 2013, and Duke-NUS Medical School, based in Singapore, have developed a vaccine, ARCT-021, based on a self-transcribing and replicating RNA (STARR™) to prevent SARS-CoV-2 infection. The vaccine contains a self-replicating RNA (saRNA) that encodes an alphavirus-based replicon and the full-length SARS-CoV-2 *spike* glycoprotein (S) and uses lipid nanoparticle delivery technology (LUNAR®), engineered to increase and extend antigen expression, allowing vaccination at lower doses.[11]

The translation of the replicon produces a replicase complex that amplifies and prolongs the expression of the SARS-CoV-2 S glycoprotein. A single dose of the vaccine in mice led to strong antibody responses in addition to activation of cell-mediated immunity that produced a strong CD8+ and CD4+ T-cell response. (Alwis, et al., 2020)

In August, the phase 1/2 trial (combined) involving 106 participants was launched in Singapore, which preliminary results demonstrated serum conversion in most volunteers, high neutralizing antibody titers, T-cell activation, as well as tolerability and safety in groups of young and old people tested.[12]

The saRNA encapsulated in lipid nanoparticles (LNP) is a relevant platform for vaccine production in the context of a global pandemic, as it can encode any antigen of interest and requires a minimal dose compared to traditional messenger RNA (mRNA) (Vogel, et al., 2018).

3.7. Imperial College London's vaccine

The vaccine developed by the Imperial College London uses a technology similar to that of Arcturus Therapeutics, a self-replicating RNA (saRNA) vaccine, encoding the stabilized prefusion SARS-CoV-2 S glycoprotein encapsulated in a lipid nanoparticle (LNP). Called LNP-nCoVsaRNA or COVAC1, preclinical trials of the vaccine has been shown to induce strong neutralization of a pseudovirus, proportional to the amount of specific IgG and in greater amounts than patients recovered from COVID-19 (McKay, et al., 2020)

Phase 1/2 trials began on June 15, 2020 and partnered with Morningside Ventures, based in Hong Kong, to manufacture and distribute the vaccine through a new company called VacEquity Global Health. Researchers expect vaccine efficacy results by the end of the year (Coronavirus Vaccine Tracker, NYT).

3.8. Academy of Military Medical Sciences / Walvax Biotechnology's vaccine

ARCoV, the potential vaccine against SARS-CoV-2 jointly developed by the Chinese Academy of Military Medical Science and Walvax Biotechnology Co., Ltd, has a technology based on thermostable messenger RNA (mRNA), which encodes the receptor binding domain (RBD, aa 319-541), of SARS-CoV-2 encapsulated in lipid nanoparticles (NPL)[13] and is the first COVID-19 mRNA vaccine to be approved for clinical trials in China. Studies have shown that ARCoV induces neutralizing antibodies and T-cell immunity in mice and NHPs. Vaccination with ARCoV conferred full protection against SARS-CoV-2 in mice and was shown to be a thermostable potential vaccine for phase 1 studies. (Zhang, et al., 2020)

A phase 1 clinical trial assessing the safety, tolerance, and preliminary immunogenicity of different doses of a SARS-CoV-2 mRNA vaccine in a population aged 18 to 59 years and 60 years or older is being carried out in China (ChiCTR2000034112) [10] .

4. OBJECTIVE/METHOD:

The objective of this study was to provide a current landscape of the knowledge related to RNA-based vaccines for the prevention of SARS-CoV-2 in the most advanced clinical stage to date, based on patent documents related to these technologies. In addition to serving as a source of technological information, identifying patent applications and their status with the Brazilian National Institute of Industrial Property – INPI and worldwide can help in decision making if these vaccines prove effective for preventing SARS-CoV-2

[10] https://www.curevac.com/covid-19
[11] https://ir.arcturusrx.com/news-releases/news-release-details/arcturus-therapeutics-announces-positive-interim-arct-021-lunar
[12] https://ir.arcturusrx.com/news-releases/news-release-details/arcturus-therapeutics-announces-positive-interim-arct-021-lunar
[13] https://integrity.clarivate.com/

infection. The 6 potential RNA-based vaccines under clinical trial up to now were selected for this study (see Table 1).

It is worth mentioning that, as these technologies are very recent, many of the specific patent applications for the vaccines studied have not yet been published, and information on the vaccines comes mainly from the institutions that develop them. Therefore, this study aims to demonstrate the state-of-the-art or Know-how from these developing institutions. When more than one institution is reported as a vaccine developer, efforts were concentrated on the analysis of patent documents filed by the institution indicated as "originator" by the Integrity/Clarivate database and their websites.

The search of patents and/or patent applications was conducted on the *Derwent Innovations Index* database by the name of the institution(s) that developed them. In cases in which the number of applications from the research institution was very large, patents were selected through the patent classification codes (International Patent Classification (IPC) and Cooperative Patent Classification (CPC)) and the Derwent Manual Codes, according to the technology of the vaccines analyzed. After that, the applications were evaluated as to their relevance to this study by reading the titles, abstracts, and claims.

Information on the bibliographic data of the applications was collected from the Derwent Innovation™ database, which provided INPI with its information for dissemination. The platform initiative intended to collaborate with INPI in actions that directly or indirectly contribute to the search for solutions for treating COVID-19.

The work resulted in 07 spreadsheets, which are available in Excel format for better user analysis. The spreadsheets are formed by a list of patent applications addressing technologies related to each of the 6 potential RNA vaccines, in addition to a spreadsheet describing the details of the search strategy used. Patent applications for which Brazilian correspondents have been identified (applications from the same family filed at INPI) are highlighted in blue in the spreadsheets. The progress of these applications can be accessed on INPI portal through the BuscaWeb tool.[14]

5. *RESULTS*

Considering that this study aimed to identify patent applications addressing RNA vaccines that have been developed for preventing COVID-19, 6 individual spreadsheets were generated (see annex) presenting an overview of the patent applications including technologies identified as more relevant to the potential vaccines described by the companies. The focus was on patent applications claiming RNA vaccines against viral infections, especially for respiratory viruses and other RNA viruses.

Although it is known that development of platforms using RNA for gene therapy of autoimmune, inflammatory, metabolic, and genetic diseases and disorders, cancer, and other pathologies can also be used in the development of anti-viral vaccines, patent applications that did not mention a technology specific for vaccines against viral infections were excluded, due to the high number of documents found.

Patent applications claiming general mRNA production processes for gene therapy or methods for modifying RNA, if generic, were included in the spreadsheets. When applicable, patent applications for nanoliposomes (NLP) used in the formulation of vaccines to encapsulate RNA were also included.

5.1 Moderna/NIAID (mRNA-1273)

Whereas NIAID (NIH) was responsible for the study that unraveled the prefusion structure and conformation of the SARS-CoV-2 spike protein, in addition to the spike protein RBD antigenicity assays (Wrapp, et al., 2020) and that Moderna was responsible for the development of the RNA vaccine platform, the search was carried out based on patent applications filed by Moderna.

The search for the company in the Derwent database found 544 Derwent World Patents Index (DWPI) Families.[15] Then, using the selected IPCs, CPCs, and Derwent Manual Codes (see annex for search details), 180 documents were selected and analyzed by reading the titles, abstracts, and claims, generating a total of 74 documents deemed relevant (see attached spreadsheet). Patent documents describing the use of RNA for antibody production or gene therapy (such as treatment of autoimmune diseases and cancer) and RNA vaccines against bacteria or microorganisms other than viruses were excluded. The most relevant documents found related to the COVID-19 vaccine being developed by Moderna in partnership with NIAID were US10702600 (claims mRNA vaccine for betacoronavirus encoding the S protein) and US20200030432 (mRNA vaccines against Lassa, Nipah, and betacoronaviruses), both documents report mRNA encapsulation in nanoliposomes (NLP).

In addition to both documents specifically related to coronavirus, another 26 documents describe mRNA vaccines encapsulated in lipid nanoparticles for viral infections, such as WO2017070624 (Chikungunya); WO2018151816 US10273269 e WO2019055807 (Zika); WO2018089851, WO2018170245, BR112018008078, BR112018008078 (influenza), WO2017070626 (respiratory viruses, including batecoronavirus), US20180243225A1 e WO2017015457 (ebola), among others.

15 patent applications were also identified for lipid nanoparticles formulations, which are used in RNA vaccines to encapsulate the nucleic acid and allow it to reach the host cell, such as, for example, the documents WO2017099823 and WO2019152557.

Thirty-four patent documents refer to methods of producing RNA vaccines in general, mainly modifications that can be made to the RNA, for example, modifications aimed at increasing the molecule stability. All these 74 documents can be accessed in the attached spreadsheet.

[14] https://gru.inpi.gov.br/pePI/jsp/patentes/PatenteSearchBasico.jsp

[15] https://support.clarivate.com/Patents/s/article/Derwent-Innovation-Patent-Family-Collapse-FAQ?language=en_US

5.2 Pfizer/ BioNTech (BNT-162b2)

According to data from the Integrity/Clarivate database, the German company BioNTech is the organization that created the BNT-162b2 mRNA vaccine against SARS-CoV-2. In March 2020, BioNTech signed an agreement with the multinational company Pfizer to jointly develop and market the BNT-162 mRNA vaccine program (PF-07302048) globally, except for China, where the rights have been licensed to Shanghai Fosun Pharmaceutical.[16]

Considering the information provided by the Integrity database, which identifies BioNTech as the developer of the technology, the search for patent applications related to mRNA vaccines for preventing viral infections was performed only under the Derwent name and code for this company.

378 DWPI families presenting BioNTech as patent applicant (or joint applicant) were identified. Then, 245 documents were selected based on the IPCs, CPCs, and Derwent Manual Codes (see details in the annex) and evaluated by reading titles, abstracts, and claims, when available. The vast majority of documents identified refer to RNA vaccines, especially for treating cancer and/or immunotherapies related to inflammatory or metabolic diseases. These documents were not included in the spreadsheet, unless they make some reference to the possibility of applying the process described for infectious diseases. Documents describing the use of RNA in technologies related to diagnosis or antibody production were also excluded from the sample, as well as drugs not related to nucleic acids for treating or preventing viral infections.

Among the 43 documents identified as the most relevant (see annex spreadsheet), we highlight four that mention coronavirus, three of which are compositions for treating or preventing various viral infections such as HIV, Hepatitis, influenza, and SARS (WO2019137999, WO2018010815, and WO2015176737).

Documents related to other RNA platform vaccines for preventing viral infections were also identified, as well as documents that reveal production techniques and/or RNA modifications (such as modifications of the 5' cap), aiming to improve vaccine platforms: WO2019053003, WO2019175356, WO2019053056, WO2018172426, US10729785, WO2017068013, WO2017162460, WO2017162461, WO2017162265, WO2017162266, WO2011015347, WO2007036366. Documents related to different RNA formulations and delivery systems (for example liposomes) have also been identified, such as WO2020070040, WO2019077053, WO2016155809, WO2016155809, WO2011015347. Other documents with related technologies are also found in the attached spreadsheet.

5.3 Curevac (CVnCoV)

The search strategy associated the company name to IPCs A61K and/or C12N generating 262 DWPI families. The abstracts of the documents were evaluated and 32 patent applications considered related to the vaccine technology presented by CureVac were selected (see attached spreadsheet).

The most relevant document is US20190351048, an mRNA-based vaccine developed for the MERS coronavirus. In this document, the mRNA used can encode S (spike) glycoprotein, envelope (E) protein, membrane (M) protein, or nucleocapsid (N) protein, fragments or variants thereof carried by lipid nanoparticles (NPL).

Other relevant documents describe NPL-encapsulated mRNA-based vaccines developed for other viruses: WO2017191258 and BR112019008481 (developed against influenza virus); US20190351044 and WO2020002525 (developed against Lassa virus); WO2019193183A3 (developed against yellow fever virus).

We also selected documents that refer to methods for developing mRNA vaccines mentioning the possibility that the target pathogen is a coronavirus. Among them WO2010037539; BR112017018368; WO2017109134; WO2012116811; WO2012116715; BR112014016361.

Some applications specifically address lipid nanoparticles (NPL) such as applications WO2016203025 and BR112019008481.

5.4 Arcturus/ Duke-Nus (ARCT-021)

According to Clarivate Integrity database, the vaccine developed by Arcturus Therapeutics (ARCT-021 or LUNAR-COV19) is constituted by SARS-CoV-2 mRNA comprising a self-replicating RNA (saRNA) based on the STARR technology platform and which uses the lipid delivery system called LUNAR®. The vaccine is being developed in collaboration with the Duke-Nus Medical School of Singapore.

As Arcturus appears as the developer of the vaccine, the patent search was carried out for this company only. 45 patent documents held by the company were identified and, after reading the titles, abstracts, and claims, 26 documents were selected as possibly related to the potential vaccine for COVID-19 (see attached spreadsheet).

Among the 26 selected documents, 16 refer to RNA delivery methods, mainly those based on lipid structures such as nanoliposomes. Considering the low number of documents related to RNA vaccines for preventing viral infections, mRNA vaccines against other non-viral diseases were included in the spreadsheet, as well as RNA modification methods (WO2018075827, WO2008147824), and vaccine technologies containing acids nucleic in general, which can be applied for preventing a virus disease, such as WO2020118239, which addresses mRNA constructs that generate high efficiency of target protein expression, and WO2019191780, addressing pharmaceutical composition for treatment or immunization of humans against several diseases comprising nucleic acid in lipid nanoparticles. Documents related to the treatment of diseases through gene therapy containing interfering RNA were excluded.

No documents were found mentioning the saRNA technique described by the company as the basis for its COVID-19 vaccine platform, indicating that it is a new technology with no patent document yet filed by this company that has already been published.

[16] https://integrity.clarivate.com/

5.5 Imperial College London (LNP-nCoVsaRNA)

The search based on the institution name and code in Derwent database found 2,780 DWPI families. The classification codes IPC, CPC, and Derwent Manual Codes were then used to select the most relevant documents for RNA vaccine technology (see the detailed methodology in the annex, spreadsheet 7). After this selection, 295 documents were manually analyzed by reading the titles, abstracts, and claims, 30 of which were considered closest to the vaccine, and presented in the attached spreadsheet.

Despite the large number of applications related to gene therapies, the vast majority refer to techniques like interference RNA (siRNA), gene editing techniques like CRISPR, and the use of viral vectors encoding the gene of interest, mainly Adeno Associated Vectors (AAV) and not the use of mRNA or saRNA platforms.

This study did not consider patent documents referring to gene therapies for cancer, metabolic disorders, or even infections that were not of viral origin.

The most relevant document is the WO2017098281, which claims a vaccine composition containing RNA where this RNA is a saRNA (self-amplifying RNA). Additionally, the claimed vaccine contains a delivery system based on synthetic lipid nanoparticles. The claims are broad and provide for the possibility of the vaccine being used for infections, not mentioning the possible pathogens.

Four documents referred to vaccination and protection against viral infections, citing, among others, coronaviruses. None of them, however, refer to RNA vaccines. Namely: EP2997151 (lentiviral vectors expressing virus glycoprotein); EP1684796 (formaldehyde treated antigens); GB201816873 (fusion proteins expressed in virus-like particle (VLP)); and KR2020008288 (antibodies to different viruses).

Another four documents refer to RNA vaccines against other viruses such as EP1254657 (for Hepatitis B, Influenza, and HIV encapsulated in liposomes); GB201007531 (Flavivirus); EP2215221 (*Reoviridae*); and EP700441 (diagnostic and possible HMSV vaccine).

Four documents refer to the production of liposomes that can be used for RNA vaccine formulations (WO2019092437, EP2731591, EP1506019, and EP1506019). The other documents in the spreadsheet refer to other vaccines against viral infections produced by the institution and mention the possibility of using polynucleotides, using techniques other than saRNA in the vaccine composition.

5.6 Academy of Military Medical Sciences / Walwax Biotechnology (ARCoV)

Through the search for the applicant's name, 30 DWPI families held by the Chinese biotechnology company Walvax Biotechnology were identified. Several of the documents are related to vaccines, but none refers to the RNA vaccine platform. One document (CN104706596) refers to the production of liposomes to be used in the encapsulation of vaccine for Influenza.

According to the Integrity/Clarivate database, the Chinese Academy of Military Medical Sciences would be the developer of the RNA vaccine encoding the receptor binding domain (RBD, aa 319-541) of SARS-CoV-2 encapsulated in lipid nanoparticles (LNP). Based on the applicant's name and DWPI Assignee code and further selection of IPCs A61K and/or C12N, 2,258 DWPI families held by the Chinese Academy of Military Medical Sciences were identified. Using a new filter for the IPCs and Derwent Manual Codes (see detailed description in the annex), the titles, abstracts, and claims of 475 documents were analyzed. 41 patent documents considered more relevant were selected. Among these, 36 documents referring to the treatment, detection, or prevention of infections caused by coronaviruses and 7 documents specifically referring to the new coronavirus, SARS-CoV-2. Namely: CN111265528, CN111297882, CN111265527, and CN111265532 (addressing drugs to treat COVID-19), CN111303280 (monoclonal antibody to SARS-CoV-2), CN111218459 (claims the SARS-CoV-2 S protein sequence and viral vector vaccine), and CN111333704, claiming a vaccine for COVID-19, antigen, antigenic protein sequence, nucleotide sequence, fusion protein, antibody, and viral protein expression vector. Although none of these documents refer specifically to an mRNA vaccine, they are all listed in the attached spreadsheet, as they are considered relevant to the topic.

Among the other applications referring to coronaviruses prior to SARS-CoV-2, we highlight the applications referring to genetic vaccines such as: CN1566144, CN103316337 and CN101948516 (describe vaccine for coronaviruses based on RNA or cDNA or recombinant coronaviruses); CN1566144 (shows 3 structural proteins of SARS-CoV (N, S, and M) and claims the application of genes encoding such proteins to prepare diagnostic reagents and/or vaccines); CN102021145 (DNA vector vaccine), and CN1194003C (treatment and prevention of SARS using siRNA).

Regarding the other applicant's patent documents, only those referring to RNA vaccines to prevent viral infections were selected; therefore, all other documents were excluded, even if they mentioned viral vaccines using other technologies such as: vaccines based on viral vectors, plasmids, DNA vaccines, cDNA, virus-like particles (VLP), and other gene therapies such as those involving siRNA (RNA interference), CRISPR, and other therapies for autoimmune diseases, cancer, and metabolic disorders.

6. Final considerations

Genetic vaccines are those that deliver one or more genes from the coronavirus itself to the cells of immunized individuals generating an immune response. They can be DNA or RNA-based encoding a protein or protein fragment of the pathogen of interest. In the case of this study, the new SARS-CoV-2 coronavirus.

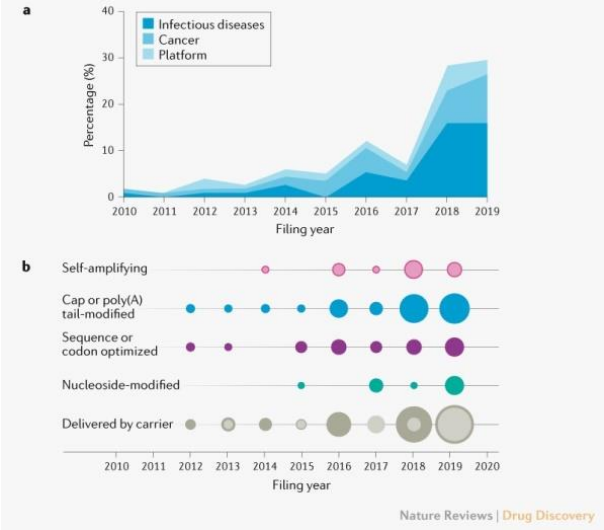
A recent study identified that patenting activity on mRNA vaccines has grown dramatically over the past 5 years, and the number of mRNA vaccine patent applications for infectious diseases exceeded that for cancer in the past 3 years, which may reflect the increased interest in vaccines after epidemic outbreaks like MERS-CoV, Ebola virus, and Zika virus (Figure 4a). Moderna, CureVac, BioNTech, and GSK collectively hold nearly half of the mRNA vaccine patent applications. (Martin & Lowery, 2020)

Certainly, prior investment in RNA vaccine research allowed the development of vaccines against SARS-CoV-2 in such a short time and arrival to the market, even with emergency authorization, in record time. It can also be noted that the companies that achieved this success are among those that have already been researching more intensively in this area, as evidenced by the filing of patent applications from the biotechnology companies Moderna and BioNTech.

Numerous patent documents are related to the protection of pharmacological modifications to reduce instability and/or increase the immunogenicity of mRNA, in addition to many documents that seek to protect, with patents, methods to improve the efficiency of mRNA delivery, such as lipid nanoparticle compositions (LNP) (Figure 4b). There is expected an exponential growth in the filing of patent applications related to RNA vaccine technologies, as a result of the increased investment in the development platforms and ongoing accelerated clinical trials, which are potentially proof of concept for mRNA vaccines, which, to date, have not yet been approved for large-scale commercialization and use.

Indeed, positive results in these trials would not only resolve an urgent and immediate need for a vaccine against SARS-CoV-2, but would also provide a potent and versatile therapeutic tool for developing vaccines against future outbreaks of infectious diseases. (Martin & Lowery, 2020)

Figure 4. (a) Percentage of RNA vaccines against infectious diseases, cancer, and vaccine platforms and (b) quantitative of patents according to the technology disclosed



Source: Martin & Lowery, 2020

Several clinical trials are being carried out around the world for the different types of treatment, prophylaxis, and vaccines that have been proposed to inhibit SARS-CoV-2 infection. (Lythgoe & Middleton, 2020) The different products and the level of development of each one, including the testing stage, dosages, and specific protocols, can be accessed on the websites of the developing companies or the websites of organizations linked to health, governments, and research institutions.[17,18]

Although RNA-based vaccine platforms represent an important technological advance in the area, which makes it possible to shorten the response time and cost for the development of new vaccines, the technology also presents new challenges for developers, such as scaling up production through good manufacturing practices (GMP), the establishment of regulations and documentation around safety, and increased efficacy (Pardi, et al., 2018). Other considerations include producing large amounts of medical-grade RNA and developing methods that increase the stability of the compositions. RNA is naturally unstable and needs to be stored frozen at about -20°C, which complicates the transport logistics and clinical use of RNA-based vaccines. CureVac and other companies are, however, working to stabilize the molecule at higher temperatures, for example, by lyophilization (Dance, 2020).

Curevac, a German pharmaceutical company, affirms that its potential COVID-19 vaccine, CVnCoV, can remain stable for at least three months at 5°C. This storage temperature would make this vaccine more easily distributed than the Pfizer/BioNTech's, which must be kept in an ultrafreezer at -70°C (FDA News).

The potential vaccines from Pfizer/BioNTech and Moderna, both mRNA platform vaccines presented in this study, will most likely be not only the first vaccines against COVID-19, but also the first genetic-based vaccines to reach the market. This technology is believed to revolutionize the history of immunizations.

The Pfizer/BioNTech vaccine was the first RNA vaccine approved in the world, on December 2, 2020, even though for emergency use (restricted to certain groups and for a limited time) in the United Kingdom. Moderna already applied for authorization for emergency use of its vaccine in the United States, but it has not been approved yet.

Among more than 200 vaccines under development against COVID-19, thirteen are in the final stage of clinical trials (Phase 3) before approval and distribution, two of which have the RNA delivery technology (Coronavirus Vaccine Tracker, NYT).

As they are vaccines that use a new platform, with no vaccine approved for commercial use in the world, many doubts and fears hover over the non-scientific community, especially considering the accelerated approval process, forced by the pandemic.

Regarding safety, as the mRNA manufacturing process does not require toxic chemicals or cell cultures that may be contaminated with viruses, its production avoids the common risks associated with other vaccine platforms, including live viruses, viral vectors, inactivated viruses, and subunit protein vaccines. Additionally, the short manufacturing time of mRNA presents few opportunities for the introduction of contaminating microorganisms. In vaccinated people, the theoretical risks of infection or integration of the vector into host cell DNA are not a concern for mRNA. mRNA is rapidly degraded after transcription, thus not generating toxic residues for the cell. There is also no possibility of integration into the genome, since the mRNA molecule never reaches the cell nucleus, where the host's DNA resides, so that, considering the above reasons, mRNA vaccines were considered a relatively safe vaccine format. (Pardi, et al., 2018).

[17] https://clinicaltrials.gov/

[18] https://www.who.int/health-topics/clinical-trials/

This study is part of a series of publications under development at INPI that aim to identify technologies involved in vaccines against COVID-19 that are in the most advanced development stages. Thus, the study Annex presents the list of patent documents related to RNA-based vaccines platform against COVID-19 that are currently under clinical trials. It is worth mentioning that, since the pandemic started less than a year ago, and patent documents are usually kept secret for 18 months (except in specific situations that provide for early publication), the specific documents for vaccines against SARS-CoV- 2 may not have been found in the search. Additionally, considering the international filing routes under the Paris Convention and Patent Cooperation Treaty (PCT), it is also not possible to determine whether the most recently filed documents will have an equivalent application in Brazil.

This study can be used as a source of technical information both by researchers and decision-makers in the public and private spheres.

The list of patent documents related to the vaccines analyzed in this study can be found in the attached spreadsheet in Excel format with the main data from the documents, as well as their international and national correspondents, when applicable.

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