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ORIGINAL ARTICLE

Analysis of the COVID-19 Vaccine Development Process: an Exploratory Study of Accelerating Factors and Innovative Environments

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Abstract

Purpose The pace of the COVID-19 vaccine development process is unprecedented and is challenging the traditional paradigm of vaccinology science. The main pressure comes from the pandemic situation, but what makes it possible is a complex set of factors and innovative environments built along the times, which this manuscript aims to study.

Methods Through an exploratory study within the scope of innovation management, the present manuscript aims to identify and explore factors that are promoting this accelerated development scenario. The method comprises the monitoring of the strategies adopted by the developers and other stakeholders, as regulatory and humanitarian agencies, specific mechanisms from governments and non-governments bodies, and the background technology that has paved this pathway.

Results Technology-based and R&D strategy factors are the two main factors identified and explored herein. The breakthrough in the field of biotechnology and molecular biology is considered the main base-science that enables the rapid development of new vaccines. Additionally, new technological platforms can also be pointed out. Relating to R&D strategies, the parallelism of phases and adaptive clinical trials in consonance with regulatory agencies are the most relevant.

Conclusions The need to rapidly develop a vaccine against COVID-19 occurs at a time of great excitement in basic scientific understanding, as well as strategies learned in the past by industry and optimization of regulatory pathways. It is expected that these factors, arising from the global emergency, may redirect the R&D processes for new drugs, especially in times of pandemic.

Keywords Vaccine · Product development process · COVID-19 · Innovation management

Introduction

The world has witnessed an unprecedented series of events triggered by the pandemic of COVID-19 (coronavirus disease), a disease caused by SARS-CoV-2, a new virus belonging to the Coronavideae family, of great impact on individual and collective health worldwide, and high impact implications for the global economy. On the other hand, it is possible to identify positive aspects in facing the pandemic, ranging from humanitarian solidarity aid actions to accelerating strategies for the development of vaccines, which assumes the position of main hope in solving this problem of global scope.

On December 31, 2019, the World Health Organization (WHO) was alerted of several cases of pneumonia in the city of Wuhan, Hubei Province, in the People's Republic of China. It was a new strain (type) of coronavirus not yet identified in humans. A week later, on January 7, 2020, Chinese authorities confirmed the identification of a new type of coronavirus, and a few days later, on January 11, 2020, the genetic sequence for SARS-CoV-2 was published, triggering intense global research and development (R&D) activity and the rush to develop a vaccine against the disease [1, 2].

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On January 30, 2020, WHO declared that the outbreak of the disease caused by the new coronavirus (COVID-19) constitutes a Public Health Emergency of International Importance—the Organization's highest level of alert, as established by the International Health Regulations. This was the sixth time in history that a Public Health Emergency of International Importance has been declared. The other five were the H1N1 pandemic (2009), international poliovirus spread (2014), Ebola outbreak in West Africa (2014), Zika virus and increased cases of microcephaly and other congenital malformations (2016), and Ebola outbreak in the Democratic Republic of Congo (2018). On March 11, 2020, COVID-19 was characterized as a pandemic by the WHO [3].

It is notable that the experience acquired over the years in confronting other epidemics of international importance brings greater experience and preparedness in fighting these global problems, as in the case of the current COVID-19 pandemic. The current scenario, as frightening as it may be, contrasts sharply with the lack of preparation, as well as lack of adequate and available tools and technologies, as in the case of the Spanish flu, which along 2 years, between 1918 and 1919, brought 3 waves of infection, plaguing a third of the world population at the time and approximately 100 million deaths [4].

In the process of preparing to face such threats, and in particular, invisible threats, such as those coming from microorganisms, the knowledge acquired in the last century is indisputable regarding the understanding of the scientific class on the best strategy to combat these pathogens, which is the provision of an effective and safe vaccine. In view of this, the advance in vaccine technologies together with the recent financing promises, medicine regulatory flexibility, and R&D strategies adopted by developers have contributed to the rapid COVID-19 vaccine licensing process bringing an important breath of hope for humanity.

According to continuous monitoring carried out by the WHO (up to December 8, 2020), the current COVID-19 vaccine development scenario (Fig. 1) has 214 candidates, 51 in the clinical stage, and 14 already in late-stage clinical development (phase III), with the expectation that others will soon enter this phase [5].

A great effort of research and global coordination, which has resulted in a rapid process of development of vaccines and other medical products considered strategic in the fight against COVID-19, is evident. Considering the initiatives for the rapid development of vaccines, the present manuscript aims at identifying the main factors and innovative environments that are promoting this phenomenon. It also seeks to understand the ways and processes that lead to the resolution of problems that plague our society, such as infectious diseases of global relevance, and, based on accumulated learning, to provide new perspectives of pathways and strategies that can be used for new vaccines within the scope of innovation management, specially in pandemic context.

This work is divided into 4 sections. The first is the introduction, which contextualizes and provides an overview of the theme to be studied; the second section presents the objectives and the methodology used. In the third section, the main factors that accelerate the R&D process in the context of the current pandemic will be discussed, and for the last section, a conclusion is presented with future perspectives of the positive legacy of this global crisis, focused on vaccine development process.

Objective and Methodology

The main objective of this work is to identify and explore the main factors that provide the rapid advance in the development of vaccines against COVID-19, classifying and

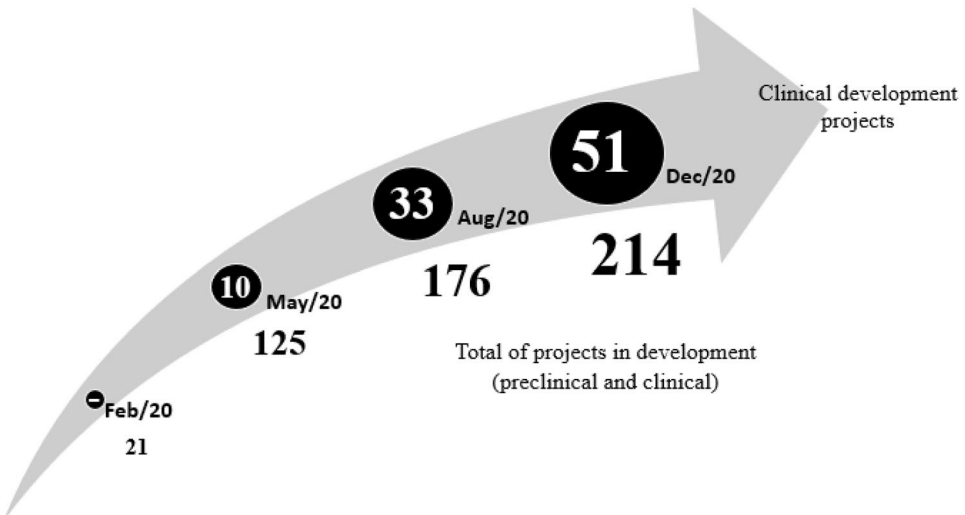

Fig. 1 Overview of vaccine development for COVID-19 in the last ten months (Note: data collection date related to the corresponding total number of vaccines under development and those in clinical development, respectively: 1. 02/18/2020 (21/0); 2. 05/27/2020 (125/10) 3. 08/31/2020 (176/33) and 12/08/2020 (214/51*). Figure based on documents found at the WHO website: DRAFT landscape of COVID-19 candidate vaccines [5]. *One candidate vaccine included in the WHO list was not considered in this study due the lack of information.)

characterizing them in different groups in order to facilitate the understanding and thus enabling an appropriate analysis of the complex innovation ecosystem, that contributes to the acceleration of R&D processes of COVID-19 candidate vaccines. The analysis period attempted to cover from the very beginning of the scientific effort focused on the development of COVID-19 vaccines (based on the first document released by the WHO—DRAFT landscape of COVID-19 candidate vaccines—February 18, 2020) until the most updated data regarding these projects (last update based on the WHO documents December 8, 2020), what comprised 10 months of analysis and data collection.

The methodology used for the study is exploratory and is divided into two stages according to Fig. 2. In the first stage, the monitoring of COVID-19 candidate vaccines under development around the world, through access to reports and public databases, was sought and a study database was generated.

The criteria for select the main sources of data considered the reputation of the institution, reliability, and constant updating of the interest data. It is important to emphasize that the rapid pace, which the candidate vaccines forward in the development process, was not followed timely by the publication of scientific peer reviewed papers. So, the strategy adopted for this study was to use one main source to track and collect the vaccines under development data (WHO) together with complementary sources to capture detailed information, especially about the clinical trials. Regarding this complementary information, we collected data from official clinical trials registry platforms, considered by the most regulatory agencies as requirements to the clinical studies approval in their respective countries. Thus, the continuous monitoring and data collection of these sources of information enabled the construction of the study database, which was used as a basis to explore the accelerating factors in the development process of the COVID-19 vaccines.

Below is pointed out the sources used to generate the study database:

- WHO report on the panorama of candidate vaccines against COVID-19: DRAFT landscape of COVID-19 candidate vaccines, updated periodically;
- Nine online databases of clinical trials: Clinicaltrial.gov, Australian New Zealand Clinical Trial Registry (ANZCTR), Pan African Clinical Trials Registry, EU Clinical Trials Register, ISRCTN Registry, Chinese Clinical Trial Registry, Clinical Trial Registry India (CTRI), Indonesia Registry Web Portal (Clinical Research Registry), and Cuban Public Registry of Clinical Trials (RPCEC), which aimed at complementing the background overview information of the vaccine development projects, mainly with regards to the clinical development strategies adopted by developers.

In relation to stage 2, based on the database study and literature review on the topic, the authors proposed a framework of five blocks, called here the acceleration factors, that are used to describe and characterize the innovation ecosystem, in which the candidate vaccines pass through. This set of factors was created with the intention of grouping smaller elements, which present similar characteristics and purposes, what makes them belong to a common factor. The elements include, but are not limited to technological aspects, as types of vaccine technological platforms and their advantages; R&D strategies lead by developers; and programs, instruments, procedures, and strategies adopted by medicines regulatory agencies, governments, international organizations, and other stakeholders in order to foster and speed up the development

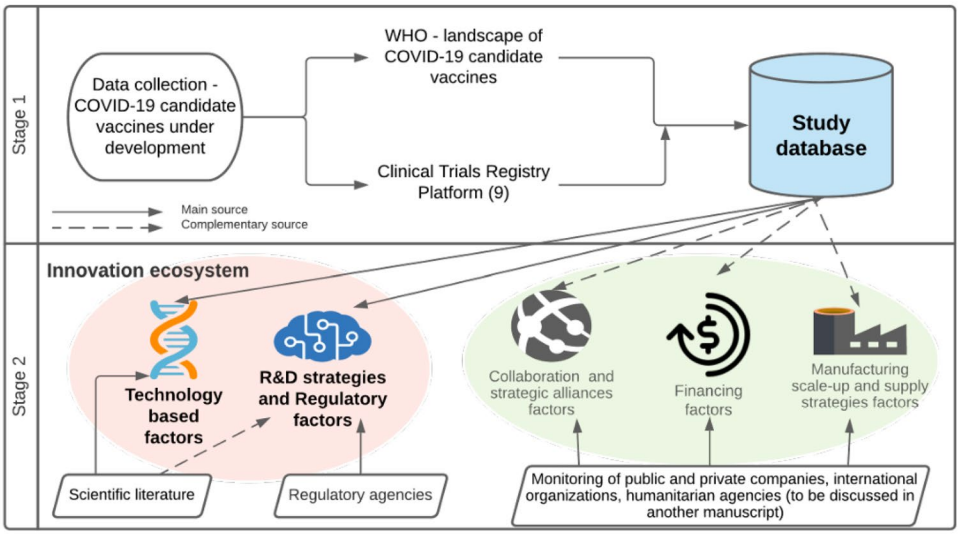

Fig. 2 Schematic presentation of the methodology applied to the study. Source: created by the authors (Lucidchart®)

processes of COVID-19 vaccines. The 5 acceleration factors, as presented in the Fig. 2, are as follows: (1) factors based on technology, (2) regulatory and R&D strategy factors, (3) collaboration and strategic alliances factors, (4) financing factors, and (5) manufacturing scale-up and supply strategies factors.

As depicted in Fig. 2 the study database was used as the main source for those factors related to technology and R&D strategies (solid arrows). Additionally, scientific literature was used to track the main vaccine technological platforms and pre-clinical studies conducted in the COVID-19 vaccines candidate projects, especially to the technology-based factors, and for the regulatory and R&D strategy factors, the monitoring of clinical trials and medicine regulatory agencies were key aspects to understand this second factor. For the other acceleration factors, which focus on less technological aspects, the study database served as a driver, represented in Fig. 2 with dotted arrows. The main information to explore these 3 factors were obtained by monitoring of public and private companies, international organizations, humanitarian agencies, reference institutions in the area, governments, and other stakeholders. These acceleration factors will be discussed and addressed in a future article.

Therefore, the present manuscript attempts to give a comprehensive overview about the innovation ecosystem, in which the candidate vaccines are being developed, through identification of strategies and practices adopted by the developers and regulatory agencies that lead to shortening and accelerating the COVID-19 vaccine development process.

Results and Discussion

According to the methodology adopted in the present work, firstly, a strategy for monitoring the COVID-19 candidate vaccines under development was established, through access to different public databases, in order to generate the study database, which focused in the 51 candidate vaccines under clinical development. The reason to select this set of candidate vaccines for data collection and analysis is based on the existence and reliability of data, once the availability of information related to these types of projects become official as it enters in clinical trials, pushed by ethical requirements.

This first stage of the study provided a clear view of how fast the new projects emerged over the study period (10 months, from February to December 2020), as well as how many projects advanced to clinical stages (Fig. 1). These results served as input for the development of stage 2 of the research, by providing a more detailed view of the most advanced projects, focused at exploring the mechanisms and strategies adopted by the companies to accelerate the development of these vaccines.

As mentioned in the methodology, the authors preferred to separate this work into two manuscripts, for the sake of didactics and contents, once the actual panorama, inclusive in terms of data generation, is considered a complex theme presenting interfaces with different areas of knowledge and from worldwide efforts. For the present manuscript, the first two factors presented in the methodology section, of a technological nature and regulatory and R&D strategies, were explored in more detail. A future manuscript will explore the other three factors, which are related to aspects of financing, collaboration, and global coordination programs of the COVID-19 vaccines production and supply chain.

Therefore, in the next sections, an overview of the most advanced COVID-19 candidate vaccines will be presented followed by the two acceleration factors, as mentioned previously, in the scope of innovation management and in the perspective of pointing out future paths for the development of new vaccines to combat other epidemics and pandemics that may arise.

Overview of the COVID-19 Candidate Vaccines Most Advanced

According to the Fig. 3, the total number of clinical trial registered in the platforms monitored is 107, comprising approximately 534.921 participants expected to be enrolled. From these clinical trial, 33 are phase I, 37 phase I/II, 11 phase II, 3 phase II/III, and 23 phase III. This magnitude of clinical trials approved in a short time (10 months) for one unique purpose (to reach an efficacious and safe vaccine against COVID-19) reveals a noteworth global effort, both from the companies and governments involved, as well as from regulatory agencies and ethical approval bodies.

Based on the most advanced candidate vaccines, which are currently in clinical development, we identify a close dispute between the USA and China (Fig. 4), which emerges in the race to develop a COVID-19 vaccine, being the USA the main player with 15 candidate vaccines (25%), followed by China with 12 (20%) and Germany with 5 (8%).

In general, it is possible to note that most of the developer companies or institutions are located in developed countries or in traditional countries in the vaccine segment, as are the cases of Cuba, India, and Russia (Fig. 4). However, when we analyze the countries involved in the execution of clinical trials (recruiting countries, as shown in the Fig. 5), it is noted that there is greater heterogeneity, especially in phase III clinical trials, where the determinant for the choice of clinical research centers is conditioned to transmission rates of SARS-CoV-2 locally. For phase I, I/II, or II clinical trials, this characteristic is no longer so evident, since they focus on the safety and immunogenicity of the vaccines under study, with no protection (efficacy) assessment at this stage.

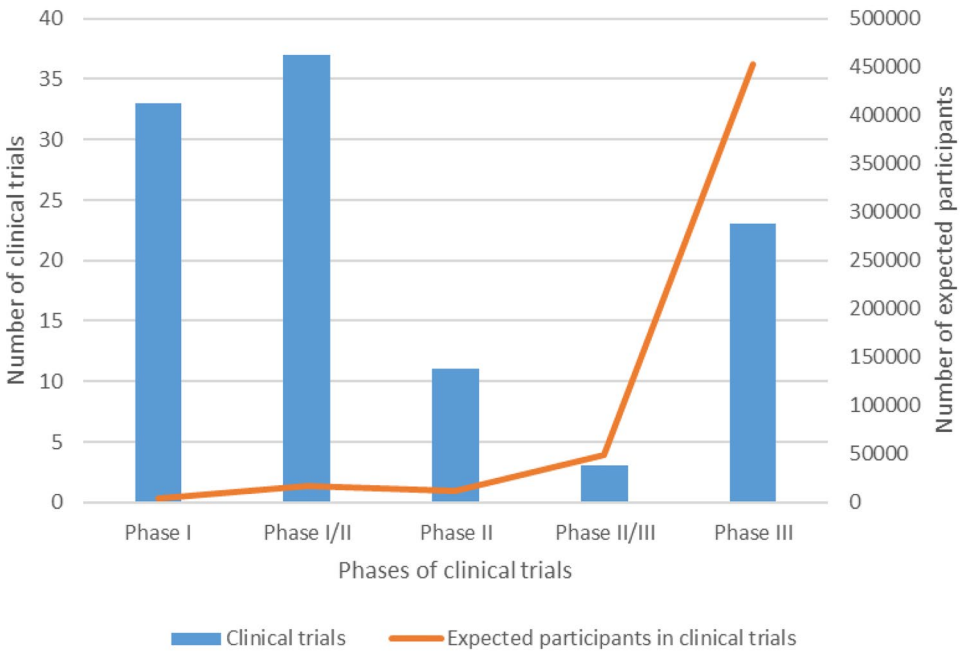

Fig. 3 Distribution of COVID-19 candidate vaccine clinical trials among phases

This geographical analysis demonstrates a wide involvement and effort of the 5 continents in the search for an effective and safe vaccine, unlike other epidemics and pandemics, in which the initiatives were adopted by a smaller number of companies, most of them recognized as belonging to the vaccine segment cluster. The emergence of new technological platforms enabled the entry of other companies outside the traditional vaccine segment in this race, mainly those focused on R&D and innovative technological platforms, such as those of nucleic acids and recombinant proteins, which is considered having great potential on research of therapeutic molecules. Moderna (USA), BioNtech (Germany), Inovio (USA), and Arcturus (USA) are examples of new entrants that build scientific bases on nucleic acid

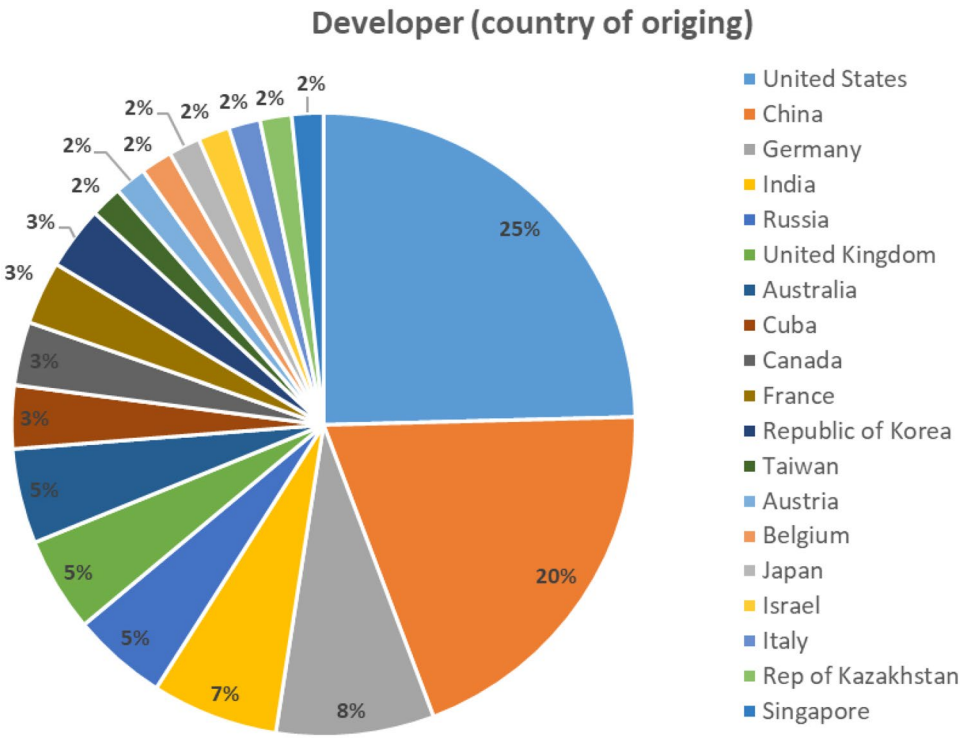

Fig. 4 Distribution of the COVID-19 candidate vaccine developers based on the country of origin

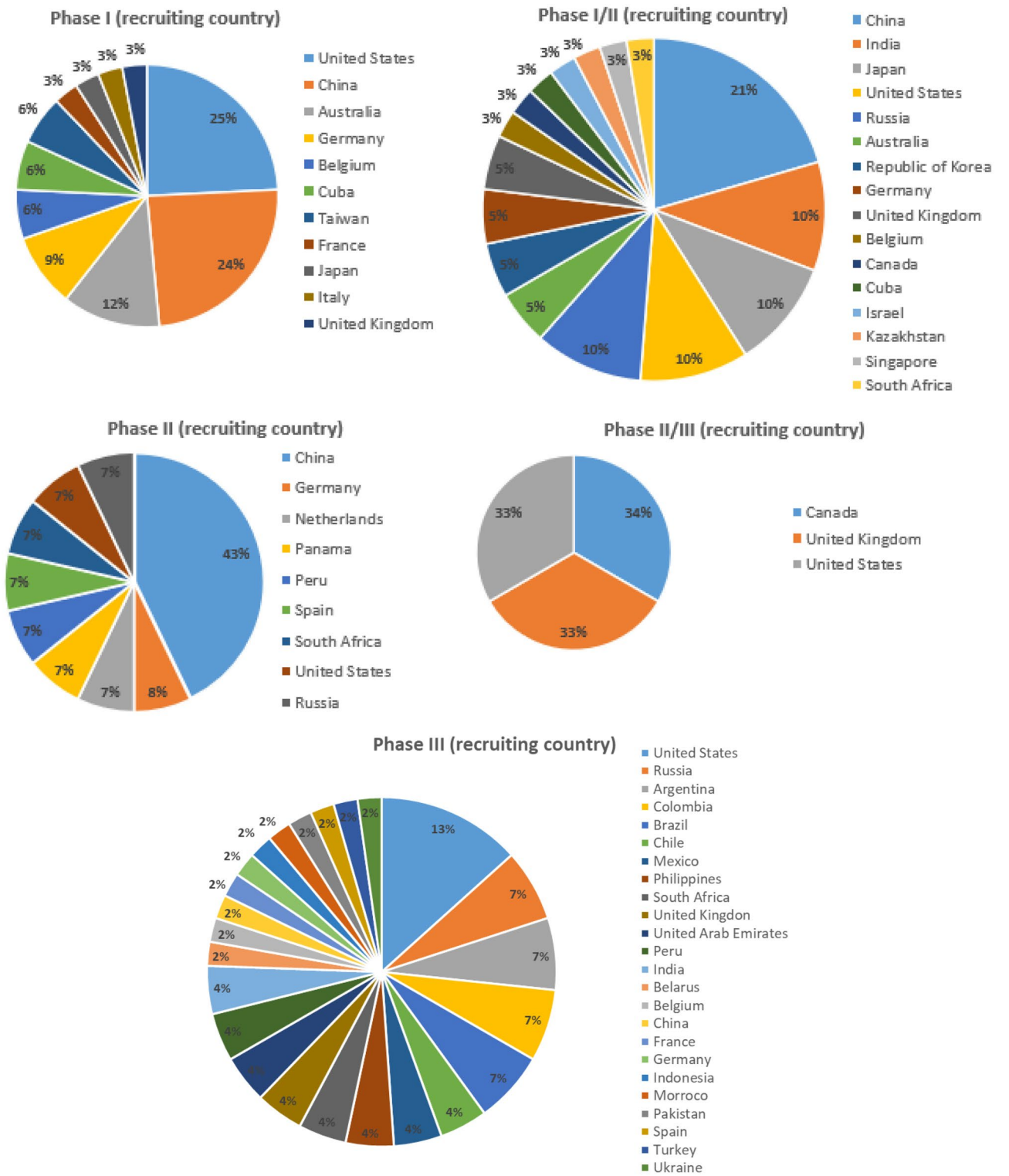

Fig. 5 Distribution of the recruiting countries based on the COVID-19 candidate vaccine clinical trials

platforms. Janssen (USA) and Astrazeneca (UK), by investing in viral vector platforms, demonstrate a movement of large pharmaceutical companies hitherto recognized for their position in therapeutic areas to also aggregate in their acting field the diseases preventable by vaccines [6–11].

Technology-Based Factors

In the last century, epidemic control was successfully achieved, thanks to vaccines and vaccination strategies, promoted by governments, private industries, and international organizations, such as humanitarian agencies. These vaccines developed in the past used different technologies predominantly following the strategies of inactivation or classical attenuation of pathogens. This worked efficiently for cholera, typhoid fever, polio, measles, plague, tetanus, and among others. Conjugate and subunit vaccines have also provided a breakthrough in vaccinology, enabling the prevention of diseases such as pneumonia, sepsis, and meningitis, for example. Compared with vaccines of the twenty-first century, the pace of development of these vaccines was comparatively slow since more recent vaccines use recombinant genetic technology, as the emblematic case of the vaccine against Hepatitis B, and even slower when compared with current achievements in the race for a vaccine against COVID-19 [12, 13].

Currently, more than 200 vaccine candidates are in development worldwide. According to Table 1, a wide and diverse number of technological platforms are being used, which may increase the chances of obtaining, as soon as possible, one or more vaccines with adequate efficacy and safety [14]. In this context there is still a great knowledge gap regarding SARS-CoV-2, such as its mechanism of action, the pathophysiology of COVID-19 disease, and the duration of immunity provided by the different vaccines under study; thus, the use of different technological platforms for the development of these vaccines is strategic.

The humanitarian and economic impact of the COVID-19 pandemic is driving the evaluation of new technological vaccine platforms considered innovative, aimed at accelerating the development of a safe and effective vaccine and make them available to the entire population more quickly. To this end, research groups involved in vaccine R&D are exploring new paradigms in the science of vaccinology, which is evidenced by the large number of vaccine candidates in clinical stages based on technologies not yet licensed for wide use. Examples of them are the nucleic acid (RNA/DNA) and recombinant viral vectors vaccines, that make up the majority (51%) of candidate vaccines that are in the clinical stage of development to this date, being 27% (14) based on viral vectors, and 24% (12) on RNA/DNA technology.

The use of these innovative technological approaches can be pointed out as one of the major factors in accelerating the development of vaccines, especially for the nucleic acid platform, as exemplified by the vaccine of the American company Moderna, which marked its position as the first COVID-19 candidate vaccine to enter the clinical phase (March 2020). More recently, another so waited and noteworthy event were the first approvals of a COVID-19 vaccine by relevant medicine regulatory agencies (MHRA—Medicines and Healthcare products Regulatory Agency, Health Canada, and FDA—Food and Drug Administration) given to BioNtech/Pfizer's vaccine. This was possible due to the safety profile already demonstrated by this platform and rapid development provided by the easily manufacturing reproducibility and validation process of nucleic acids. Moreover, the existence of previous safety data of this type of component enabled the companies to conduct some studies in parallel, as Moderna that skipped some stages of the pre-clinical development process, especially studies carried out in animal models, which occurred concurrently with its first clinical trial [2, 13, 20–22].

Based on the technological advancement of genetic sequencing, combined with the increasing capacity of nucleic acid synthesizers, it is clear to understand how quickly these RNA/DNA vaccines entered the clinical stages. Based on the knowledge of the virus genome, the development strategies in this type of platform are focused on the study of genes that encode proteins considered immunogenic, and then, on a larger scale synthesis of the target gene. The validation and production processes are considered simpler and faster since cell culture and recombinant genetic approach is not required. The challenge today falls on the low production capacity of nucleic acid synthesizers (thinking about a global demand), as well as the high cost of this process, that tend to decrease in the coming years [17].

This scenario is only possible due to advances in biological sciences, which have been gaining pace since the human genome was mapped—a 13-year process completed in 2003. This revolution in biotechnology was driven by the rapid progress of computing, automation, and artificial intelligence (AI). The cost of mapping the human genome has decreased—from approximately $ 3 billion in 2003 to less than $ 1000 in 2016. That number could drop to less than $ 100 in a decade. The complete SARS-CoV-2 genome was sequenced and published within weeks of its identification, in contrast to the sequencing of SARS-CoV, which caused the 2002 epidemic, taking several months to be completed [23].

Although they have not yet reached the market, candidate vaccines based on non-replicating viral vectors represent technological approaches already used in the development of vaccines for other epidemics, as in the case of MERS (Middle East respiratory syndrome coronavirus), Chikungunya, Influenza, Zika, Meningitis B, and among other diseases. In this sense, once the genetic modifications of a specific viral vector for insertion of the gene of interest is developed (usually of the pathogen that causes the disease), the platform for insertion of other genes may be considered as validated thus accelerating

Table 1 Technological platforms for COVID-19 vaccine candidates in clinical development [2, 15–19]

Technological platform	Description	Amount vaccines (clinical stage)
Viral vector vaccines	The strategy of this technique lies in the selection of a viral vector, which can be replicating or non-replicating (deactivation of genes involved in viral replication), and subsequent genetic modification of this vector to insert genes that encode proteins, considered immunogenic. The protein expression process occurs in the human organism, and after vaccination, it triggers an immune response. A possible disadvantage of this approach is the pre-existing immunity to the viral vector, which can impact the effectiveness of these vaccines, depending on the virus (vector) used and their circulation in the populations to be vaccinated	14
Nucleic acid vaccines (RNA/DNA)	The principle of this technological approach is simple and uses nucleic acid molecules (RNA or DNA) properly stabilized in a formulation, which may include the use of lipid particles, which generally encapsulate RNA molecules, considered thermolabile, or in the case of molecules of DNA insertion into plasmids is the strategy most adopted by developers. The nucleic acid molecule is inserted into human cells, which then uses its machinery for the local production of proteins, stimulating an immunogenic response by the body, either by producing neutralizing antibodies or even by activating T cells	12
Protein subunit vaccine	Vaccines that use this strategy have protein subunits as antigen, which are part of their formulation and are obtained in the production process using recombinant DNA technology. Most projects under development focus on the S protein of SARS-CoV-2 or part of it. Disadvantages of this approach include the difficulty of large-scale production, the need to use adjuvants, or multiple doses to produce an adequate immune response	12
Inactivated or attenuated virus vaccines	A technological approach that uses the live and whole virus, as starting material that can be inactivated, through different mechanisms, such as chemical, radioactive, or thermal inactivation or attenuated by a method to make the virus weakened. This is a well-known platform, considered easy to prepare, develop, and produce, but it requires infrastructure with a level of biosafety 3 (BSL-3) and high reliability in the validation of the inactivation process, which requires long-term surveillance, with regard to, mainly the safety in the use of these vaccines. Despite this, inactivated vaccines demonstrate high immunogenicity and the potential for activating the innate immune response	8
Peptide vaccines	Peptide vaccines usually uses in silico informatics-based approach to identify the most immunogenic protein and hence multiple epitopes that can trigger not only B cell response (antibody generation against SARS-CoV-2) but also T cell immune response, that is considered to provides long-lasting immunity. In terms of production, this kind of platform has some advantages like feasibility of manufacturing peptides and epitopes, through chemically synthesis, stability of the active ingredient, and the lack of the infectious component of the virus, what makes them as a promising candidate vaccine for prevent COVID-19	3
VLP vaccine (virus like particle)	These vaccines use empty viral particles, in formats that mimic the structure of the coronavirus, which are self-assembled and carry SARS-CoV-2 proteins on the surface. This strategy uses the immunogenic power obtained by both characteristics: protein composition of the virus and spatial conformation of the structure, which can provide a strong immune response. As they do not carry the genetic material of the virus, they are considered safe and do not carry a risk of vaccine infection. The biggest disadvantage of this technology lies in its difficulty in production	2
Total		51

the development process of new vaccines. Astrazeneca/Oxford (UK), CanSino (China), Gamaleyia (Russia), and Janssen (USA) are examples of companies leading the development of the most advanced candidate vaccines (phase III), using this approach of non-replicating viral vectors [2, 17]

Regarding to vaccines based on replicating viral vectors, experience from other studies and license products, as Ervebo® (a vesicular stomatitis virus vectored ebolavirus vaccine, developed by MSD and licensed to combat the Ebola outbreak) has facilitated the path to constructs targeting SARS-CoV-2, considered an important previous knowledge

to speed up current endeavor to reach a vaccine based on this platform. This technological approach tends to generate high protein expression in the body, inciting a strong immunogenic response, in addition to being considered safe [2, 17, 24].

For diseases such as HIV, Ebola, Zika, and Chikungunya, the use of vector-based vaccines including adenovirus (Ad), measles virus (VM), vesicular stomatitis virus (VSV), alphavirus, poxvirus, and herpesvirus, demonstrated the ability to stimulate cellular and humoral immunity allowing the insertion of 5 kb or more of the transgene. It is worth mentioning that these viral vectors are weakened and cannot cause diseases in humans but depending on the type of vector and their circulation in certain populations, pre-immunity may exist, which leads to less effectiveness of the vaccine [18].

The whole virus platforms, such as those of inactivated or attenuated vaccines, are considered traditional technologies, and despite the low representation in the current panorama of projects under development for COVID-19, they are considered as advanced in this scenario, with a total of 8 candidate vaccines in clinical phase, being 4 in late-clinical stage (phase III). Interestingly, China is the most relevant country in what concerns to develop COVID-19 candidate vaccines using inactivated approach, leading 6 projects out of 8. The broad knowledge of this technique may be one of the factors that provide a rapid advance in the development of these vaccines and, consequently, the entry into clinical studies. On the other hand, because inactivated vaccines require the handling of the live (wild) virus in the development process, as well as in the future production process, this may be one of the reasons that hinder its use. Compared with other technological platforms, this approach is being pursued by few companies, that venture into this strategy, since it would require biosafety levels 3 (BSL-3 containment), both for research laboratories and for manufacturing plants [25].

Two other innovative technological platforms that appeared latter among the candidate vaccines in the clinical development were those based on multi-peptides and VLP (Virus Like Particles). Vector Institute (Russia), University Hospital Tuebingen (Germany), and COVAXX (USA)/ United Biomedical Inc. Asia (China and Taiwan) represent those candidate vaccines based on multi-peptides under clinical development, while SpyBiotech (USA)/Serum Institute of India (India) and Medicago (Canada) represent the VLP approach, being the last in late-stage clinical trial. Important to highlight that these two technological platforms are also based on DNA recombinant techniques and molecular biology, considered ones of the knowledges in health and biology science that most advanced in the last decades.

Another particularly important factor in the rapid advance of research was the use of previous studies related to other coronaviruses and more specifically to the etiologic agents of two other diseases, which have caused in the last 20 years several outbreaks of severe respiratory syndromes associated with high mortality rates, SARS (severe acute respiratory syndrome coronavirus),and MERS [18].

Coronaviruses have a large genome of about 30 Kb (30,000 nitrogenous bases) forming a single strand of RNA surrounded by a helical nucleocapsid (N) and an outer envelope composed of matrix protein (M), envelope protein (E) and spike (S) proteins. Protein S, which occurs naturally in the trimeric form, contains the receptor-binding domain (RBD) responsible for binding to the angiotensin-converting enzyme 2 (ACE2) and for entering the cell. For SARS-CoV, during the outbreak in 2003, protein S was evaluated as a promising target for vaccine development, for its ability to stimulate the generation of neutralizing antibodies. Moreover, recent research has demonstrated that the linkage affinity of SARS-CoV2 S protein to ACE2 is 10 to 20 times stronger than SARs-CoV; this might explain the contagious nature of SARS CoV2 and poses as a potent target for a COVID-19 vaccine [18, 26, 27].

As no vaccine has been licensed to prevent SARS and MERS diseases, mainly because the outbreaks were limited and resolved before their development, the accumulation of knowledge generated was fundamental for the onset of new development projects for SARS-CoV-2 vaccine. Based on these previous studies, most of the COVID-19 vaccine development projects aimed at protein S (spike) as a target with immunogenic potential. Thus, the discovery process, a phase in which different targets are tested and the first proof of concepts is carried out in vitro, could be shortened as the developers target the S protein of SARS-CoV-2, even considering different technological platforms. This was possible because the gene that encodes the SARS-CoV-2 protein S is quite similar in sequence and structure to the SARS-CoV protein S gene sharing a global protein folding profile similar to that of the S protein of the MERS-CoV virus [28].

According to the Fig. 6, the most frequent route of administration used by the COVID-19 candidate vaccines under clinical development was the intramuscular route (82%), similar scenario to most vaccines current commercialized.

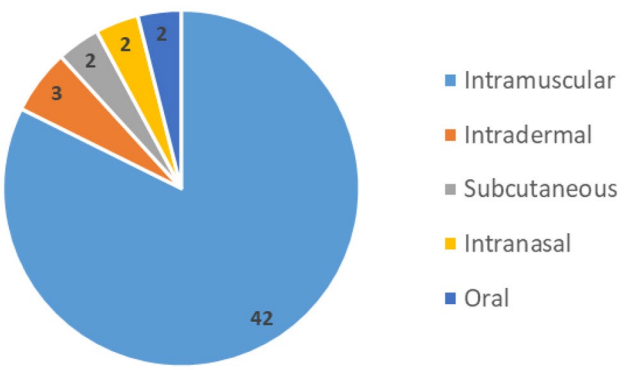

Fig. 6 Route of administration studied in the COVID-19 candidate vaccines under clinical development

The intradermal route (6%) is particularly important for those candidate vaccines containing DNA plasmids, because they are administered using electroporation devices, that increase the permeability of the cells to the DNA. Inovio Pharmaceutical (USA), Cadila Healthcare (India), and Providence Health and Services (USA) are companies following this strategy, despite some of them are also evaluating in the clinical trials the option without the device. As the RNA molecules cannot be stabilized into circular plasmids, the strategy adopted from the developers of this kind of vaccine is to incorporate them into lipid-particles or nanoparticles, as vehicle to deliver the RNA molecules to the cells.

Other routes of administrations, as oral (4%) and intranasal (4%), recently appeared in the clinical trials of candidate vaccines, which brings additional advantages mostly related to the manufacturing process and adherence of vaccination once it seems to be easier to take. Symvivo (Canada) and Vaxart (USA) represent the companies studying oral route, while Beijing Wantai Biological Pharmacy/Xiamen University (China) and Codagenix (USA) represent the intranasal strategy. Symvivo, through its bacTRL™ proprietary platform, enables oral and intravenous vaccines to selectively colonize hypoxic tissue, while simultaneously being cleared from healthy tissues. It uses a live genetically modified bacteria as a vehicle to carry the DNA plasmid, that according to the company, produce and deliver genetic material to the surrounding tissues, providing consistent and progressive levels of gene delivery and expression. Regarding subcutaneous route of administration (4%), ImmunityBio (USA) and University Hospital Tuebingen (Germany) are following this strategy [29].

Regarding the vaccination schedule, most of the developers's strategies rely on two doses, being 44 COVID-19 candidate vaccines studying this scheme. Among them, 30 candidate vaccines are only researching the two doses schedule, while 14 developers are still evaluating different schedules in their clinical development programs (10 are evaluating single or two doses and 4 two and three doses). It is possible to note that in the most clinical development programs, the definition of the vaccination schedule seems to be established in phase I or II, but some developers continue to evaluate different schedules even in phase III (what can be illustrated by the case of University of Oxford/AstraZeneca). With respect to the period between the doses, there is not a standard or schedule most adopted. The variation between the clinical development programs is great, and the types of schedules comprise 14, 21, 28, and 56 days apart between the doses. Interestingly, the COVID-19 candidate vaccine developed by the partnership between CanSino Biological Inc and the Academy of Military Medical Sciences of China is proposing in one of the study groups to evaluate an uncommon schedule, two doses at the same time in both arms of the participants. It may represent a strategy to increase the vaccine dosage without changing the formulation.

Another technological advance for accelerating studies in the area is the speed with which results from the RT-PCR (reverse-transcriptase polymerase chain reaction) used for testing SARS-CoV-2 infection are released. But the ability to analyze biological systems and processes is only part of that story. At the core of today's bio-revolution is our growing ability to "design" biology using modern gene-editing tools, such as CRISPR—Clustered Regularly Interspaced Short Palindromic Repeats [23]. These technologies may have accelerated the process of genetic modifications and recombination of cells, vectors, and other bio-based components that are involved in the process of developing new vaccines for COVID-19.

It is important to consider the risk of the rapid advance of these technological approaches without adequate monitoring of the impact on the environment and permanent assessments of genetically modified organisms, using advanced techniques of genetic editing. Biological systems are organically self-sustaining and self-replicating, increasing the risk of unknown impacts on the environment. Therefore, the evolution of biosafety approaches is extremely important, as genetic editing technologies advances [23].

Regulatory and R&D Strategy Factors

The elements considered in this group of factors were explored in two approaches: the first was related to the regulation of the pharmaceutical sector, through the monitoring of "fast track" procedures, by technical and guidance support from the main regulatory agencies, and the second is more related to the strategies adopted to accelerate the stages of R&D vaccine process, associated with regulatory flexibilities.

Regulatory Procedures

The role of regulatory agencies and international harmonization bodies are fundamental in combating the COVID-19 pandemic, as they guide the paths to be followed in the development of vaccines, while providing support and taking action in accelerating the approval processes of clinical studies and vaccine licensure for immunizers. Regulatory agencies face great pressure. As expectations to accelerate the stages of vaccine development are high, caution, and rigor in efficacy and especially safety assessments are necessary before moving on to human studies and licensing for commercialization. Although not addressed in this study but no less important, the research ethics review board carry out evaluations concurrently with the regulatory agencies, focusing on studies in human beings.

Many countries, under the leadership of their respective regulatory agencies, such as the European Medicines Agency (EMA), FDA, and the National Health Surveillance Agency (ANVISA), have been establishing greater flexibility in the regulatory pathways, as well as prioritizing analysis, improving existing processes and mobilizing the workforce internally in response to the challenges of the COVID-19 pandemic. The agencies are using the emergency routes previously established to add procedures and task forces concurrently in a transparent, reliable, and global manner [30].

Table 2 lists the main guides, instruments and/or procedures focused on the process of development, manufacture, and registration of products indicated for COVID-19 used by the ANVISA, FDA, and EMA and exemplify the support and speed given by these institutions in the context of the pandemic. We can assume that many of these processes are specific to public health emergencies of international importance, but it is worth reflecting on the possibility of maintaining the procedures, which have been optimized and left as a legacy for the future of these agencies.

The European agency's COVID-19 EMA pandemic Task Force (COVID-ETF) initiative is one of the examples of regulatory support that has enabled the acceleration of the COVID-19 vaccine and drug development processes in this community. It is a program that includes a set of procedures coupled with groups of experts that provide rapid regulatory action in the development), authorization, and safety monitoring of medicines intended to treat and prevent COVID-19 [32].

Over the past few months of the pandemic, the American agency, FDA, has published a series of guides and protocols related to the development of products aimed at the treatment, prevention, and diagnosis of COVID-19, as well as in relation to the impact on the pharmaceutical and food

Table 2 Main guides, instruments, and procedures focused on the regulatory process for the development, manufacture, and registration of products indicated for COVID-19, from the regulatory agencies ANVISA, FDA, and EMA[31–34]

Programs/Procedures/Instruments	Description	Regulatory agency
COVID-19 EMA pandemic Task Force (COVID-ETF)	This program is responsible to coordinates and enables fast regulatory action on the development, authorization, and safety monitoring of treatments and vaccines intended for the treatment and prevention of COVID-19. The mains mechanisms used by EMA for this propose are as follows: 1. Rapid scientific advice; 2. Rapid agreement of a pediatric investigation plan and rapid compliance check; 3. Rolling review, that allow EMA to continuously assess the data for an upcoming highly promising application as they become available; 4. Marketing authorization approval process in an expedited manner for products indicated to COVID-19, what is also applied to the Extension of indication and extension of marketing authorization	EMA
PRIME: Priority medicines	PRIME is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier	EMA
Development and Licensure of Vaccines to Prevent COVID-19 (Guidance)	This guidance describes FDA's current recommendations regarding the data needed to facilitate clinical development and licensure of vaccines to prevent COVID-19. It provides an overview of key considerations to satisfy regulatory requirements set forth in the investigational new drug application (IND) regulations and licensing regulations for chemistry, manufacturing, and controls (CMC); nonclinical and clinical data through development and licensure; and for post-licensure safety evaluation of COVID-19 preventive vaccines	FDA
COVID-19: Developing Drugs and Biological-Products for Treatment or Prevention (Guidance)	Provides the FDA's current recommendations on later stage clinical trials intended to establish safety and effectiveness for COVID-19 products. The guidance outlines critical sponsor considerations such as appropriate patient selection, how to design adequate trials, including considerations of study duration, assessment of efficacy, and safety monitoring	FDA

Table 2 (continued)

Programs/Procedures/Instruments	Description	Regulatory agency
General Considerations for Pre-IND Meeting Requirements for COVID-19 medicines (Guidance)	Outlines a more efficient process for developers to receive agency feedback on their supporting data with the goal of starting clinical trials as soon as possible. The guidance provides sponsors clarity on the types of data and information they should provide to address clinical, nonclinical, and quality considerations before submitting an application to initiate studies	FDA
RDC 415/2020	Define extraordinary, updated criteria, and procedures for handling registration petitions and post-registration changes for medicines and biological products due to the international public health emergency arising from the new Coronavirus	
RDC 444/2020	Establishes temporary authorization for emergency use of COVID-19 candidate vaccines, on an experimental basis, to cope with the public health emergency of national importance resulting from the outbreak of the new coronavirus (SARS-CoV-2)	ANVISA
Technical Note (NT) 78/2020 – Rolling submission	Guidelines on the submission of technical documentation for analysis by ANVISA related to vaccines for prevention of COVID-19. This technical note establishes the process "rolling submission" specifically for the licensing process of COVID-19 vaccines, in order to speed up the ANVISA's analysis term	ANVISA
RDC 346/2020	Defines the extraordinary and temporary criteria and procedures for the certification of good manufacturing practices (GMP) for the purposes of licensure and post-licensure changes of active pharmaceutical ingredient (IFA), medicines, and medical devices due to the emergence of international public health of SARS-CoV-2	ANVISA
Technical Note (NT) 22/2020-Clinical Trials	Gathers a series of guidelines for sponsors, research centers, and researchers involved in conducting clinical trials authorized by ANVISA and bioequivalence studies. Among other actions, an Evaluation Committee for clinical studies, licensure, and post-licensure of medicines for prevention or treatment of COVID-19 was created, which analyzes, among other duties, requests for consent for clinical studies with drugs for the prevention and treatment of COVID-19, as a priority, within an average period of 72 h after the formal submission of the protocol	ANVISA

RDC Resolution of the Collegiate Board

production chain, generated by the current pandemic. It is important to note that given the public health emergency, the FDA is proceeding to release these guidances to the public, even before the public consultation stage. They are being implemented immediately but remain subject to comments in accordance with the Agency's good guidance practices [33].

ANVISA, in turn, instituted, by means of a technical note, an evaluation committee for clinical studies, licensure, and post-licensure of medicines for the prevention or treatment of COVID-19 (NT 22/2020), and established a continuous process, known as "rolling submission" specifically for the licensing process of COVID-19 vaccines, which aims at speeding up the evaluation of technical documents, as they are generated by the companies. Another fundamental action carried out by ANVISA while the pandemic lasts concerns the publication of three exceptional and temporary laws, RDC 346/2020 and recently RDC 415 and 444/2020, which deal with guidelines for certification of good manufacturing practices (GMP), licensure of medicines indicated for COVID-19, and authorization for emergency use of COVID-19 candidate vaccines, respectively.

Regarding particularly to the rolling submission procedure, implemented recently by ANVISA, it is important to say that this practice is already adopted by other more experienced agencies, such as FDA and EMA, to provide greater interaction and exchange of information timely between regulated entities and regulators. This practice enables an acceleration in the final evaluation of the licensure process, as it allows the sharing of data by the developer of a given vaccine, as it is obtained throughout

the studies, and not only at the end of the submission of the final licensure dossier.

In general, it is possible to note that the rapid regulatory response of the main agencies around the world has been facilitated due to closer monitoring of COVID-19 vaccine development projects, which provides regulatory bodies with a better understanding of the complex R&D development, enabling clarification of issues during the process. This follow-up, which used to happen only for the beginning of the clinical stages, started to occur also in the most preliminary stages, specifically in the preclinical development. Noteworthy is also the endeavor the regulatory agencies have allocated to expedite the COVD-19 vaccine development process, from the workforce mobilization to evaluate issues related to COVID-19 vaccines to international cooperation in the scope of ICH (International Conference of Harmonization) to avoid duplicate work, already done by other agencies, and so accelerate all the analysis process. The dedication and professionalism of regulatory agency staff members have played a vital role in this battle against this pandemic.

Strategies for the R&D Process

The conventional process of developing a vaccine encompasses numerous technical stages of high complexity, from existing knowledge about the target to be reached (pathogen), the selection of the most appropriate antigen, the development of production processes to obtain the respective antigen, formulation and analytical methodologies development, proof-of-concept studies in animal models, stability studies, until reaching at the complex and expensive clinical studies, which in the case of a new vaccine requires three phases. In the clinical stage, the vaccine under study must prove to be safe (phase I), which normally involves 6 to 12 months of data collection after the immunization of each patient. Phase II trials provide an understanding of the required dosages, and phase III is a complete efficacy study, with consolidation of the safety assessment. As companies gain more confidence that a vaccine will work, they are prepared for commercial launch. The entire process usually takes five to ten years [14, 35].

Because of the cost and high failure rates, developers generally follow a linear sequence between the main stages of development, with several breaks for data analysis or checks on the development of the manufacturing process. The accelerated development of a vaccine in pandemic situations requires a new paradigm in the R&D process. One of the main strategies adopted by COVID-19 candidate vaccine developers in this pressure times is the parallelism of phases; in other words, they initiate a sequential phase before the results from the previous phase. Figure 7, which comprises the fourteen candidate vaccines on phase III of clinical trials (most advanced COVID-19 candidate vaccines), clearly shows this parallelism concept, between the clinical phases. For this current analysis, the clinical trials from the same phase of a vaccine were added in terms of timeline, so they do not appear repeatedly.

The wide availability of financial sources and government incentives, which will be better discussed in the second article, has a critical role in the vaccine development process, especially in pandemic context. As it allows companies to take more risks in the parallelism of clinical phases, as well as the conduction of several other evaluation and studies at the same time, the required data about the candidate vaccine (related to efficacy, safety, and quality) can be generated in a shorter time. Based on this scenario of relevant financial incentives raised all over the world and mobilization of the business and scientific community, the data depicted in Fig. 7 clearly show the application of these strategies by the developer companies, which would certainly be difficult to happen in different contexts.

High financial risks, in addition to ethical-regulatory risks, must be considered. A good example is happening with vaccines coming from the same technological platform as others that have been previously tested in humans. These cases have enabled phase 1 clinical trials to proceed concurrently with tests on animal models [35]. Although this was a possible strategy even before the pandemic, it was not widely used, mainly because the regulatory agencies demand justifications for this acceleration, plausible in the current scenario.

More specifically in relation to clinical development, some factors accelerate the work of the teams involved in this stage, as they put pressure on taking advantage of the temporal opportunity of the pandemic, which in this case, is related to the dynamics of virus transmission and epidemiology of the disease. In this sense, companies fear what happened previously in other epidemics, as in the cases of SARS and MERS, in which vaccine candidates were under development, but clinical studies had to be interrupted, or did not advance to subsequent stages, due to the lack of a conducive transmission environment. This occurs when clinical studies evaluate vaccines for viruses considered to be new, for which protection correlates are not known yet, that is, there is no adequate biomarker that can infer protection, as are generally the protective antibody titers for known diseases. In this case, the most appropriate strategy to assess the effectiveness of a new vaccine is the infection rate of the vaccinated group in relation to the control group, considering that both are exposed to infection by the virus [34].

In addition to pressure from society, there is another more scientific aspect, which depends on the assessment of conditions for conducting a phase III clinical study, such as the curve of cases in a given population, the transmission

Developer	Nº of participants / Nº of Clinical trials*	Developer Country	Technological platform
Moderna / NAID	30720 (3)	United States	Nucleic acid (RNA)
CanSino/Beijing Institute of Biotechnology	46678 (6)	China	Viral vector
University of Oxford/AstraZeneca	62509 (8)	United Kingdon	Viral vector
Inovio Pharmaceuticals	7498 (4)	United States	Nucleic acid (DNA)
Wuhan Institute of Biological Products/Sinopharm	15920 (3)	China	Inactivated
Sinovac Research & Development Co., Ltd.	29378 (6)	China	Inactivated
BioNTech/Pfizer	45091 (7)	United States/Germany	Nucleic acid (RNA)
Beijing Institute of Biological Products/Sinopharm	18640 (3)	China	Inactivated
Novavax	50819 (4)	United States	Protein subunit
Gamaleya Research Institute	40286 (5)	Russia	Viral vector
Anhui Zhifei /Chinese Academy of Sciences	30216 (5)	China	Protein subunit
Medicago Inc.	30792 (2)	Canada	Virus Like Particule (VLP)
Janssen Pharmaceutical Companies	91845 (5)	United States	Viral vector
Bharat Biotech International Ltd	25800 (3)	India	Inactivated

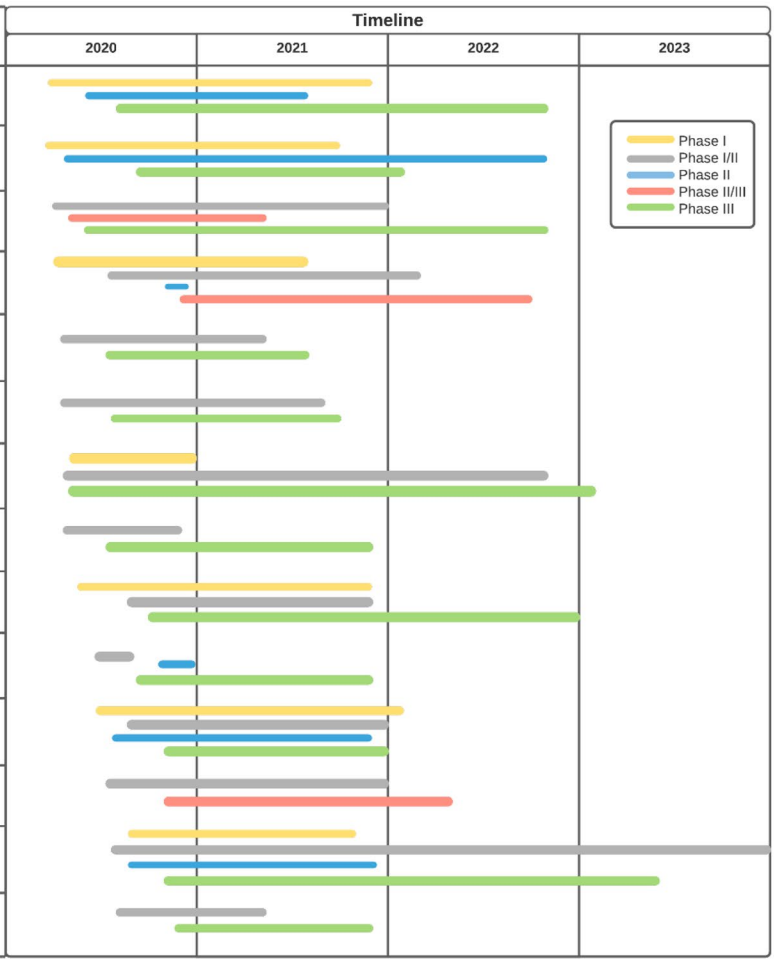

Fig. 7 Parallelism of clinical phases (most advanced COVID-19 candidate vaccines). Source: Created by the authors (Lucidchart®)

rate and the need to recruit research participants with SARS-CoV-2 negative serology, which becomes even more difficult as the virus spreads.

Another strategy most used by companies that are leading the vaccine race against COVID-19 is the so-called adaptive clinical trials. This type of study is based on an adaptative scientific concept for drug development and data generation that allows early and progressive patient access to medicines.

In this regard, Pfizer/BioNtech, interestingly, conducted one large study (NCT04368728), in an adaptive way, which included the three clinical phases at one unique clinical trial. Together with the reasons mentioned previously about the nucleic acid platform, this one-in-three adaptive clinical trial can be pointed out as an important factor that enabled accelerate the vaccine development process to be the first approved by relevant regulatory agencies, as FDA, Health Canada and MRHA (UK).

According to the EMA, adaptive pathways are based on the following principles:

- Iterative development, which means approval in stages, starting with a restricted population of research subjects and then expanding to larger populations, in a continuous process of assessment of a product's risk-benefit profile. After conditional approval based on initial data, substitute parameters are used, considered predictive of important clinical results;
- Collection of evidence through previous real-life studies that might supplement data from clinical trials;
- Early involvement of patients and health technology assessment bodies in discussions on drug development [36].

The efficiency of studies with adaptive designs depends on the time and frequency of interim analyzes. Decision making in this type of study requires availability of information from a sufficient number of research participants [37].

This strategy is usually applied, mainly, in the investigation of treatments in areas of high medical need,

where collecting data through traditional routes is difficult and where large clinical trials would unnecessarily expose patients who would hardly benefit from the drug. However, this same adaptive path is being used for the strategies of clinical development of vaccines against COVID-19, in order to accelerate the evaluation of the candidate vaccine, without unnecessarily exposing a large number of healthy volunteers at the same time.

The World Health Organization has played an important role in confronting COVID-19 worldwide at the most varied fronts of action, ranging from individual and collective health guidelines, contingency plans, and social distance in order to support companies that are developing strategic inputs for COVID-19, such as vaccines, drugs and diagnostics.

In order to guide the efforts of vaccine developers, WHO, through the R&D Blueprint group, a group formed as epidemics of international importance arise, has developed a Global Target Product Profile (TPPs) for vaccines against COVID-19. The TPP describes the minimum and desired attributes required for safe and effective vaccines. TPPs cover two types of vaccines: vaccines for the long-term protection of people at greatest risk from COVID-19, such as healthcare professionals; and vaccines for use in response to outbreaks with rapid onset of immunity [38].

The work developed in the R&D Blueprint group strategy aims at responding promptly to outbreaks, preventing epidemics by knowledge assimilated by this structure according to the work carried out in past epidemics. The roadmap for the COVID-19 vaccine is an important document published by WHO in March 2020. This report is intended to guide the development of these candidates, as well as to facilitate compliance with regulatory and data integrity standards. Roadmaps are prepared for all diseases considered a priority by WHO, including COVID-19 [38].

The Solidarity study is another WHO strategy to coordinate a large multicenter and multinational phase III clinical study with several candidates for the vaccine against COVID-19, which meet the criteria for this stage. The study proposes the simultaneous evaluation of the phases, enabling optimization of the complex structures required for this type of study and accelerates the results. Evidence of efficacy and safety for each vaccine candidate entering the study is expected to be obtained within three to six months of inclusion in the study. According to the WHO, these results may guide the registration and use on a larger scale [39]. However, this initiative still does not seem to have achieved the collaboration of the companies that lead the projects of the most advanced candidates, which by principles, prefer to follow their own development strategies.

ACTIV—Accelerating COVID-19 Therapeutic Interventions and Vaccines, developed and coordinated by NIH (National Institute of Health) is another acceleration program, aimed at technical support in the design of vaccine and drug development processes. This initiative, which also includes other US and European government partners, and more than a dozen biopharmaceutical companies, providing the development of a collaborative structure to prioritize vaccine and drug candidates, thus optimizing clinical trials, coordinating regulatory processes, and providing an adequate environment to quickly accelerate reach vaccines against COVID-19 and prepare for future pandemics [40].

Conclusion and Perspectives

As discussed throughout the article, there are many technological advances as well as the accumulation of knowledge and past experiences that are part of the current scenario in the field of innovative capacity, seeking a more accelerated path of the Research and Development process for new vaccines. It is evident that the COVID-19 epidemic generates pressure from society in the search for this vaccine, both in terms of health preservation and of its economic impacts, which in itself accelerate this complex R&D process.

However, as highlighted here, there are many aspects that provide the rapid advance of the state of the art of vaccinology and basic technologies that allow this advance. The need to rapidly develop a vaccine against COVID-19 occurs at a time of great increases in basic scientific understanding, including areas such as genomics, structural biology, recombinant DNA technology, and the exponential advance in automation and high throughput techniques, which are supporting a new era in vaccine development. Innovative technological platforms as acid nucleic and viral vectors have demonstrated their potential to expedite the vaccine development process, representing the main technological approach applied by the most advanced COVID-19 candidate vaccines.

With regard to factors related to R&D strategies and optimization of regulatory channels, it is clear that there are possible ways to shorten this process, especially in the context of a pandemic. Factors such as the parallelism of phases, innovative and adaptive designs for clinical studies, constant information exchange between the regulated and regulatory entity throughout the development process, and the innovative strategies adopted by regulatory agencies contribute greatly to the acceleration of studies and development of the COVID-19 vaccines.

On the other hand, pressure from the population, governments, and the private sector to establish an immediate response to the problem that has plagued the world, may not match the time required to have robust statements based on scientific parameters. For this reason, many answers may be changed over the course of studies, as it is evident that science

is also subject to errors. In this sense, it is extremely important that regulatory agencies, as well as companies monitor the use of the respective vaccines that may arrive on the market, in order to constantly assess their benefit-risk profile. As much as the paths to reach a new vaccine may be innovative and optimized, scientific common sense cannot be ignored.

As a by-product and future perspectives, it is expected that these factors, arising from the global emergency in public health, may redirect the Research and Development processes for new drugs, including new vaccines, especially in times of pandemic. Likewise, it is important that learning also serves to optimize and accelerate development routes in the search for solutions for diseases considered of great global impact.

References

1. Pan American Health Organization (PAHO). Public Health Emergency of International Concern (PHEIC) - history. [cited 19 Jun 2020]. Available from: https://www.paho.org/bra/index.php?option=comcontent&view=article&id=6101:covid19&Itemid=875.
2. Le TT, Andreadakis Z, Kumar A, Román RG, Tollefsen S, Saville M, Mayhew S. The COVID-19 vaccine development landscape. Nat Rev Drug Discov. 2020;19(5):305–6.
3. Pan American Health Organization (PAHO). COVID-19 timeline. [cited 19 Jun 2020]. Available from: https://www.paho.org/bra/index.php?option=comcontent&view=article&id=6101:covid19&Itemid=875.
4. Arora NK, Das MK. COVID-19 vaccine development and the way forward. Indian J Public Health. 2020;64:S108–11.
5. World Health Organization (WHO). Landscape of COVID-19 candidate vaccines. [cited 31 Jul 2020] Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
6. Moderna, Inc. Moderna's technological platform information. [cited 10 Dec 2020]. Available from: https://www.modernatx.com/modernas-mrna-technology.
7. BioNtech. BioNtech's technological platform information. [cited 10 Dec 2020]. Available from: https://biontech.de/science/platforms.
8. Inovio Pharmaceutical. Inovio's technological platform information. [cited 10 Dec 2020]. Available from: https://www.inovio.com/dna-medicines-technology/.
9. Arcturus therapeutics. Arcturus's technological platform information. [cited 10 Dec 2020]. Available from: https://arcturusrx.com/proprietary-technologies/.
10. Janssen Pharmaceutics. Janssen's portfolio information. [cited 10 Dec 2020]. Available from: https://www.janssen.com/us/our-products.
11. Astrazeneca. R&D focus areas of Astrazeneca. [cited 10 Dec 2020]. Available from: https://www.astrazeneca.com/r-d.html.
12. Nascimento IP, Leite LCC. Recombinant vaccines and the development of new vaccine strategies. Braz J Med Biol Res. 2012;45(12):1102–11.
13. Kim YC, Dema B, Reyes-Sandoval A. COVID-19 vaccines: breaking record times to first-in-human trials. Nat Partn J Vaccines. 2020;5(1):1–3.
14. Boston Consulting Group (BCG). The timelines and implications for COVID-19 vaccines. [cited 15 Jul 2020]. Available from: https://www.bcg.com/pt-br/publications/2020/covid-vaccines-timelines-implications.
15. Bhatnager R, Bhasin M, Arora J, Dang AS. Epitope based peptide vaccine against SARS-COV2: an immune-informatics approach. J Biomol Struct Dyn. 2020:1–16.
16. Oany AR, Emran AA, Jyoti TP. Design of an epitope-based peptide vaccine against spike protein of human coronavirus: an in silico approach. Drug Des Dev Thera. 2014;8:1139.
17. Callaway E. The race for coronavirus vaccines: a graphical guide. Nat. 2020;580(7805):576–7.
18. Koirala A, Joo YJ, Khatami A, Chiu C, Britton PN. Vaccines for COVID-19: the current state of play. Paediatr Respir Rev. 2020;35:43-9.
19. Khan I, Ahmed Z, Sarwar A, Jamil A, Anwer F. The potential vaccine component for COVID-19: a comprehensive review of global vaccine development efforts. Cureus. 2020;12(6).
20. Medicines and Healthcare products Regulatory Agency (MHRA). The first COVID-19 vaccine for the UK approved by MHRA. [cited 02 Dec 2020]. Available from: https://www.gov.uk/government/news/uk-medicines-regulator-gives-approval-for-first-uk-covid-19-vaccine.
21. Health Canada. Health Canada authorizes first COVID-19 vaccine. [cited 09 Dec 2020]. Available from: https://www.canada.ca/en/health-canada/news/2020/12/health-canada-authorizes-first-covid-19-vaccine0.html.
22. Food and Drug Administration (FDA). The first emergency use authorization (EUA) for a vaccine for the prevention of COVID-19. [cited 11 Dec 2020]. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine.
23. Mckinsey global institute. COVID 19 and the Bio Revolution. [cited 15 Jul 2020]. Available from: https://www.mckinsey.com/mgi/overview/in-the-news/covid-19-and-the-bio-revolution.
24. Food and Drug Administration (FDA). Information about ERVEBO. [cited 20 Nov 2020]. Available from: https://www.fda.gov/vaccines-blood-biologics/ervebo.
25. Huibin L, Nicholas CW, Chris KPM. COVID-19 vaccines: knowing the unknown. Eur J Immunol Comment. 2020.
26. Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S, Zhou Y, Du L. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: Implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol. 2020;17(6):613–20.
27. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Sci (New York, N.Y.). 2020;367(6483):1260–1263.
28. Trevor RFS, Ami P, Stephanie R, Dustin E, Xizhou Z, Jian Yan, et al. Immunogenicity of a DNA vaccine candidate for COVID-19. Nat Commun. 2020;11:2601.
29. Symvivo. Information about the bacTRL™ proprietary platform applied in the COVID-19 candidate vaccine. [cited 14 Dec 2020]. Available from: https://www.symvivo.com/bactrl.
30. Lumpkin MM, Lim JCW. Pandemic best regulatory practices: an urgent need in the Covid-19 Pandemic. Clin Pharmacol Ther. 2020;108(4);703-5.
31. National Health Surveillance Agency (ANVISA). Specific legislation to COVID-19 pandemic. [cited 15 Jul 2020]. Available from: http://portal.anvisa.gov.br/coronavirus/regulamentos.
32. European Medicines Agency (EMA). Specific legislation and procedures to COVID-19 pandemic. [cited 15 Jul 2020]. Available from: https://www.ema.europa.eu/en/documents/other/ema-initiatives-acceleration-development-support-evaluation-procedures-covid-19-treatments-vaccines_en.pdf.
33. Food and Drug Administration (FDA). Specific guidelines to COVID-19 pandemic. [cited 15 Jul 2020]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-

19-update-fda-takes-new-actions-accelerate-development-novel-prevention-treatment.
34. Food and Drug Administration (FDA). Guidance for industry: development and licensure of vaccines to prevent COVID-19. 2020.
35. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. N Engl J Med. 2020;382(21):1969–73.
36. European Medicines Agency (EMA). Definition of adaptive study design. [cited 17 Jul 2020]. Available from:https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways.
37. Kunz CU, Jorgens S, Bretz F, Stallard N, Lancker KV, Xi D, et al. Clinical trials impacted by the COVID-19 pandemic: adaptive designs to the rescue? arXiv preprint: 2005.13979. 2020.
38. World Health Organization (WHO). R&D Blueprint. [cited 18 Jul 2020] Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/accelerating-a-safe-and-effective-covid-19-vaccine.
39. World Health Organization (WHO). Solidarity study. [cited 18 Jul 2020] Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coroavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments.
40. National Institute of Health (NIH). ACTIV information. [cited 29 Jun 2020]. Available from: https://www.nih.gov/news-events/news-releases/nih-launch-public-private-partnership-speed-covid-19-vaccine-treatment-options.