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EDITORIAL

Vaccines against severe acute respiratory syndrome coronavirus-2 (March 23th 2021)

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Vaccination is the most effective and specific prevention to avoid the development of infectious diseases. In the face of the coronavirus disease-19 pandemic, the application of vaccines against severe acute respiratory syndrome coronavirus (SARS-CoV-2) with wide coverage of the world's population is the way to overcome the current health crisis faced by humanity. Vaccines are used to expose the immune system to an immunogen that stimulates a response that blocks or destroys the infecting agent without causing disease.

The development of a vaccine has taken a long time (years or decades) between the discovery of the causative agent and its readiness for application in the population. For this pandemic virus, vaccines already approved and in use in different countries were developed in the year 2020, which was possible thanks to the knowledge that was previously available for SARS-CoV and Middle East respiratory syndrome-CoV.

Different teams in different countries are developing more than 200 vaccines against SARS-CoV-2 virus. Different types of technologies are used for these vaccines, some have been tested and used while others are to be applied for the 1st time in humans (technology types: live attenuated viruses, Inactivated viruses, Non-replicating viral vector, Replicating viral vector, Recombinant proteins, Peptides, Viral-like particle and DNA or RNA nucleic acids). As can be expected, to have a vaccine ready requires a very well integrated team of people and material, leading to huge financial costs, the latter being largely supported by the private sector, as well as academic groups and the public sector[1-4].

To date (March 23th 2021), according to information from the World Health Organization, there are 267 vaccines classified by stage of development: 184 in pre-clinical phases and 83 vaccines that have reached the clinical trial stage. According to WHO, 19 vaccines are the most promising, 13 of which are already approved for emergency use in one or more countries[1].

The different technologies used in the SARS-CoV-2 vaccines under development according to the World Health Organization (WHO) (Table 1).

Virus vaccines

Attenuated live virus vaccines conventionally use viruses weakened by passage through animal or human cells until they acquire mutations that make them less virulent[2,3].

As for inactivated virus vaccines, the viruses lose their virulence through the use of chemicals (such as formaldehyde). In this case, large amounts of viruses are required to produce an immune response[2,3].

Codagenix is working with the Serum Institute of India, on an attenuated vaccine, which is in the pre-clinical phase. In addition to other teams in various stages of development with this technology, we have the

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Table 1. Technologies in clinical phase used in SARS-CoV-2 vaccines in development

Platform	Candidate vaccines No.	%
Protein Subunits	27	33
Viral Vector (non-replicating)	12	14
DNA	10	12
Inactivated Viruses	11	13
RNA	11	13
Viral Vector (replicating)	4	5
Viral Like Particles	3	4
Viral Vector (replicating) + Antigen Presenting Cell	2	2
Live Attenuated Virus	2	2
Viral Vector (non-replicating) + Antigen Presenting Cell	1	1
Total	83	100

following vaccines in Phase 1: the Research Institute for Biological Safety Problems, Erciyes University, Valneva, National Institute for Health Research UK and Codagenics/Serum Institute of India. In Phase 2, the vaccine from Beijing Minhai Biotechnology Co., and in Phase 3 the vaccines from Sinovac Research and Development Co., Sinopharm + China National Biotec Group Co. + Wuhan Institute of Biological Products, Sinopharm + China National Biotec Group Co. + Beijing Institute of Biological Products, Institute of Medical Biology + Chinese Academy of Medical Sciences[1,4].

At least seven teams are developing vaccines using whole viruses, in an attenuated or inactivated form. Many of the vaccines in use today are made with this technology, such as the measles or rubella vaccine, but require extensive safety studies[1,4].

Vaccines with this technology licensed for emergency use in Mexico are:

– Sinovac biotech (Coronavac) vaccine announced in a statement, the preliminary results of their study of an inactivated SARS-CoV-2 virus vaccine, given in two doses at 0 and 14 days. About 50.65% vaccine effectiveness (VE) was reached, 14 days after the second application for all cases, 83.70% VE for cases that required medical treatment, and 100.00% VE for hospitalized patients in severe and fatal condition. In Turkey, another study reported 91.25% VE after 14 days of the two-dose vaccination[5].

Viral-like particle vaccines

Virus-like particles are structural proteins of viruses that are assembled without nucleic acid, so they are called virus-like particles or empty capsids. They can also be viral proteins that occur inside a lipid membrane. As vaccines, they are highly immunogenic with strong stimulation of the immune system and induction of T and B lymphocyte response, without the ability to develop disease, as they have no viral nucleic acid[2,3].

Empty viral capsids are used that mimic the Coronavirus structure, but are not infectious because they have no genetic material. Five research teams are working on these “virus-like particle” vaccines, which can generate a robust immune response, but can be difficult to produce. The vaccines with this type of technology are the Medicago Inc. vaccine, which is in phase 2/3; while the Serum Institute of India + Accelagen + Spybiotech vaccine is in phase 1/2[1,4].

Viral protein vaccines

These vaccines use viral proteins, protein fragments or surface proteins that mimic the external proteins of the Coronavirus[2,3].

There are 28 teams working on protein subunit vaccines, mostly targeting the viral S protein, or a region there of known as receptor binding domain. These vaccines have been successful with SARS-CoV in apes, but have not been tested yet in humans, as this type of vaccine requires the use of adjuvants and multiple doses. Phase 3 vaccines with this type of technology are: Novavax vaccine, Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology vaccine, and the Chinese Academy of Sciences vaccine. In Phase 2/3: Clover Biopharmaceuticals Inc./GSK/Dynavax vaccine, Medigen Vaccine Biologics + Dynavax + National Institute of Allergy and Infectious Diseases vaccine, and the COVAXX + United Biomedical Inc. vaccine. In Phase 2: Finlay Vaccine Institute vaccine and West China Hospital + Sichuan University vaccine. Vaccines in phase ½ are being developed by the following institutions: Kentucky Bioprocessing Inc., Sanofi Pasteur + GSK, Federal Budgetary Research Institution State Research Center of Virology and Biotechnology “Vector,” Center for Genetic Engineering and Biotechnology, Biological E. Limited, Nanogen Pharmaceutical Biotechnology, Shionogi, University Medical Center Groningen + Akson Biosciences Inc., Vaccine and Infectious Diseases Organization + Seppic and the Vaccine Formulation Institute[1,4].

Viral vector vaccines

A virus that infects humans is used as a vector; the most commonly used is an Adenovirus. Its genome is altered to express viral proteins of the virus against which we want to achieve a protective response. These vaccines produce a strong immune response and their possible drawback is the existence of a previous immune response against the Adenovirus (vector), which makes the intended vaccine response less efficient[2,3].

Nearly 25 teams are working on viral vector vaccines. A virus that is genetically engineered, so that it can produce SARS-CoV2 proteins in the human body. There are two types: those that can replicate inside cells and those that cannot replicate because genes for this function have been disabled[1,4].

Replicating viral vector vaccines: the recently approved Ebola vaccine is an example of this technology. These vaccines are safe and produce a strong immune response. However, the existence of immunity to the vector could diminish the VE[2,3].

Non-replicating vector vaccines: there are no approved vaccines using this technology, but they have been widely used in gene therapy. Booster vaccines may be necessary to induce long-term immunity[2,3].

Vaccines using this technology that are in Phase 3 are the CanSino Biological Inc./Beijing Institute of Biotchnology vaccine, Gamaleya Research Institute vaccine, Jansen Pharmaceutical vaccine and the AstraZeneca + University of Oxford vaccine. The University of Hong Kong + Xiamen University + Beijing Wantai Biological Pharmacy vaccine is in Phase 2. The following institutes and entities are developing vaccines that are currently in phase ½: Shenzhen Geno-Immune Medical Institute, Israel Institute of Biological Research, Aivita Biomedical Inc. + National Institute of Health and Development, Republic of Indonesia and Cellid Co. The following vaccines are in Phase 1: ReiThera + Leukocare+ Univercells vaccine, Vaxart vaccine, University of Munich vaccine, Shenzhen Geno-Immune Medical Institute vaccine, ImmunityBio Inc. & NantKwest Inc. vaccine, City of Hope Medical Center + National Cancer Institute vaccine and Altimmune Inc. vaccine[1,4].

Vaccines with this type of technology that is licensed for emergency use in Mexico[6,7]:

- The Oxford and Astra Zeneca vaccine. It is a safe and effective vaccine against symptomatic COVID-19, it is made from a replicant-deficient chimpanzee adenovirus vector ChAdOx1, which contains the SARS-CoV-2 structural surface glycoprotein antigen gene (spike protein; nCoV-19), are applied in 2 doses, stored at conventional refrigerator temperature (2-8º) and the effectiveness reported is as follows:
- In an interim analysis of a phase 3 study, in 3 countries, the United Kingdom, Brazil and South Africa, in 11,636 participants > 18 years included in this analysis, two doses of the vaccine were administered with an interval of 28 days, in the Group 1 with 2 standard doses with 62.1% efficacy and in group 2 a reduced dose and one standard dose with 90.0% efficacy, resulting in a mean efficacy of 70.4%, 14 days after the second doses and 3 adverse events possibly attributable to vaccination[8].
- In another analysis of the ChAdOx1 nCoV-19 Vaccine (AZD1222) with 24,422 participants > 18 years of age included in this analysis, in 3 countries, the United Kingdom, Brazil and South Africa, with two doses of the vaccine with an interval of 3 months, with efficacy 22-90 days after dose 1 of 76% and 14 days after dose 2 of 81.3%, without any deaths from COVID-19[9](Tables 2 and 3).
- Another study with 2 doses of the ChAdOx1 nCoV-19 vaccine, showed an efficacy of 21.9% against the variant B.1.351 of the SARS-CoV-2 virus, in conclusion the vaccine does not show protection against COVID -19 mild to moderate caused by this variant[10].
- The Sputnik V vaccine from the Gamaleya Research Institute of Epidemiology and Microbiology uses an adenovirus viral vector that expresses the spike protein of SARS-CoV-2, is administered in two doses at an interval of 4 weeks, is stored at conventional refrigerator temperature (2-8º), and is 92% effective[11].
- The CanSino vaccine uses an adenovirus viral vector expressing the SARS-CoV2 spike protein, one dose, reported in press releases to have an efficacy rate of 65.7% in preventing symptomatic cases according to an analysis of late stage trials[12].

Nucleic acid vaccines

Nearly 20 teams use this type of genetic technology (through RNA or DNA) to make Coronavirus proteins to produce an immune response. The nucleic acid is inserted into the human cell, which will produce copies of the viral protein, most of these vaccines encode the S protein of the virus[2,3].

RNA- and DNA-based vaccines are safe and simple to develop; only the production of the genetic material is required. RNA vaccines in Phase 3 are: Moderna + National Institute of Allergy and Infectious Diseases

Table 2. Efficacy of the first dose after several days. *Adapted from: Voysey M, et al.*[9]

Time (days)	22-30	31-60	61-90	91-120	22-90
Documented infection	62.3%	56.3%	79.4%	28.2%	63.9%
Symptomatic infection	76.7%	72.8%	78.3%	31.6%	76%
Hospitalization	100%				

Table 3. Efficacy of the vaccine according to the interval between doses, and after 14 days of the application of the second dose. Adapted from: *Adapted from: Voysey M, et al.*[9]

Interval between doses (weeks)	< 6	6-8	9-11	≥12
Documented infection	47.1%	32.6%	61.9%	59.9%
Symptomatic infection	55.1%	59.9%	63.7%	81.3%
Hospitalization	100%			

Table 4. Safety over a median of 2 months was similar to that of other viral vaccines.

Doses + days	Doses 1 + 21 days	Doses 2 + 7 days	> 7 days doses 2
Efficacy	52%	91%	95%

vaccine, Pfizer/BioNTech + FosunPharma vaccine, CureVac AG vaccine. In Phase 2 is Arcturus Therapeutics vaccine. Phase 1 vaccines are being developed by the Imperial College London, Academy of Military Science + Walvax Biotechnology + Suzhou Abogen Bioscience and Chulalongkorn University[1,4].

DNA vaccines in Phase 3: Zydus Cadila vaccine; in Phase 2/3: Anges + Takara Bio + Osaka University vaccine, Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co. vaccine; in Phase 1/2 is the Genexine Consortium vaccine and GeneOne Life Science Inc. vaccine. Phase 1 vaccines are being developed by Entos Pharmaceutical Inc., Providence Health and Services and Symvivo Corporation[1,4].

Vaccines with this technology licensed for emergency use in Mexico[11] and other countries are:

- The Pfizer and BioNTech vaccine, called BNT162b2 messenger RNA (mRNA), is authorized for emergency use in Mexico[13], it is a modified RNA with 3 nucleosides (modRNA) formulated with lipid nanoparticles that encodes the full-length spike of SARS-CoV-2 anchored to a stabilizing membrane with prefusion, the RNA is modified by 2 proline mutations (P2 S) to block it in the prefusion conformation, to increase its potential to provoke neutralizing antibodies[14]. It is applied in 2 doses with an interval of 21 days, it is stored at -70 and -20 degrees Celsius, the effectiveness has been studied in two analyzes that are:
- An analysis in 152 sites in the United States, Argentina, Brazil, South Africa, Germany, and Turkey, with 43,448 participants, two doses of 0.33 ml (30-µg) were applied intramuscularly with a 21-day interval, the results in the interval between the first and second doses, an efficacy against Covid-19 was observed was 52%, and in the first 7 days after dose 2 it was 91%. A 95% efficacy in the prevention of Covid-19 was also observed, after 7 days of the second dose, with a similar vaccine efficacy (generally 90 to 100%) in the subgroups defined by age, sex, race, ethnicity, baseline body mass index, and the presence of coexisting conditions. The safety profile of BNT162b2 was characterized by mild to moderate short-term pain at the injection site, fatigue, and headache. The conclusions are that a two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in people 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines (Table 4)[14].
- An analysis with two doses of the vaccine in a total of 596,618 people, the effectiveness of the vaccine was evaluated in various populations in an uncontrolled environment, estimating the effectiveness of the vaccine between days 14 and 20 after the first dose and 7 or more days after the second dose (Table 5)[15].
- Effectiveness was also estimated in specific subpopulations evaluated for documented infection and symptomatic Covid-19, where it was consistent across all age groups, with slightly less effectiveness in people with multiple coexisting contidions (Tables 6-7)[15].
- Moderna's vaccine is an mRNA vaccine that encodes the SARS-CoV-2 spike protein and is contained in lipid nanoparticles, is administered in two doses, stored at -20ºC, and is 94.1% effective. This vaccine

Table 5. Effectiveness of the vaccine between days 14 and 20 after the first dose and 7 or more days after the second dose

Dose + days	Dose 1 + 14-20 days	Dose 1 + 21-27 days	> 7 days dose 2
Documented infection	46%	60%	92%
Symptomatic infection	57%	66%	94%
Hospitalization	74%	78%	87%
Severe Disease	62%	80%	92%
Death	72%	82%	NA

Table 6. Documented infection

Dose + days	Dose 1 + 14-20 days	Dose 1 + 21-27 days	> 7 days dose 2
Male	41%	57%	90%
Female	50%	63%	93%
Age 16-39	49%	64%	94%
Age 40-69	47%	58%	90%
Age > 70	22%	50%	95%
No comorbidities	49%	66%	91%
1 or 2 comorbidities	43%	56%	95%
3 or more comorbidities	37%	37%	86%
Obesity	49%	48%	95%
Diabetes mellitus 2	25%	49%	91%
Hypertension	28%	45%	93%

Table 7. Symptomatic COVID-19

Dose + days	Dose 1 + 14-20 days	Dose 1 + 21-27 days	> 7 days dose 2
Male	52%	62%	88%
Female	60%	69%	96%
Age 16-39	57%	67%	99%
Age 40-69	59%	65%	90%
Age > 70	44%	64%	98%
No comorbidities	55%	73%	93%
1 or 2 comorbidities	57%	62%	95%
3 or more comorbidities	62%	47%	89%
Obesity	65%	50%	98%
Diabetes mellitus 2	48%	60%	91%
Hypertension	45%	59%	95%

is not licensed for emergency use in Mexico, but is licensed for emergency use in other countries[16].

Six SARS-CoV-2 mutations are worth mentioning, which give rise to variants of the virus with the following impact: three of them with mutation in N501Y resulting in higher transmissibility and lower response to mRNA vaccines, whereas three others with mutation in E484K resulting in the lower therapeutic response to monoclonal antibodies and lower response to vaccines.

In general, approved vaccines have few adverse reactions, most of them mild and occasionally moderate. At this point, the recommendation is to apply the vaccine that is available when the opportunity arises, in the understanding that we are immersed in a pandemic with a significant death toll. Breaking the chain of transmission can occur when the majority of the population is no longer susceptible to infection, thanks to a protective immune response, which is achieved with a vaccination coverage of over 90%.

As of today (March 23th 2021) five vaccines have been licensed for emergency use in our country: Pfizer/BioNtech[13], AstraZeneca[6], Sputnik V[7], Coronavac and CanSino. Other vaccines are in the process of being assessed by our authorities.

Conflicts of interest

The authors declare have no conflicts of interest.

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