

Vaccination in the context of the COVID-19 pandemic

La vacunación en el contexto de la pandemia de COVID-19

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Abstract

In this review, we described the history of vaccination, the different types of vaccines, and how vaccination coverage has been affected by the current COVID-19 pandemic. The effectiveness of the vaccines under metabolic host conditions is analyzed, especially when people have lost their immunocompetence, such as in patients with chronic kidney disease who are in dialysis treatment. Vaccines are produced in a variety of industrial methods, modifying costs. The novel field of vaccinomics includes the set of immune responses, the satisfactory levels of neutralizing antibodies, the production of metabolites, and the induction of protein expression. Finally, an analysis is made of the confusing messages regarding vaccination that are disseminated on social networks, and general recommendations are given.

Keywords: Vaccinology. COVID-19 vaccines. Vaccinomics. Communication media.

Resumen

En esta revisión se describen el historial de vacunación, los diferentes tipos de vacunas y cómo la cobertura de vacunación se ha visto afectada por la pandemia actual de COVID-19. Se analiza la efectividad de las vacunas en condiciones metabólicas del huésped, especialmente cuando las personas han perdido su inmunocompetencia, como los pacientes con enfermedad renal crónica que están en tratamiento de diálisis. Las vacunas se producen con una variedad de métodos industriales, modificando los costos. El nuevo campo de la vacunómica incluye el conjunto de respuestas inmunitarias, los niveles satisfactorios de anticuerpos neutralizantes, la producción de metabolitos y la inducción de la expresión de proteínas. Finalmente, se analizan los confusos mensajes sobre vacunación que se difunden en las redes sociales y se dan recomendaciones generales.

Palabras clave: Vacunología. Vacuna contra COVID-19. Vacunómica. Medios de comunicación.

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Introduction

To date (July 20, 2021), some 2 billion people have been vaccinated against SARS-CoV-2 in the world (26% of the world population), and 38 million in Mexico (30% of the population total)¹. This has involved learning new approaches to mass vaccination to minimize morbidity and mortality from COVID-19².

The SARS-CoV-2 vaccines that are used have been created with different technologies that have proven effective and have worked so far. The technology to vaccinate using nucleic acids has been investigated since the early 1990s³, therefore, it has been possible to deepen the understanding of how these new strategies work to stimulate the immune response. However, an important risk factor remains in the age of digital technology: misinformation. Anti-vaccination campaigns appeared since vaccination itself began, and for decades they have negatively modified the behavior of families to receive vaccines. Aberrations in basic scientific concepts have led entire families to make the wrong decisions. In 2019 there were more than a thousand cases of measles in 31 States of the United States of America, in families that mainly refused to receive the vaccine⁴.

This article provides a description of the history of vaccination in general, the development of new vaccines within the context of vaccination, and the consequences of vaccines in general, considering the new SARS-CoV-2 within the culture of vaccination.

One to zero: goodbye smallpox

Vaccines are made with killed or attenuated microorganisms, or with products derived from them (toxins, vectors, plasmids), to stimulate the production of specific antibodies or cellular immunity. The history of vaccinations began with the inoculation of smallpox (variola) in China and India in 400 BCE. This method was practiced in Africa and Turkey, and then spread to Europe and America in the 18th century. It is difficult to measure the epidemiological impact of variola, since it was not a widespread practice and there were no data records.

In the 18th century (variola century) vaccination was born with Jenner and her inoculation with *cowpox* (bovine smallpox, hence the name vaccination). In 1798, vaccination against smallpox spread to other countries and, thanks to technological improvements, for the next 200 years smallpox was eradicated (we achieved success).

After the development of the rabies vaccine by Pasteur (1930), the 20th century was active in the research of antitoxins and vaccines against diphtheria, tetanus, anthrax, cholera, plague, typhoid fever, and tuberculosis, among others. Methods for growing viruses in the laboratory led to vaccines against polio, measles, mumps, and rubella⁵.

Thanks to recombinant nucleic acid techniques and molecular biology, there is a push to focus vaccines against non-infectious conditions such as addiction, allergies, cancer and diabetes *mellitus* Type 1. The COVID-19 vaccine uses messenger RNA (mRNA) that carries the genetic instructions for the host to express a specific antigen.

Decrease in vaccination coverage in Mexico and other Latin American countries

There are compelling data on the impact of vaccination campaigns on the health of the child population in the world. Despite this, childhood vaccination coverage had declined in Latin America before the COVID-19 pandemic. Median coverage of DPT (diphtheria, pertussis, tetanus), polio, and hepatitis B vaccines between 1992 and 2016 was 69.9% in 8 of 18 countries⁶. Among the causes of this decline are the scarce funds allocated for health in the region^{7,8}, poor access to health services, insufficient number of health workers, inadequate supply of vaccines, government corruption and insecurity generated by lack of information^{9,10}. During the current COVID-19 pandemic, some 30 vaccination campaigns have been cancelled, which could cause new outbreaks in this year 2021 and those to come¹¹.

Effectiveness in the setting of vaccination

Vaccines reduce the costs of treatment and rehabilitation of diseases, infectious or not. Table 1 shows types of vaccines available. Entities such as the World Health Organization (WHO), the Pan American Health Organization, the *Centers for Disease Control and Prevention* and the *National Institutes of Health* monitor the effectiveness of vaccines using statistical methods to analyze the effects of age, race, and underlying medical conditions¹².

Vaccinomics is the study of genetics, epigenetics, and other host factors that explain variations in the immune response to vaccines. It uses several disciplines, such as immunogenetics, immunogenomics and bioinformatics, providing a conceptual framework

Table 1. Types of vaccines

Vaccine type	Vaccines recommended in immunization programs	Other vaccines available
Alive, dimmed	Measles, mumps, rubella (combined vaccine) Chickenpox Influenza (nasal spray) Rotavirus	Herpes zoster Yellow fever
Inactive/dead	Poliomyelitis Hepatitis A	Rage
Toxoid (inactive toxin)	Diphtheria, tetanus (part of the DTaP combination immunization)	
Subunits/conjugate	Hepatitis B Influenza (shot) <i>Haemophilus influenzae</i> type B Pertussis (part of the DTaP combination immunization) Pneumococcal Meningococcal	Human papilloma virus
DNA		Third-generation antipneumococcal Influenza
RNA		Human cytomegalovirus Rous Sarcoma Virus Simian Virus 40 (SV-40)

(understanding and prediction) of the immune response, and allows the development of new vaccines¹³⁻¹⁵. Vaccinomics describes molecular mechanisms of this complex network of interconnections with metabolism and environmental factors such as diet, allergies or psychological stress, predicting the best response to a vaccine and possible adverse effects.

Vaccinomics also develops personalized third and fourth generation vaccines. There is the possibility of creating individualized vaccines for specific conditions or, more realistically, for population groups with specific gene haplotypes and supertypes. Curiously, the main problem this strategy faces is the excess of data that is already difficult to interpret in order to analyze host conditions and obtain results in the field of aging, oncology or human immunodeficiency virus (HIV)¹⁶.

In the case of COVID-19, Pfizer-BioNTech's SARS-CoV-2 vaccine contains specific mRNA for the production of protein S in host cells, which stimulates protective

antibodies. Due to rapid mRNA degradation, this vaccine must be kept at a very low temperature (-70°C) from the time it is produced until a few days before it is injected. Moderna's vaccine is similar to that of Pfizer-BioNTech. The Russian Sputnik V vaccine uses vectors of the common cold adenovirus. In the first dose, the adenovirus 26 vector is used, which synthesizes protein S, and in the second dose, at 21 days, a second adenovirus 5 vector is inoculated to provide long-term immunity. Sino-vac's Chinese vaccine has given results with great variability in tests carried out in Brazil, Indonesia and Turkey. AstraZeneca's vaccine uses a genetically modified J&JAd26 adenovirus, is 90% effective, and requires storage at refrigerator temperatures.

Host nutritional conditions

"Let your food be your medicine and your medicine be your food" (Hippocrates). Nutritious and safe diets favor the development and preservation of the immune system. For example, the intracellular concentration of zinc influences the phagocytic capacity of macrophages¹⁷; iron promotes lymphocyte and macrophage differentiation, metabolism, and antimicrobial immune effector function¹⁸; and vitamin A deficiency is associated with impaired intestinal immune responses and increased mortality from gastrointestinal and respiratory infections¹⁹.

Micronutrients modify the response to vaccines. Vitamin A deficiency increases delayed-type hypersensitivity of type 1 (Th1) helper T cells and a reduction in Th2-directed antibody responses to vaccines (supplementation reverses these responses). However, vitamin A supplementation has shown no effect on response to measles vaccine, oral polio vaccine, or BCG vaccine, and there was even less response in children who received vitamin A supplementation at 2 months. Zinc improves antibody titres after cholera vaccination in children, but this has not yet been studied. And regarding iron deficiency, it has been shown that it does not affect antibody responses to vaccination (including responses to T cell-dependent antigens), although data are limited²⁰.

There is no specific nutritional management for COVID-19 or special food suggestions for vaccination against SARS-CoV-2.

Host conditions and immunodeficiency

People with primary or secondary immunodeficiency in B lymphocytes produce variable degrees of

antibodies to the stimulus produced by any vaccine. In severe cases, such as X-linked agammaglobulinemia, oral vaccines against polio, yellow fever, BCG (tuberculosis), Ty21a (live typhoid), measles, mumps and rubella, and seasonal influenza are contraindicated. In less severe cases, such as selective IgA or IgG subclass deficiencies, oral polio vaccine, yellow fever, and BCG should be avoided, but the rest appear to be safe. In the case of T-lymphocyte defects, such as DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia, or interferon-gamma or interleukin-12 deficiencies, live vaccines should be avoided. The pneumococcal vaccine is recommended, but the response is variable.

In immunodeficiency conditions due to HIV or immunosuppression due to drugs, radiation or associated with cancer, the same vaccines are contraindicated as in primary deficiencies. Asplenia (absence of the spleen) and chronic kidney disease are special cases; the seasonal influenza vaccine is contraindicated in them.

Patients with chronic kidney disease present an immunosenescence phenotype, which accompanies other chronic diseases (diabetes *mellitus* type 2), which does not occur in all cells of the body or to the same degree in all. There is a reduction of T cells, but at the same time CD4 and CD8 T cells are characterized by a cytotoxic capacity with high concentration of granules with proteins, such as perforins and granzyme B, which induce cell death²¹.

Patients with chronic kidney disease at any stage should receive the recommended vaccination schedules, despite their diminished immune response and the fact that patients on peritoneal dialysis have a progressive loss of antibodies, making it necessary to apply boosters²². Early vaccination in these patients improves the immune response. It should preferably be vaccinated at a young age and before stage 4 (glomerular filtration rate of 15-29 ml/min)²³. Vaccination schedules must be complete before renal transplantation²⁴.

People with chronic conditions should follow the recommended vaccination schedules; for example, people with diabetes *mellitus* type 2 are more likely to have shingles than the general population, and it is recommended that they get vaccinated against shingles, influenza, pneumococcus, hepatitis B, tetanus, diphtheria, and whooping cough²⁵.

People with diabetes *mellitus* type 2 or with arterial hypertension present low-grade systemic inflammation, which causes endothelial damage and can exacerbate the inflammatory response derived from COVID-19,

increasing severity and mortality²⁶. Studies have shown that people with obesity and COVID-19 are 113% more likely to be admitted to hospital, 74% more likely to be admitted to the intensive care unit, and 48% more likely to die; furthermore, this condition can make vaccines against the disease less effective^{27,28}.

Moderna and Pfizer-BioNTech vaccines have shown good safety and efficacy profiles in people with chronic lung disease, heart disease, severe obesity, diabetes *mellitus* type 2, liver disease, HIV infection, hepatitis B virus infection, and asthma, among others^{29,30}.

Patients with immunosuppressive treatments have not been shown to have a greater severity of COVID-19 compared to the rest of the population. The data collected to date suggest that the innate response is similar in transplant recipients and healthy individuals³¹.

Technological development of vaccines

Vaccine development is regulated by strict rules for comparing control groups and those receiving the vaccine. Control principles, comparable groups, blinding (to reduce bias), and randomness are key elements.

Traditional vaccinology methods to inactivate or attenuate viruses or bacteria require processes that use heat or chemicals (adjuvants), such as formaldehyde³². These procedures are time consuming and may carry risks of contamination or hypersensitivity. Attenuated microorganisms can stimulate humoral and cellular immunity³³, such as vaccines against rubella, measles, mumps, tuberculosis, chicken pox, typhoid fever, yellow fever and cholera.

Second-generation vaccines are made with genetic engineering, like the hepatitis B and smallpox vaccines. Although the induction of humoral immunity is important, cellular immunity is not optimal. This is reflected in the trials of vaccines against HIV, malaria and hepatitis C, which have not been able to progress due to the costs and the doubtful effectiveness of this type of vaccine.

Gene-associated vaccines are third generation and use nucleic acids that are injected into plasmids. They may be fragments of DNA that have the ability to produce recombinant proteins in the body to stimulate the immune system. New biotechnological strategies make mRNA vaccines cheaper (less manufacturing time) and easier to store and transport than their conventional counterparts. In addition, they do not contain infectious material that could accidentally cause disease. This is the case with vaccines against COVID-19.

Table 2. Differences between traditional vaccines and third generation vaccines

	Conventional vaccines	RNA vaccines
Production time	Most vaccines against viral diseases are made from viruses that are grown in chicken eggs or mammalian cells. The process of collecting viruses, adapting them to grow in a laboratory, and shipping them around the world can take months and is complex. For new viruses, such as SARS-CoV-2, for which a new vaccine is needed as soon as possible, these steps can slow development.	RNA (encoding an infectious agent antigen) is made from a DNA template in the laboratory. It is possible to synthesize DNA from an electronic sequence that can be sent around the world in an instant, by computer. It currently takes about a week to generate an experimental batch of an RNA vaccine.
Biosecurity	Growing large amounts of virus to produce each batch of vaccines creates risks	Viruses are not needed to make a batch of an RNA vaccine. Only small amounts of virus are used for gene sequencing and vaccine testing
Immune response	The antigen (a part of the virus) is injected into the body. Upon recognizing the antigen, the immune system produces specific antibodies in preparation for the next time the body encounters the pathogen.	The RNA is injected into the body and enters cells, where it provides instructions for making antigens. The cell presents the antigens to the immune system, triggering responses by T cells and antibodies that can fight the disease.
Flexibility	A specific production process is required for each new vaccine, including purification and complex testing.	It is hoped that the RNA vaccine production process can be expanded and standardized, with the potential to allow replacement of the sequence encoding the target protein of interest, for a new vaccine with minimal changes to the production process.
Routes of administration	Subcutaneous or hypodermic route Intradermal route Orally Via nebulization, intranasal or oral-nasal spray	Edible vaccines Mucosal vaccines Transcutaneous vaccines
Production cost	From moderate to high due to the type of infrastructure required	Relatively moderate, with high chances of reducing it

More than 200 candidate vaccines against COVID-19 have been registered and just over 50 of them are already being tested in humans. The vaccines that are currently being distributed in the world are those manufactured by BioNTech (BNT162b2) in Germany; Pfizer (BNT162b2) and Moderna (mRNA-1273) in the United States of America; AstraZeneca (ChAdOx1 nCoV-19) in the UK; CanSino (Ad5-nCoV) and Sinovac (CoronaVac) in China; Sputnik V (Gam-COVID-Vac) in Russia; and Soberana 01 and 02 (RBD protein, VAMENGOC) and Mambisa (CIGB 669) in Cuba. The recombination methodology meant that the vaccine was manufactured in less than 1 year. Recently, genetic engineering has developed preventive and therapeutic fourth-generation vaccines^{3,4} (Table 2).

WHO-approved vaccines are those from Pfizer/BioNTech, AstraZeneca, Janssen (a subsidiary of the US laboratory Johnson & Johnson), Moderna, Sinopharm and Sinovac. Others, such as the Chinese CanSino, the Indian Covaxin and the Russian Sputnik V, are used in other countries, such as Mexico, even with controversies

on the part of the WHO and the regulatory agencies of the United States of America and the European Union (Table 3).

Routes and forms of nucleic acid inoculation

It is known that only 1-10% of the total inoculated nucleic acid is adequately processed to express the protein of interest in inoculation routes including skin, skeletal muscle, and mucosa. Injection of DNA coupled to gold or tungsten spheres into the dermis and subdermal layers is the most used method, since it does not require specialized training and is also low cost, but the use of the gene gun (*gene gun*) produces the best results. Taking into account that many pathogens have mucous membranes as a gateway, this is another route used to induce an immune response with DNA vaccines³⁵⁻³⁸.

Regardless of the form of inoculation, various types of cells take up the DNA, although it is necessary for

Table 3. Vaccines approved in Mexico

Vaccine and country	Type and dose	Efficiency and stability	Price (\$)	Date of approval by COFEPRIS
Pfizer-BioNTech, United States of America	mRNA 2 doses	95% 6 months at -80°C	19.5	11 December, 2020
AstraZeneca, Great Britain	Viral vector 2 doses	79% 6 months at 8°C	2.8	5 January 2021
Sputnik V, Russia	Viral vector 2 doses	92% 6 months at -20°C	10	2 February 2021
SinoVac, China	Inactivated viruses 2 doses	51% 6 months at 8°C	13.6	9 February 2021
Cansino, China	Viral vector 1 doses	66% 6 months at 8°C	4	10 February 2021
Covaxin, India	Inactivated virus 2 doses	81% 6 months at 8°C	16.4	6 April, 2021
Jansen, United States of America	Viral vector 1 doses	66% 3 months at 8°C	10	27 May, 2021

it to be taken up by the antigen presenting cells (APCs), since they are the only ones capable of activating cells of the immune system by presenting antigens. These cells can capture DNA directly by inoculation (transfection) or they can take up antigen from other cells, such as skeletal muscle cells or keratinocytes, by phagocytosis, by a mechanism called “cross-presentation”³⁵.

Unfounded fears

None of the available vaccines are 100% effective, and neither are they without potential risks. In the field of vaccinology “confidence has been obtained in recognizing how much [control disease] has been achieved with so little [a picket]”, as stated by Donald Henderson in the smallpox eradication campaign in the 1970s³⁹.

There is clear evidence that vaccines have achieved many successes in public health, however, vaccination has been the subject of various controversies. In the world (as of May 17, 2021), after 273 million doses administered against SARS-CoV-2, 4,647 deaths (0.0017%) have been reported as adverse events⁴⁰. Serious adverse events for most vaccines are less than 1/10,000; anaphylaxis from hepatitis B vaccine is 1/1,000,000; in the case of the influenza vaccine, Guillain-Barré syndrome occurs in 1/1,000,000; and with the rotavirus vaccine, 1/17,000 children present intussusception⁴¹. In all cases, the benefits far outweigh the risks.

This infodemic or overexposure to information is something relatively recent that contributes to indecision on the part of people, which, when understood, is legitimate.

Conclusions

The technology used for the new vaccines is fast, cheap and reasonably safe. Vaccinomics (includes systems vaccinology and adversomics) studies the genotypes and phenotypes associated with the immune response, dose adjustment, administration routes, and the probability of suffering an adverse effect.

The coverage problem is not the technological gap, since there is a willingness to get the vaccine to the different economic strata of the population. The challenge is the administration of the adequate channels that the governments in Latin America have to have the vaccine and deliver it to the population.

We must counteract the ambiguous and confusing information that comes from social networks, and thus avoid fatal outcomes. We continue to learn from these challenges for the health system and must respond rationally using administrative tools combined with the screams (or whispers) of the data obtained.

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Conflicts of interest

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Ethical disclosures

Protection of people and animals. The authors declare that no experiments were carried out on humans or animals for this research.

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