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COVID-19 vaccines in Mexico: A recount of three years of pandemic

Vacunas contra la COVID-19 en México: Un recuento de tres años de pandemia

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Abstract:

Vaccines represent one of the most impactful public health advances in the history of mankind, playing a fundamental role in reducing the transmission and, in some cases, eliminating infectious diseases. Since the sudden appearance of the SARS-CoV-2 virus and the public health emergency of international concern, several vaccines have been designed and licensed to address the COVID-19 (COronaVIrus Disease 2019) pandemic in 185 countries around the world, so it is important to know the different types of vaccines available and the facts related to their efficacy and safety. The World Health Organization (WHO) reported on November 8, 2022 that the number of doses of COVID-19 vaccines administered were a total of 12,885,748,541 worldwide, while, in Mexico, the Ministry of Health reported 227,341,091 doses of vaccines administered against COVID-19 as of December 23, 2022. As more vaccines are approved, it is important to track data on vaccination efforts in Mexico and discuss the need to incorporate effective preparedness and response mechanisms that include innovative vaccine production platforms in our country. The objective of this manuscript is to present to the reader the current vaccines approved in Mexico against COVID-19, the variants of interest and concern identified by WHO, vaccines that are used within the country without WHO approval, and to provide an opinion on the implications regarding the emergence of new variants of the virus on the safety and efficacy of vaccines.

Keywords:
SARS-CoV-2, COVID-19, vaccines, variants of interest, variants of concern, Mexico

Resumen:

Las vacunas representan uno de los avances en salud pública más impactantes de la historia de la humanidad, desempeñando un papel fundamental en la reducción de la transmisión y, en algunos casos, en la eliminación de enfermedades infecciosas. A partir de la aparición repentina del virus SARS-CoV-2 y la emergencia de salud pública de importancia internacional, diversas vacunas han sido diseñadas y autorizadas para enfrentar la pandemia por COVID-19 (del inglés, COronaVIrus Disease 2019) en 185 países alrededor del mundo, por lo que es importante conocer los diferentes tipos de vacunas disponibles y los hechos relacionados con la eficacia y la seguridad de las mismas. La Organización Mundial de la Salud (OMS) reportó el 8 de noviembre de 2022 que el número de dosis de vacunas contra la COVID-19 administradas ascendía a 12,885,748,541 en todo el mundo, mientras que, en México, la secretaria de salud reportaba 227,341,091 dosis de vacunas administradas contra COVID-19 al 23 de diciembre de 2022. A medida que se aprueben más vacunas, es importante realizar un seguimiento de los datos sobre los esfuerzos de vacunación en México y discutir la necesidad de incorporar mecanismos efectivos de preparación y respuesta que incluyan plataformas innovadoras de producción de las mismas en nuestro país. El objetivo del presente manuscrito es presentar al lector las vacunas actuales aprobadas en México contra COVID-19, las variantes de interés y preocupación identificadas por la OMS, vacunas que se utilizan dentro del país sin la aprobación de la OMS, y dar una opinión sobre las implicaciones respecto de la aparición de las nuevas variantes del virus sobre la seguridad y eficacia de las vacunas.

Palabras Clave:
SARS-CoV-2, COVID-19, vacunas, variantes de interés, variantes de preocupación, México

INTRODUCTION

Vaccines prevent millions of deaths caused by infectious diseases each year and represent the simplest and most cost-effective intervention to protect against epidemics and pandemics.[1,2] Under normal conditions, it takes 10-15 years for an experimental vaccine to reach the market and the probability that it will eventually be approved for human use is estimated at less than 12%.[3] The cost of getting a new vaccine from the laboratory to patients ranges from $314 million to $2.8 billion

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(2018 USD).[4] Basically, these amounts reflect the cost of developments that fail in clinical trials and the cost of time invested in development. In addition, companies that produce vaccines are at the forefront of biomedical innovation, so they protect their products and processes with strong intellectual property policies in competitive markets that reward their investment.[5]

SARS-CoV-2 emerged in December 2019 in Wuhan, capital of Hubei Province, central China, at a time of scientific and technological maturity in several areas of knowledge. This enabled global collaborative scientific research and vaccine development with several paradigm shifts.[6] The first complete genome of the virus was released on January 7, 2020 and, to date, more than 8 million sequences are deposited in public and private databases (including 78,405 sequences from Mexico).[7,8] On January 30, 2020, WHO declared the new outbreak as a public health emergency of international concern (PHEIC) and subsequently on March 11, 2020 as a pandemic, allowing the use of novel vaccines developed on platforms not used in humans until then. Conducting clinical trials during this pandemic has also posed additional challenges, including how human trials are conducted and how approval processes are developed by national regulatory agencies. The first COVID-19 vaccine candidate entered clinical trials on March 16, 2020 in the U.S. and, as of today, there are a wide variety of vaccines licensed for human use in 185 countries worldwide.[9]

Currently, more than 12 billion doses of COVID-19 vaccines have been administered worldwide.[10] The countries with the highest number of doses applied are: China (3,465,113,661 doses), India (2,296,521,180 doses) and the United States (664,718,300 doses), while the countries with the lowest number of doses applied are: Tuvalu (25,591 doses), Niue (4,920 doses) and St. Eustatius (4,318 doses).[11]

With dozens of vaccines in clinical trials, the importance of understanding the accelerated processes for development and approval, the different types of vaccines available for human use, and the data related to vaccine safety and efficacy increases. In addition, as more vaccines are approved, it is important to monitor Mexican vaccination data against COVID-19.

This review presents the current vaccines approved against COVID-19 in Mexico, the variants of interest and concern identified by WHO, and provides an opinion on the implications of the emergence of new variants on the safety and efficacy of licensed vaccines.

COVID-19

COVID-19 is a disease caused by SARS-CoV-2 infection, whose clinical spectrum can range from asymptomatic infection to life-threatening complications. The disease can affect the lower respiratory system, bringing with it complications such as acute respiratory distress, multi-organ failure and, in the worst cases, death, which requires hospital care, especially intensive care and mechanical ventilation, and can also affect the gastrointestinal, neurological and cardiovascular systems.[12]

CLINICAL TRIALS.

A clinical trial is a carefully designed study that evaluates the benefits and risks of a specific treatment or medical intervention. These trials comprise 3 main stages, Discovery (identification of the potential new treatment and development of the research protocol), Non-Clinical Testing (performed on animals or tissues) and finally Clinical Development, which is performed following a series of steps known as phases, ranging from Phase I to Phase IV.[13]

In Phase I, research teams evaluate the vaccine in a small group of volunteers in order to obtain information regarding safety and possible side effects; Phase II evaluates the vaccine in a larger group of people, continuing to evaluate safety and risks; Phase III includes an even larger group of participants and begins comparative testing with standard, similar or placebo treatments or drugs and collecting data for its safe use; finally, Phase IV begins public use of the new drug once it has been approved by the body in charge in each country and long-term data on its use is collected.[13]

DEVELOPMENT OF VACCINES AGAINST COVID-19

The SARS-CoV-2 genome has 29,903 nucleotides and codes for 4 structural proteins (S, M, N, and E), 16 nonstructural proteins (Nsp1-16), and 8 accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and ORF14). The transmembrane protein S, which protrudes from the viral surface recognizes the host receptor angiotensin-converting enzyme 2 (ACE2) and mediates entry of the coronavirus into host cells.[14] Protein S remains the primary target of many anti-coronavirus drugs, including neutralization by monoclonal antibodies, vaccines, and other inhibitors.

The technological advances available today have allowed the development of new and diverse types of vaccines, very different from those used during the 20th century. Some examples of these are: Protein subunit (PS) vaccines, which are produced based on viral proteins or peptides that are expressed in a systematic manner in cellular expression systems, be they bacteria, yeast, etc. Non-replicating Viral Vectors (NRV) and Replicating Viral Vectors (RVV), which are designed on the basis of genetically modified viruses that replicate or not in an attenuated manner, carrying within them the genetic material of viral proteins or peptides; DNA (based on viral antigens encoded in a recombinant plasmid, viral proteins are produced by transcription and translation processes within the host cells) and RNA (based mainly on mRNA encapsulated in viral vectors or proteins that are produced in the translation process of the host

cells); Inactivated Viruses (IV), which are produced by inactivating viruses grown in vitro with the aid of chemical reagents, maintaining their integrity as immunogens; Virus-Like Particles (VLP), designed as non-infectious particles based on viral structural proteins expressed in vitro; Attenuated Viruses (LAV), which are based on viruses obtained by reverse genetic methods or adaptations to reduce their virulence and to be used as non-pathogenic antigens.[15, 16]

PFIZER-BIONTECH BNT162B2, THE FIRST VACCINE.

The first vaccine approved for emergency use (USA) during the COVID-19 pandemic in the world by WHO was the vaccine produced by Pfizer-BioNTech Pharmaceuticals.[17] It is a modified mRNA vaccine, approved on December 31, 2020 that codes for the viral spike protein, which enables the immune system to produce antibodies against the antigen.[18] The vaccine is designed for a base schedule of 2 doses administered between 4 and 8 weeks in 5 year-old people and older. A booster dose is administered in order to restore the effectiveness of the vaccine within 4 to 6 months after completion of the schedule and a second booster for older or immunocompromised persons. Adverse events to the vaccine include myocarditis, especially in males, although in a very small percentage of vaccinated persons.[19] The vaccine is currently marketed under the name Comirnaty.

MODERNA VACCINE (SPIKEVAX)

Vaccine approved by WHO on April 30, 2021, produced by Moderna Pharmaceuticals. Like the first one, it is an mRNA vaccine that encodes the production of the viral spike protein and enables the immune system to develop an immune response against the antigen.[20] A vaccination schedule of 2 doses is recommended, applied between 4 weeks and booster doses from 6 months after completion of the basic schedule in persons from 6 months of age. Caution is recommended in persons who have presented anaphylaxis and should be administered only in settings with the capacity to treat it. Myocarditis has been reported as a very rare adverse effect for all vaccines designed under the mRNA platform.[21] It is marketed under the name Spikevax.

ASTRAZENECA VACCINE (AZD1222 OR CHADOX1-S)

The AstraZeneca/Oxford vaccine was licensed for emergency use on February 15, 2021 by WHO to increase the number of vaccines available worldwide.[22] It is manufactured by the pharmaceutical company AstraZeneca in association with the University of Oxford and is a monovalent vaccine, composed of an adenovirus vector (chimpanzee adenovirus) incapable of replication and whose material codes for the SARS-CoV-2 spike protein.[23] It should be administered to persons 18 years of age and older in a 2-dose schedule with 8 to 12 weeks difference between each dose and a booster dose 4 to 6 months after completion of the schedule. Adverse effects of the vaccine include thrombosis syndrome with thrombocytopenia (TTS) in a proportion of 1 per 100,000 persons, with most cases reported in European countries.[24] It is currently marketed under the name Vaxzevria.

JOHNSON & JOHNSON VACCINE (JANSSEN).

The vaccine, approved for use by the WHO on March 12, 2021, is produced by the pharmaceutical company Johnson & Johnson.[25] It was designed as a recombinant vector vaccine, which employs as a vector a human adenovirus (adenovirus type 26 vector, Ad26) capable of expressing the SARS-CoV-2 spike protein.[26] The vaccine is administered in a 2-dose schedule from the second month after the first vaccine is administered and only to persons over 18 years of age. The vaccine may present effects such as thrombosis syndrome with thrombocytopenia (TTS) and Guillain-Barré syndrome (GBS) in a small population of vaccinated persons.[27]

SINOPHARM VACCINE

The Sinopharm vaccine is a vaccine produced by Beijing Institute of Biological Products Co Ltd (BIBP). The WHO authorized its use on May 7, 2021.[28] It is an inactivated viral vaccine (a traditional vaccine).[29] Its use is restricted to persons over 18 years of age, with the application of 2 doses 3 weeks apart, followed by a booster dose 4 months after the second dose. Rare complications with respect to its application include hypersensitivity reactions and anaphylaxis.[30]

SINOVAC VACCINE (CORONAVAC)

The pharmaceutical company Sinovac is in charge of producing the vaccine known as CoronaVac. The authorization for emergency use was given on June 1, 2021 by the WHO under the premise of the need for vaccines to solve the inequality in access to them.[31] The vaccine has been developed, like the Sinopharm vaccine, as a viral vaccine from samples isolated from hospitalized patients, samples closely related to the original strain.[32] It should only be applied to persons over 18 years of age, with 2 doses applied between 2 and 4 weeks, and a booster dose after the fourth month from the last dose. Side effects may include hypersensitivity reactions and anaphylaxis.[33]

BHARAT VACCINE (COVAXIN®)

Developed by Bharat Biotech, the vaccine known as COVAXIN® was licensed for emergency use on November 3, 2021.[34] It has been designed as a vaccine of inactivated virions, unable to replicate.[35] It can be administered to persons 18 years of age and older, in a two-dose schedule with 4 weeks difference between each one, together with a booster at 4 or 6 months after completing the schedule. Anaphylaxis has been reported as a side effect of the administration of this vaccine. [36]

NOVAVAX VACCINE (COVOVAX™)

It was authorized for emergency use by the WHO on December 17, 2021, in order to increase the catalog of available vaccines and allow access to the most marginalized countries, introduced and marketed under the name CovovaxTM is produced by the pharmaceutical company Novavax.[37] CovovaxTM is a protein-based vaccine, specifically, nanoparticles of recombinant SARS-CoV-2 spike protein.[38] Applicable to persons 12 years of age and older, 2 doses are recommended at an interval of 3 weeks together with a booster dose 4 months after the initial schedule. Side effects of vaccination include anaphylaxis and, in very rare cases, myocarditis and pericarditis.[39]

CANSINO VACCINE

The vaccine known as Ad5-nCoV, produced by the pharmaceutical company CanSino Biologics, received authorization for emergency use in March 2022. Although in many countries it was already being used prior to this authorization, as in the case of Mexico, where it was approved for emergency use in February 2021.[40] It is a recombinant vector vaccine that uses a human adenovirus (Ad5) expressing and presenting the spike protein as a vector.[41] Applicable only in persons older than 18 years of age in a single initial dose and a booster after the fourth month of vaccination. Reported adverse effects include anaphylaxis, as well as thrombosis syndrome with thrombocytopenia (TTS) in a small number of vaccinated persons.[42]

VACCINES USED IN MEXICO WITHOUT WHO APPROVAL AND IN DEVELOPMENT

SPUTNIK V VACCINE

Also known as Gam-COVID-Vac, Sputnik is a vaccine of Russian origin that uses adenovirus 26 and 5 vectors (Ad26 and Ad5 respectively) that allow the expression of the SARS-CoV-2 characteristic spike protein, being the only vaccine to use the technology of 2 different adenoviruses. The vaccine has been designed by the Gamaleya National Center of Epidemiology and Microbiology of Russia (GNCEM).[43] Despite not having been authorized for emergency use by the WHO, Mexico decided to use it as part of its catalog in the vaccination campaign against COVID-19 in February 2021, a decision made by the Federal Commission for Protection against Health Risks (Cofepris).[44]

ABDALA VACCINE

Abdala is a vaccine developed based on recombinant protein subunits, which uses the yeast P. pastoris as expression vector. It has been designed by the Center for Genetic Engineering and Biotechnology of Cuba (CIGB).[45] It does not have WHO authorization for emergency use, which has not been an impediment for countries such as Mexico to start using it in their vaccination campaigns. Cofepris authorized its use in the country in December 2021, although the first Abdala vaccines arrived in our country at the end of November 2022.[46]

PATRIA VACCINE

Of Mexican origin, Patria is a vaccine that is in the final stage of development in conjunction with the National Council of Science and Technology (Conacyt) and the laboratory Avi-mex S.A. de C.V.[47] The vaccine has been developed based on a vector of Newcastle disease virus (NVD), an avian virus, which allows the expression of a highly optimized version of the viral spike protein both on the surface and in infected cells.[48]

SARS-COV-2 VARIANTS

Variants of a virus appear through nucleotide changes that occur naturally in the genome during replication. These genomic changes provide the virus with a wide range of advantages with respect to replication, transmission, and immune evasion.[49] Since the initial appearance of the virus in 2019 the virus genome has undergone more than 10,000 modifications due to the rapid spread among the population.[50]

The WHO has classified SARS-CoV-2 variant strains into two major groups: Variants of Concern (VOCs) and Variants of Interest (VOIs); a wide range of VOCs have emerged from the initial strain, that isolated in Wuhan in 2019. VOCs are defined, by the Centers for Disease Control and Prevention (CDC), as those that have increased transmissibility, virulence, resistance to available vaccines or acquired immunity to vaccines following previous infection, and have developed the ability to evade diagnostic methods for identification. Currently, there are 5 variants classified as VOCs and 9 classified as VOIs.[49]

VARIANTS OF INTEREST:

WHO defines a VOI as: a SARS-CoV-2 variant that exhibits genetic changes known to affect virus characteristics (transmissibility, virulence, etc.) and that has an identified growth advantage over other variables circulating in more than one WHO region together with an increasing number of cases over time or some other apparent epidemiological impact suggesting a global public health risk. The currently identified VOIs are: Epsilon (ε): Identified in California, United States; Zeta (ζ): Identified in Brazil; Eta (η): Identified in Nigeria and United Kingdom; Theta (θ): Identified in the Philippines; Iota (ι): Identified in New york, United States; Kappa (κ): Identified in India; Lambda (λ): Identified in Peru; Mu (μ): Identified in Colombia; Delta Plus (δ+, B.1 .617.2.1): Identified in India.[49, 51]

VARIANTS OF CONCERN:

WHO defines VOC as a variant of SARS-CoV-2 that meets the definition of VOI and, through a risk assessment, meets one of the following criteria: detrimental change in clinical disease

Table 1. *Effectiveness of vaccines licensed in Mexico before and after the omicron variant, prevention of severe disease.*[27, 30, 36,42, 45,54-57]

Vaccine	Manufacturer	Design platform	Number of doses	Pre-Omicron Effectiveness	Post-Omicron Effectiveness
BNT162b2 (Comirnaty)	Pfizer-BioNTech BNT162b2	mRNA	2	91%	65.5%
			3		67.2-73.9%
Spikevax	Moderna	mRNA	2	98%	75.1%
			3		64.9-66.3%
AZD1222 o ChAdOx1-S	AstraZeneca	VVnr	2	92%	48.9%
			3	94-97%	55.6-70.1%
Janssen	Johnson & Johnson	VVnr	2	94%	74%
Sinopharm	BIBP	IV	2-3	84-94%	Not reported
CoronaVac	Sinovac	IV	2	90%	91.7%
			3	85.1%	98.5%
COVAXIN®	Bharat Biotech	IV	2	78%	Not reported
			3	Not reported	
Covovax™	Novavax	PS	2	100%	70.1-83.5%
			3		
Ad5-nCoV	CanSino Biologics	VVnr	1	70%	Not reported
			2		
Sputnik V	GNCEM	VVnr	2	85.7%	87.6%
			3	97.5%	97%
Abdala	CIGB	PS	3	Not reported	94.1-99.4%

mRNA: Messenger RNA. VVnr: Non-replicating viral vectors. IV: Inactivated viruses. PS: Protein subunits .

severity, change in COVID-19 epidemiology that causes a substantial impact on the ability of health systems to provide care for patients with COVID-19 or other diseases and, therefore, requires major public health interventions, or significant decrease in the effectiveness of available vaccines to protect against severe disease.[51] The following VOCs have currently been identified: Alpha (α): Detected at the end of September 2020, becoming the predominant strain in the United Kingdom. Beta (β): Detected in October 2020, it became, at the time, the predominant strain in South Africa. Gamma (γ): Detected in Brazilians visiting Japan in January 2021, responsible for reinfection in Manaus. Delta (δ): Detected in India in December 2020. Omicron: Detected in November 2021 in South Africa, currently the dominant strain worldwide. These VOC share common modifications on the S protein and particular changes in each of them.[49] The symptoms detected in the infection caused by these variants may vary from case to case, as mentioned above, the Omicron variant is the dominant variant worldwide at present and the characteristic symptoms of this variant are: runny nose, headache, sore throat, sneezing, persistent cough and hoarse voice. On the other hand, the characteristic symptoms of the Delta variant (dominant prior to Omicron) are: runny nose, headache, sneezing, sore throat and loss of smell.[52]

OMICRON SUBVARIANTS

After the appearance of the Omicron variant, a large number of subvariants have rapidly emerged. Currently, they can be found scattered all over the world, among these there are the subvariants: BA.1, BA.2, BA.5. BQ1.1 and XBB which can be immuno-evasive to antibodies produced by available vaccines.[53]

EFFECTIVENESS OF VACCINES AGAINST SARS-COV-2 OMICRON VARIANTS

Because the currently existing vaccines began their development in early stages of the pandemic, they were not designed to act in the same way on the variants of the virus that appeared. The dominant variant in the world is omicron, even so, the companies responsible for its manufacture and the WHO have provided information assuring its effectiveness in vaccination schedules of 2 or more doses. This information is summarized in Table 1.

CONCLUSIONS

Vaccines represent one of the most impressive advances in public health in the history of mankind, playing a fundamental role in reducing the transmission and, in some cases, eliminating

infectious diseases. In the first 20 years of this century, we have faced a series of public health emergencies of international concern and two pandemics (Influenza H1N1 2009 and COVID-19). Vaccines have played a central role in the global response to these threats. To be used in humans, vaccines undergo a rigorous research and development process to ensure their safety and efficacy, and continue to be monitored long after approval by national regulatory agencies. All of this places vaccines at the forefront of biotechnology innovation, with the complexity and costs inherent in their research, development, intellectual property protection, clinical trials and commercialization. The extraordinary development of new vaccines against COVID-19 is an example of this in modern history, however, the emergence of several variants of the original virus may render current vaccines obsolete and pose a new challenge for future vaccine development. Therefore, it is necessary to continue developing new techniques and technologies for the production of new vaccines, as well as a constant vigilance towards any potential danger that could lead to a similar or worse situation in the future.

In Mexico, 10 vaccines have been authorized by the national regulatory agency, Cofepris, including two vaccines (Sputnik V and Abdala) not authorized by WHO for human use. This situation requires analysis and in-depth discussion by expert groups. Our country must incorporate effective preparedness and response mechanisms that include innovative vaccine production platforms. Failure to do so will condemn us to the technological dependence that has already cost us so many resources and so many human lives.

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