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Research Article

Vaccines: Origin and evolution throughout history

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Abstract

Throughout the history of medicine, vaccines have been one of the most used weapons by humans to prevent diseases and create immunity, having a great impact on both society and the health of individuals and communities, constituting an authentic guarantee to achieve stability and the maintenance of the public health of the population.

In this monograph, a compilation, reflective, detailed, and specific study of vaccines within the history of medicine are carried out through a bibliographic search to know in depth the vaccines, their origin, evolution, and role-played throughout all time.

Vaccination is one of the greatest advances in public health at the global, national, community, and individual levels, the introduction of immunization has allowed unquestionable benefits, impacting social systems, reducing the cost of treatments, and the incidence of infectious diseases and the mortality from them.

Vaccines will have, among others, a social and economic impact, since preventing diseases favors the economic level, the quality of life, and social well-being.

Vaccines and their administration techniques evolve in parallel since over time both have progressed, they have experienced progress both in their preparation and in the way they are administered, and with it the material and human resources used to do so.

Abbreviations

BCG: Bacillus Calmette-Gurein; B. Pertussis: Bordetella Pertussis; CAV-AEP: Vaccine Advisory Committee of the Spanish Association of Paediatrics; COVID-19: Coronavirus; DeCS: Descriptors in Health Sciences; DPT: Diphtheria, Tetanus and Pertussis; FDA: Food and Drug Administration; Hib: HaemophilusInfluenzae type b; MeSH: Medical Subject Headings; NIH: National Cancer Institute; WHO: World Health Organization; PAI: Expanded Program on Immunization; RAE: Royal Spanish Academy; HPV: Human Papilloma Virus; VPO: Live Attenuated Virus

Introduction

Throughout the history of medicine, man has sought not only the cure of diseases but also their prevention and immunity, one of his most used weapons for this being vaccines. For centuries, through the discovery of vaccines, both the eradication and the prevention and control of diseases and infections have been achieved worldwide, constituting one of the greatest successes of public health, carrying out important research and advances in the field. Of microbiology and immunology.

Vaccination has had the purpose of protecting and immunizing the individual and the community against certain diseases, although it would not be until the 20th century when it was implemented in the form of massive vaccination campaigns and routine programs with a public health objective aimed at achieving disease control in the population. In such a way the importance of vaccines lies not only in their ability to eradicate the disease but also in the prevention of subsequent infections through inoculation with a potentially infectious agent.

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Mass vaccination population policies are very recent, and consequently, we still have part of the adult population, before the vaccinated populations, who, not benefiting from this preventive method, could come into contact with the infectious agent and, therefore, be the cause of the incidence of some outbreaks of these diseases subjected to vaccination programs. Likewise, vaccines administered in childhood that do not produce lifelong immunity must have booster doses after years so that they cannot be infected in the future. Therefore, it is essential to extend vaccination policies and strengthen their impact on infection control.

Vaccines have evolved. Since the seventh century, there is evidence of its origin when Indian Buddhists used them to be immune to the effects of poisonous animals [1]. Today, with the use of new technologies, the production of vaccines is increasingly sophisticated, and with it their development. In this sense, it is important to demonstrate not only their immunogenicity but also their safety and reactogenicity, since their effectiveness to tackle a wide range of diseases allows these conditions to be reduced to residual limits.

Currently, in the XXI century, specifically in this year 2020, and in the face of the globalized health crisis, in which we are submerged, suffering by the global pandemic of the Coronavirus (COVID-19), the activities carried out both in research and preventive nature They have focused on the restoration of public health through the empirical search for a vaccine to stop the massive spread of the pandemic and its subsequent relief and control of the disease.

The impact of vaccination on the population has been tremendously important since, except for the achievement of hygienic control of water and hand hygiene, there has been no other preventive or therapeutic measure, not even antibiotics, which has had the greatest effect on reducing the mortality of the world's population [2].

Vaccines prevent and reduce deaths worldwide by training individuals to protect themselves and defend themselves against microorganisms that attack them, causing their immune system to produce antibodies, constituting one of the public health measures to save lives. Likewise, they help control, reduce, eliminate and even eradicate the incidence of many infectious diseases. They manage to reduce mortality and protect not only individual health but also sometimes create community immunity both for the general population and for certain risk groups.

They have both social and economic benefits since they will lead to savings in the cost of treatments. It is for all these reasons that the incorporation of immunization has made unquestionable benefits possible. As vaccines constitute a real guarantee to achieve stability and maintenance of the public health of the population throughout all time, it has been considered to carry out this monograph based on them, since vaccines have lasted since the beginning. From time to the present, having a great impact on society and the health of its individuals and communities.

Through this document, it is intended to investigate, deepen and reflect on the role that vaccines have developed throughout history and continue to develop today in medicine, how they have evolved and what they have contributed. Not only have the administration techniques and geographical expansion of vaccines been analyzed throughout history, the evolution of their preparation and preparation has also been studied from their origins to the present, where the objective of obtaining vaccines, powerful, safe, cheap, easy to prepare, store and administer, if possible with a single application and without the need to administer reinforcements.

For all the above, we proceed in this work to the compilation, reflective, detailed, and specific study of vaccines within the history of medicine to know in depth the vaccines, their origin, evolution, and role-played throughout the history of medicine. Throughout all times, carrying out a systematic bibliographic search and review for its elaboration.

Development of the theme

Infectious diseases have been and are one of the main scourges of humanity, whose health, social, economic, political, and military impact are devastating [3]. Many historians blame different plagues for the deterioration of many cities of the Roman Empire and affirm that this contributed to its fall. To the known cases of epidemics that led to the death of 25% of the Aztec population in a single year, or the death of 24,000,000 Europeans during the years of the Black Death, many other episodes must be added. The misnamed Spanish flu killed 3% of the world's population between 1918 and 1920, five times more deaths than those caused by the Great War that had just ended.

Discoveries are determining factors in social changes. The desire to improve that we find in the human being and the constant search for knowledge and knowing the pillars on which those revelations of which we are creditors are based. In the same way that we have surpassed ourselves in different spheres, and among them in medicine, perhaps as a result of the need to know the interior of our body and to treat what affects us, vaccines appear as a finding of great importance in the so-called preventive medicine [4]. So much so, that from the point of view of public health interventions there is no better strength than that which allows preventing the transmission or appearance of the disease. Within the field of infectious diseases, vaccines have become the best weapon, allowing the non-development of numerous diseases to be controlled [3].

According to the World Health Organization (WHO), a vaccine is understood [5]: as "any preparation intended to generate immunity against disease by stimulating the production of antibodies. It can be, for example, a suspension of killed or attenuated microorganisms, or products or derivatives of microorganisms. The most common method of administering vaccines is by injection, although some are administered by nasal or oral spray.

The WHO establishes three levels of preventive action: primary, secondary, and tertiary, acting the last two when

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the disease has already occurred, while at the primary level it acts in the pre-pathogenic period. It includes health protection measures, such as environmental sanitation and food hygiene, and health promotion and disease prevention, such as preventive immunizations, chemoprophylaxis, and health education. Regarding the transmission mechanisms, the most important health actions are, among others, both sanitation and the supply of drinking water, and mechanical barriers, such as the use of gloves or masks. On the susceptible healthy person, action can be taken to reduce susceptibility to infection or increase resistance, through chemoprophylaxis, passive immunization, immunoglobulins or seroprophylaxis, and active immunization or vaccines [6].

The objectives of vaccination are to acquire both individual immunities, through which the individual receives active immunity similar to that conceived by natural infection, but without presenting the clinical picture; as a group, with which the chain of transmission is broken and results are obtained that are greater than the sum of individual immunities. Among the most notable vaccines, we can highlight, among others, tetanus, diphtheria, whooping cough, polio, triple viral (measles-rubella-mumps), anti-Haemophilus influenza type B [7].

For the WHO, immunization "is an essential component of the human right to health as well as a responsibility of all individuals, communities, and governments, and should be considered as such" and estimates that thanks to vaccination some 2.5 million deaths are prevented. Deaths each year, affirming that through vaccination children immunized and protected from the threat of preventable diseases have the opportunity to develop and more possibilities to take advantage of their full potential. These advantages are further enhanced by the vaccination of adolescents and adults. Vaccines and immunization are considered an essential investment in the future of society as part of a comprehensive set of interventions to prevent and control disease [8].

From this work, a bibliographic analysis has been carried out, to analyze the origin, evolution, changes, and modifications that vaccines have suffered throughout their history, in addition to what they have meant and what significance they have had. in the contribution, development, and improvement of public health and with it of society.

For the preparation of this document, a systematic bibliographic search and review have been carried out, in the Spanish and English languages, identifying the keywords and fundamental concepts in the DeCS and MeSH Descriptors of Health, during February and March of 2020, in the following databases: Virtual Library of the Andalusian Public Health System, Cochrane Plus, Cuiden, Dialnet, Enfispo, ÍnDICEs-CSIC, PubMed and Scielo and as well as information provided by official bodies and health organizations and associations. The search strategy was to carry out a systematic search for studies carried out and documents related to vaccines without considering their date of publication, since it is intended to make a journey through the history of vaccines, and for this, it is necessary not only for current documentation, also of yesteryear, to go back to its origins.

Although vaccines have been linked to the evolution of human history, it was in 1798 when Edward Jenner coined the term with the discovery of the smallpox vaccine and marked this fact a before and after in the history of vaccines. That is why in this monograph, before beginning the development of the history of the vaccine itself, we will refer to the prehistory of vaccines that is, to the account of the first signs of their existence, and then move on to its history and evolution.

Prehistory of vaccines

The first indications of the existence of vaccines appear in the seventh century when Indian Buddhists ingested snake venom to be immune to its effects. Although the first writings related to vaccination, specifically smallpox vaccines, date from the 11th century and correspond to texts of Chinese literature: "The correct treatment of smallpox". This book was attributed to a Buddhist nun who lived during the reign of Jen Tsung (1022 to 1063) and practiced the art of smallpox inoculation from patients suffering from smallpox. Another Chinese medical book, "The Golden Mirror of Medicine," described four forms of smallpox inoculation. However, in China, the belief persisted that variolation (or variolation: smallpox inoculation) was a foreign technique, originally from India [9].

Smallpox inoculation was originally practiced in China and India. This method spread throughout Asia Minor and the Near East and from there it passed to the Western world at the beginning of the 18th century, thus constituting a new therapeutic tool to defend against the disease, which implied a change of innovative concept in the empirical verification of the who had suffered from smallpox and had survived are exempt from it forever [9].

SIGLO	Principales acontecimientos en la prehistoria de las vacunas en el mundo oriental.
VII	Los primeros indicios de la existencia de vacunas.
XI	Los primeros escritos relacionados con la vacunación, vacunas contra la viruela.
XVII	Se practica la inoculación más o menos de forma generalizada.
XVIII	Aparición de dos escuelas: la escuela de Huzhou y la escuela de Songjiang.

In the seventeenth century, the Chinese practiced inoculation more or less widely in three ways: on the one hand, they introduced a piece of cotton soaked in pus extracted from fresh pustules, taken from sick individuals, into the nostrils, with the exception that these individuals were passing the disease smoothly. A second way was to use the scabs that they collected a year before and by drying them, introduce them through the nostrils using small bamboo canes. Interestingly, boys were introduced through the left nostril and girls through the right nostril. And a third way was to put a healthy child in the used clothes of a variloso. Thus, at the end of the 18th century, there were two schools: the Huzhou School, which preferred to use fresh pus, and the Songjiang School, which recommended dried scabs. Both schools gave instructions on the development of the techniques and the best time of year to use them: spring or autumn [10].

On the other hand, in Eastern India they used a method based on producing a strong irritation on the forearm,

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immediately, they made the application with cotton soaked with pus from a variloso. This method of inoculation was recognized as safer than the Chinese and was the one that spread to the Middle East. Women had an important role in the application and dissemination of the inoculating practice and they show that the societies of the time, dominated by men, leave little space for women, therefore there is a clear separation of the sexes. The girls were inoculated from a very young age to preserve their beauty so that the signs of scarification would not be noticed, those in charge of this work were also women who had acquired skills over years of practical experience. Inoculation becomes a female practice where the woman exerts her influence on health. In the Western world, the oldest mention of variolation is found in a note by Heinrich Vollgnad, published in the Bulletin of German scientific society in 1671. Greek, Welsh, Scottish or Russian peasants were familiar with this practice, which he also described. The Danish doctor Thomas Bartholin in 1673. Years later England would become the place where much of the medical knowledge of the time was collected. The tradition of scientific societies, born in this country, will contribute decisively to the history of smallpox [11].

SIGLO	Principales acontecimientos en la prehistoria de las vacunas en el mundo orientaL.
VII	Los primeros indicios de la existencia de vacunas.
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In 1680 the Royal Society of London publicly recognized the observations of a Dutch scientist, Antonie Van Leeuwenhoek, on the existence of microscopic unicellular organisms, stating that there could be "entities" that cause great epidemics, although it had already been proposed even before the observations of Leeuwenhoek by the likes of GirolamoFracastoro. But it was the work of the Dutchman and later of other scientists such as Semmelweis (in the field of hygiene) and John Snow (in the field of epidemiology) that supported the formulation of the so-called Germ Theory. This theory postulated that many of the most common diseases were really due to infections by microorganisms and got definitive support from the work of Louis Pasteur and Robert Koch. Many of the causative agents of major epidemics were described in the 19th or early 20th century, and identifying them led to an era of innovation in the prevention, diagnosis, and treatment of infectious diseases [12].

Then, and as announced, we will proceed in the next section to carry out the development of the history of vaccines as such, once we have previously detailed and analyzed what their first signs of them were.

History of vaccines

The era of vaccination was not inaugurated until the end of the 18th century, first Francis Home, an English doctor, made some attempts at immunization against measles, and secondly, his countryman Eduardo Jenner, a British doctor, designed the first vaccine against smallpox and thus in In June 1798, a work written by Edward Jenner (1749-1823) was published that would revolutionize the fight against smallpox, whose consequences until then were atrocious for humanity. In said work, a variant in inoculation practice based on the empirical observation of people infected by smallpox developed in cattle that became rebellious to human smallpox was captured. The beginning of this discovery took place on May 14, 1796, when Jenner injected, through two superficial cuts in the arm of an 8-year-old boy named James Phipps, material from a cowpox sore in a woman who milked cows. Later he repeated the same experiment, this time adding a small amount of smallpox to the same child, who became immunized against smallpox [13].

The Jennerian method was called a vaccine, and for this reason, its discoverer will be recognized worldwide as the father of vaccination. Spain soon adopted this method and in this way, the doctor and academic Francisco Piguillem y Verdaguer (1770-1826) inaugurated his practice on December 3, 1800, in Puigcerdá (Catalonia). Cattle pus was sent from Paris by François Colon (1764-1812), thanks to the contact between Catalan and French medicine [14].

During the reign of King Carlos IV (1788-1808) he decided to undertake vaccination campaigns in all his kingdoms. The most important overseas campaign was the one directed by the doctor Francisco Xavier de Balmis and which received the name of the Royal Philanthropic Expedition of the Vacunale (1803-1806). The feat lived by the components of this expedition can be considered the first act of international health cooperation carried out by our country and was the first great step in the eradication of smallpox in the world [15].

In 1885, Dr. Louis Pasteur showed that disease could be prevented by using weakened germs. He did this by using a vaccine to successfully prevent rabies in a boy named Joseph Meister, who had been bitten by a rabid dog [16]. This same year, the Spanish bacteriologist Jaime Ferrán discovered an anticholera vaccine, which was tested in the Alicante epidemic [17]. In 1890, Emil Von Behring, a pioneer in immunology and discoverer of vaccines against tetanus and diphtheria, was awarded the first Nobel Prize in Physiology and Medicine and was called the "savior of soldiers and children", starting with it the development of immunology [18].

AÑOS	principales acontecimientos en la historia de las vacunas.
1798	Publicaciones de Jenner sobre la lucha contra la viruela.
1803	Primera acción de cooperación sanitaria internacional: "La Real Expedición Filantrópica de la Vacunale (1803-1806).
1885	Pasteur: Vacuna antirrábica. Ferrán: Vacuna Anticolérica.
1890	Emil Von Behring: Vacunas contra Tétanos y Difteria.
1896	Implementación de la serología diagnóstica. Wriyht: Vacuna antitifoidea.
1922	Albert Calmette y Camile Guerin: Vacuna BCG.
1926	Thorvald Madsen: Vacuna B. Pertussis.
1936	Vacuna antigripal de primera generación.
1937	Max Theiler: Vacuna de la fiebre amarilla (Cepa 17-D).
1944	Ley de Bases de Sanidad: declara obligatoria la vacunación contra la viruela.

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The Ministry of Health, Consumption and Social Welfare (2006) in the Training Programs of Specialties in Health Sciences reports that the word immunology derives from the Latin immunis which means "without charge", understanding by charge a tax, law, or disease. Those individuals who do not succumb to disease when infected are said to be immune and this state of disease-specific resistance is called Immunity. It further states that the WHO defined immunology as a discipline dealing with the study, diagnosis, and treatment of patients with diseases caused by alterations in immunological mechanisms and situations in which immunological manipulations form an important part of the treatment and/or prevention [19].

In 1899 bacteriology was very advanced, Eberth had shown that Bacillus Typhosus was the causative agent of typhoid fever in 1880, paratyphus bacilli were discovered later. Diagnostic serology was implemented in 1896 and with it the Typhoid vaccine of Wright, vaccination beginning in that same year [20]. During the first years of the preparation and use of vaccines, their elaboration and control were a completely rudimentary process. There were no standardized methods to check the purity of the bacterial seeds used, therefore, strict sterility tests were not always carried out and potency tests on animals were less frequently carried out. This lack of precaution caused accidents, for example in 1902 one of the vaccines against the bubonic plague, prepared by the also Russian WaldemarMondecar Wolff, was contaminated with Clostridium Tetani causing the death of 19 people from tetanus in the town of Mulkwai in India. (twenty-one).

Another advance in vaccination was the discovery of the vaccine in 1922 against Tuberculosis Bacillus Calmette-Guerin (BCG) which owes its name to its discoverers Albert Calmette and Camile Guerin [22]. With this vaccine, one of the greatest catastrophes in the history of vaccine safety occurred, in 1930, in the German city of Lubeck, 75 infants died after being vaccinated with BCG, which contained a strain of Mycobacterium Tuberculosis [23]. The first whole-cell vaccine was produced by Thorvald Madsen, in 1926, in Denmark, composed of a suspension of Bordetella pertussis (B. pertussis) [24].

The first references we have to the flu are found in the writings of Hippocrates, although the first detailed description appears in the 17th century by the Englishmen Willis and Sydenham. Since then, 15 pandemics have been recorded, approximately 4 in each century. In the 20th century, the most serious was that of 1918, which produced 200 million cases among which 10 million deaths were recorded, and the others took place in 1957, 1970, and 1978. The first generation flu vaccine would reach us in the year 1936 and be based on whole inactivated viruses. It was withdrawn from the market due to its great reaction capacity by generating significant adverse effects [25]. In 1937, the vaccine against yellow fever (strain 17 D) appeared, which had been developed in 1930 by Max Theiler, who received the Nobel Prize in Physiology and Medicine in 1951 [26].

AÑO	principales acontecimientos en la historia de las vacunas: premios nobel.
1890	EMIL VON BEHRING. PREMIO NOBEL DE FISIOLOGÍA Y MEDICINA. Pionero de la Inmunología. Descubridor de las Vacunas contra el Tétanos y la Difteria.
1951	MAX THEILER. PREMIO NOBEL DE FISIOLOGÍA Y MEDICINA. Descubridor de la Vacuna contra la Fiebre Amarilla (cepa 17 D).

Throughout the 19th century, orders and laws were created to implement smallpox vaccination, but it was not until 1944, with the Health Bases Law, when smallpox vaccination was declared compulsory, achieving its elimination in 1954, except for an isolated outbreak due to an imported case from India in 1961 in the capital. On May 8, 1980, in Geneva, the WHO officially declares the eradication of smallpox in the world, becoming the first great success of the WHO in the eradication of infectious diseases. The last patient who had smallpox was Ali MaowMaalín, 23 years old in 1977, a resident of Merca (Somalia) [3]. The great forgotten man is made, who would become in 1963 the man who saved the most lives during the second half of the 20th century, he is not well known, but today almost all children receive the so-called Triple Viral vaccine, measles vaccine, mumps, and rubella, which she developed from the smear she collected from her daughter's guarantee [27].

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1890	EMIL VON BEHRING. PREMIO NOBEL DE FISIOLOGÍA Y MEDICINA. Pionero de la Inmunología. Descubridor de las Vacunas contra el Tétanos y la Difteria.
1951	MAX THEILER. PREMIO NOBEL DE FISIOLOGÍA Y MEDICINA. Descubridor de la Vacuna contra la Fiebre Amarilla (cepa 17 D).

The Community Nursing Association tells us that to Dr. Florencio Pérez Gallardo, we owe the gestation and realization of the First National Vaccination Campaign, 1963 the first massive and free vaccination campaign against polio took place, aimed at children between 2 months and 7 years. Two doses were applied, the first with monovalent Live Attenuated Virus (VPO) oral vaccine and the second with trivalent (VPO). Two years later, another massive campaign is carried out, in which the two doses of trivalent VPO are used. Likewise, vaccination against Diphtheria, Tetanus, and Pertussis, (DPT) or Triple Bacterial, which contains diphtheria toxoids (against Diphtheria) and tetanus toxoids (against Tetanus), as well as protein fragments of the B. Pertussis bacteria that cause whooping cough in children between 3 months and 3 years of age. Such was its success of it that from then on, two annual campaigns were carried out, in spring and autumn, continuously. The creators of the inactive and active poliomyelitis vaccine were, respectively, Dr. Jonas Salk and Dr. Albert Sabin, a disease that, when not fatal, left sequels with enormous repercussions for life [14].

In 1968, a vaccination campaign against measles was carried out in several provinces of the nation, encompassing children between 9 and 24 months [16]. In the 1970s, vaccines

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reached their peak, thus the rubella vaccine appeared in 1969, the meningococcal A + C vaccine in 1972, the Japanese encephalitis vaccine in 1974, and the rabies vaccine from diploid cells appeared in 1976. and in the 1980s we must point out the appearance: in 1981 the hepatitis B vaccine, in 1982 the meningococcal A, C, Y, W-135 vaccine, in 1983 the chickenpox vaccine, in 1984 the Haemophilus influenza type B, in 1986 the recombinant hepatitis B vaccine, and in 1987 the Haemophilus type B conjugate vaccine, stating that in the last quarter of the 20th century the development of vaccines acquired special relevance9. Special mention should be made of one of the great achievements in the history of Cuban medicine, which was undoubtedly the discovery in 1987 of the meningococcal B vaccine by Dr. Concepción de la Campa [28].

The Community Nursing Association tells us that throughout the 20th-century mass vaccinations of smallpox, tuberculosis (BCG), DPT, attenuated and inactive vaccines against poliomyelitis and measles were carried out, first in developed countries, and later in developed countries. in developing countries, through the Expanded Program on Immunization (EPI) that the WHO implemented in 1974 to make vaccination available. In 1993, vaccination against hepatitis B and yellow fever was included in this program in those countries where the disease is endemic. In 1998, five years later, vaccination against Haemophilus influenza type b (Hib) was introduced [14]. The Community Nursing Association tells us that thanks to the massive vaccination campaigns mentioned above, it is estimated that 5 million deaths from smallpox, 2.7 million from measles, 2 million from neonatal tetanus, and 1 million from whooping cough have been avoided per year. , 600,000 for paralytic poliomyelitis and 300,000 for diphtheria. Without a doubt, the list of serious diseases that have been eradicated or whose numbers have been drastically reduced thanks to vaccines, and continues to increase [14].

The National Cancer Institute (NIH) reports that in the 21st century, specifically in 2006, the vaccine that protects against infection by the Human Papillomavirus (HPV) appears. HPVs are a group of more than 200 related viruses, and of these, about 12 can cause some types of cancer. The US Food and Drug Administration (FDA) announced the approval of three vaccines for the prevention of infection caused by this group of viruses [29].

From the genetic point of view, pathogens, like human populations, are not homogeneous but have accumulated changes throughout their evolutionary history. There are pathogens with a high genetic diversity, which even present pathogenic and non-pathogenic types, as is the case with Escherichia coli, and highly specialized pathogens with very low diversity, as is the case with leprosy and tuberculosis bacilli. Some exhibit a high level of recombination, eg Neisseria meningitides and some viruses, while others are genetically monomorphic. In the context of vaccines, this preexisting variation must be taken into account, as well as the ability of the pathogen to mutate and find variations that escape the action of the immune system or the protection conferred by the vaccines. All these aspects related to the evolution of the pathogen can affect the development and universality of new vaccines. Through a better understanding of the interaction between the immune system and the pathogen, better vaccines can be developed, since with this we can distinguish those elements that are part of the protective immune response against those interactions that can benefit the pathogen [3].

Currently, there is a large number of emerging infectious diseases for which there are no vaccines, some with devastating consequences such as COVID-19, against which the clock is being fought to find an effective and safe vaccine against it. It is essential to develop a vaccine, in addition to an adequate design, to take into account the genetic diversity of the pathogens. Its study can give us indications of how the pathogen adapts to the pressure of the immune system and what part of the immune response is beneficial for the host and what part for the pathogen. Understanding this relationship will make it possible to predict how effective and universal a vaccine can be and help to design them better.

Then, in the following lines, as it could not be otherwise, we proceed to refer to the origins and evolution of vaccine administration techniques throughout its history.

Vaccine administration techniques

The Royal Spanish Academy (RAE) defines the term to vaccinate as [30]: "inoculate a vaccine to a person or an animal to provoke a defense response in them and protect them from a specific disease". And he defines the term inoculate [31]: "introduce into an organism a substance that contains the germs of a disease".

The Advisory Committee on Vaccines of the Spanish Association of Pediatrics (CAV-AEP) defines the vaccination act as32 "the set of processes, protocols, and techniques that are applied from the moment a user is received from the health system demanding action in relation to vaccinations, until the moment in which this action has been completed". Therefore, it is not limited exclusively to the fact of the administration of the vaccine preparation, but rather includes a series of differentiated processes such as the verification of the vaccination document, the previous anamnesis, the choice and preparation of the biological product, the asepsis of the skin, the choice of route and injection site, the correct disposal of waste, the prevention of accidental occupational exposures, the prevention of adverse events and the vaccination record. The act of vaccination or action and effect of vaccinating is a key element in vaccination practices to ensure greater efficacy and safety of vaccines and will entail not only the act of vaccination itself but also a series of prior preparations and some aftercare.

For the CAV-AEP (2020), the vaccination act would go through three stages [32]:

- Preparations include necessary material and equipment; preparation to act in case of immediate adverse reaction, especially anaphylactic; monitoring of the cold chain; information and consent, and prevaccinal screening (anamnesis).

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- Vaccination includes the preparation of the material to be used, the vaccines and the patient to be vaccinated; position and restraint; routes of administration; administration of multiple vaccines in the same act, and the response to incidents.

- Aftercare includes immediate care; monitoring of adverse effects and vaccination records and proper disposal of waste.

Vaccine administration techniques arise with the appearance of the vaccines themselves, so in the seventh century, Indian Buddhists simply ingested snake venom to be immune to its effects, using this occasion as an oral form to administer the vaccine [1].

In the 11th century, a Buddhist nun explained how to prevent contagion by inoculating with pus from patients who had contracted smallpox disease with a very rudimentary use and control of the administration technique of the entire process. In the case of India, a method based on producing a strong irritation on the forearm was used and the application was immediately made with cotton wool soaked with pus from a variloso. On the other hand, the Chinese inserted a piece of cotton soaked in pus extracted from fresh pustules into the nostrils. A second way was to use the scabs that they collected a year before and by drying them, introduce them through the nostrils using small bamboo canes. And a third way, consisted of putting on a healthy child the used clothes of a variloso [10]. Throughout the history of vaccinations, women have played a crucial role in the application and dissemination of the inoculating practice. Inoculation becomes a female practice where the woman exerts her influence on health [11].

In 1796, the vaccine administration technique itself was carried out by Jenner himself, who, in addition to creating the vaccine, administered it himself, through two superficial cuts in the arm of an 8-year-old boy [14]. According to the Community Nursing Association, just as vaccines acquired their main advance in the last quarter of the 20th century, their administration techniques progressed parallel to their discovery, elaboration, and development [14].

Currently, the CAV-AEP tells us that there are academically qualified health professionals, specifically university graduates or nursing degrees, who have the function of administering the vaccines following the recommendations regarding routes of administration (oral, intradermal, subcutaneous, intramuscular, intranasal) and materials (choice of the needle: length and caliber) established in their technical sheets by the laboratories that prepare them, using the material resources provided by them: pre-filled syringes, vials, needles, among others [32].

Discussion

In this section, we will discuss the different types of vaccines and their development in the future. According to the World Health Organization (WHO)33, there are currently three tables, depending on the method in which the pathogenic agent is used:

- Inactivated vaccines are those that are obtained using whole viruses or bacteria that areas have been done throughout history and as has been reflected in this manuscript,

- Attenuated vaccines: are those that are manufactured from a fragment of the pathogenic agent and

- Vaccines are based on a physical vector: they are those that are made only with genetic material.

In the case of inactivated vaccines, the first of the strategies that can be used to design a vaccine is to isolate the pathogenic virus or bacteria, or a very similar one, and inactivate or destroy them utilizing chemicals, heat, or radiation. This strategy uses technology that has already been shown to work to treat diseases that affect humans (for example, this method is used to manufacture influenza and polio vaccines); moreover, the technique makes it possible to manufacture vaccines on an acceptable scale. However, to carry out this method it is necessary to have special laboratories to culture the viruses or bacteria safely, the technique usually entails relatively long manufacturing times, and the resulting vaccines generally must be applied in schedules of two or three doses.

To design attenuated vaccines, pathogenic viruses or one that is very similar are used and they remain active but weakened. The MMR-type vaccine (with measles, mumps, and rubella components), and varicella and zoster vaccines are examples of this type of attenuated vaccine. This strategy uses technology similar to that of inactivated vaccines; In addition, it is possible to manufacture large quantities of vaccines. However, sometimes it is not convenient to apply vaccines of this type to immunosuppressed people.

In the case of vaccines based on viral vectors, to design this type of vaccine, a harmless virus is used to transport specific fragments (called "proteins") of the pathogen of interest so that they induce an immune response without actually causing the illness. To achieve this, instructions for making specific fragments of the pathogen of interest are inserted into a harmless virus. Once this is done, the harmless virus serves as a platform (a "vector") to introduce the protein into the body. The protein then induces an immune response. For example, the Ebola vaccine is a viral vector-based vaccine. This type of vaccine can be developed quickly.

The method that uses an antigenic subunit, vaccines with antigenic subunits are those that use only the specific fragments (called "antigenic subunits") of the virus or bacteria that are essential for the immune system to recognize. These vaccines do not contain the entire pathogenic agent and do not use a harmless virus as a vector. The antigenic subunits are usually proteins or carbohydrates. Most of the vaccines listed in childhood immunization schedules are of the antigenic subunit type and protect people from diseases such as whooping cough, tetanus, diphtheria, and meningococcal meningitis.

Unlike approaches to vaccine design that use whole attenuated or killed pathogens or fragments of one, nucleic acid

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vaccines use only a sequence of genetic material that provides the instructions for making specific proteins, not the entire agent. DNA and RNA molecules are the instructions our cells use to make proteins. In our cells, the DNA code is first transduced into messenger RNA, which is then used as a template to make specific proteins. Through nucleic acid vaccines, a specific set of instructions are inserted into our cells, either in the form of DNA or mRNA, so that they make the specific protein that we want the immune system to recognize and against which we want to induce a response.

At present, the nucleic acid method is a new technique for developing vaccines. Before the COVID-19 pandemic began, no vaccine of this type had passed the full authorization process for use in humans, although certain DNA vaccines, including some intended to fight specific types of cancer, were already in the pipeline. a phase of human trials. Due to the pandemic, research in this area has advanced very quickly, and use authorization has been granted urgent use authorization, which means that they can now be administered to people and not only in the framework of conducting clinical trials. In the future, the development of vaccines will continue to be a challenge, since the human being seeks through them not to get sick, or at least as slightly as possible.

Conclusions

1. From a historical perspective, although vaccines have existed throughout the ages, it was in the last quarter of the 20th century that they acquired their greatest development, so we can say that their advance is a relatively recent event.

2. Due to the fact that the development of vaccines is relatively recent, at present, there is still a population that was not included in the mass vaccination population policies, therefore not immunized and may be responsible for possible outbreaks.

3. The search for vaccines is conditioned to the appearance of epidemics since society reacts to this natural fact by trying to protect itself and for this, it not only seeks a cure for the disease caused by the epidemic but also the way to eradicate and prevent it.

4. Despite the passage of centuries, vaccines are still very necessary, constituting a fundamental pillar in the spread of infectious diseases. Proof of this we are currently experiencing worldwide since the search for a vaccine against COVID-19 has been carried out for a few months, as has happened with the different epidemics that have occurred throughout the past few months. the history of medicine and humanity.

5. Vaccines will not only have an associated impact on health, but they will also have an economic and social impact, among others, since by preventing diseases the economic level, quality of life, and social welfare are favored.

6. Vaccination constitutes one of the greatest advances and most effective measures in Public Health at a global, national, community, and individual level, since with them it is possible to prevent, control, and even eradicate infectious diseases.

7. The introduction of immunization has allowed unquestionable benefits, having repercussions on social systems, reducing the socio-sanitary cost and the morbidity and mortality of infectious diseases for which there is a vaccine.

8. Vaccines are administered to healthy individuals to prevent diseases or at a community, level to break the chain of transmission, so it is essential that the procedures and techniques used are safe and of quality so that the benefit exceeds risks or unwanted effects.

9. Throughout history, vaccination has not been exempt from accidents and secondary effects, and as a result of its evolution we can confirm that protocol measures are currently adopted to reduce risks, accidents, complications, and adverse effects. That may arise from its preparation, handling, and administration.

10. In the first signs, the vaccines were administered by religious and non-religious women, later the vaccine discoverers themselves were the same ones who administered them and at present, the vaccination act is carried out by academically qualified health personnel, specifically a university diploma or degree in nursing.

11. Vaccines and their administration techniques evolve in parallel, since over time both have advanced, their preparation and resources, both material (syringes, needles, among others) and human (qualified health personnel) have progressed.

12. Despite the passage of time, many vaccines, such as the flu vaccine in autumn, continue to be administered to this day at the same seasonal time as was done in the past, to protect a specific risk group.

13. Along with the preparation of vaccines, infectious serologies also appear, which even today are still diagnostic techniques used.

14. In conclusion, we affirm that vaccines have evolved throughout history, since today the vaccination act is a process that implies a complete and protocolized procedure, under safety conditions.

Annexes

Glossary of terms

Vaccination Act: Set of processes, protocols, and techniques that are applied from the moment a user is received from the health system requesting action in relation to vaccinations, until the moment in which this action has been completed.

Immunization: An essential component of the human right to health as well as a responsibility of all individuals,

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communities, and governments, and should be considered as such.

Immunology: Discipline that deals with the study, diagnosis, and treatment of patients with diseases caused by alterations in immunological mechanisms and situations in which immunological manipulations form an important part of treatment and/or prevention.

Inocular: Introduce into an organism a substance that contains the germs of disease.

Vaccine: Any preparation intended to generate immunity against disease by stimulating the production of antibodies. It can be, for example, a suspension of killed or attenuated microorganisms, or products or derivatives of microorganisms. The most common method of administering vaccines is by injection, although some are given by nasal or oral spray.

Vaccinate: Inoculate a vaccine to a person or an animal to provoke a defense response in them and preserve them from a certain disease.

Variolization or variolation: Inoculation of smallpox.

Major Events in the History of Vaccines.

Main events in the prehistory of vaccines

AÑOS	Principales acontecimientos en la prehistoria de las vacunas en el mundo occidental.
1671	La mención más antigua sobre la variolación se encuentra en una nota de Heinrich Vollgnad, publicada en el Boletín de una sociedad científica alemana.
1673	El médico danés Thomas Bartholin en 1673 y que llamó *"Transferencia de la viruela"*.
1680	La Royal Society de Londres reconoció las observaciones de Antonie van Leeuwenhoek: existencia de organismos microscópicos unicelulares. Pudieran existir «entidades» que causaran grandes epidemias.*"Teoría del Germen"*.
1796	El inicio del método jenneriano por Edward Jenner.
1798	El método jenneriano se denominó vacuna, y por ello, su descubridor será reconocido mundialmente como el padre de la vacunación.

AÑOS	Principales acontecimientos en la historia de las vacunas en la segunda mitad de siglo xx.
1963	Maurice Hiklleman: Vacuna Triple Vírica. Pérez Gallardo: Primera Campaña Nacional de Vacunación contra la Polio.
1968	Tiene lugar una Campaña de Vacunación frente al Sarampión.
1969	Vacuna Antirrubeola.
1972	Vacuna Antimeningocócica A+C.
1974	Programa Ampliado de Inmunización de la OMS. Vacuna contra Encefalitis Japonesa.
1976	Vacuna Antirrábica.
1981	Vacuna contra Hepatitis B.
1982	Vacuna contra Meningococo A, C, Y, W-135.
1983	Vacuna contra la Varicela.
1984	Vacuna Haemophilus Tipo B.
1986	Vacuna contra Hepatitis B recombinante.
1987	Vacuna Haemophilus tipo B conjugada. Vacuna contra Meningococo B.
1993	Programa de Vacunación contra la Hepatitis B y Fiebre Amarilla.
2006	Vacuna contra Infección del Virus del Papiloma Humano.
2020	Búsqueda de vacuna contra Covid-19

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