Universidad Europea

GRADUATION PROJECT

Degree in Dentistry

THE ORIGIN OF VACCINATION : EDWARD JENNER

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SUMMARY AND KEYWORDS:

Introduction: The creation of the first vaccine and the eradication of smallpox are considered to be among the most important achievements in medical history, establishing Edward Jenner's legacy as the pioneer of immunology. Since that time, the progress of vaccination has been influenced by various significant developments that have affected the current state of the vaccinology field.

Improvements in affordability, efficacy, safety, and efficiency have paved the way for the eradication of additional diseases in the future, indicating promising progress in the ongoing fight against infectious diseases.

Objectives: This work analyzes Edward Jenner's role in eradicating smallpox and subsequent vaccine developments, identifying significant milestones and trends in vaccination history. It focuses on the present and future state of the field. **Materials and methods:** Websites from reputable databases, including PubMed, Medline, and Google Scholar were used over the course of our research. Additionally, 57 articles were examined. **Results:** The history of vaccination was initiated in 1796 when Edward Jenner discovered that cowpox material could be used to vaccinate against smallpox. His discovery proved that a weakened pathogen could trigger an immune response to a more severe one and has influenced the field's current state and future direction. **Conclusions:** Since Jenner's time, various approaches to eliminate diseases through vaccination have been used, resulting in significant progress. However, there is still much work to be done. Despite the field's various milestones and strategies, vaccination remains vital in saving lives and protecting public health as recent advancements have demonstrated.

Keywords: Dentistry; vaccination; Origin; Edward Jenner; smallpox

RESUMEN Y PALABRAS CLAVES:

Introducción: La creación de la primera vacuna y la erradicación de la viruela se consideran algunos de los logros más trascendentales de la historia de la medicina y establecen el legado de Edward Jenner como pionero de la inmunología. Desde entonces, la evolución de la vacunación ha estado determinada por varios avances fundamentales que han influido en el estado actual del campo de la vacunología. Las mejoras en la asequibilidad, eficacia, seguridad y eficiencia allanaron el camino para la erradicación de enfermedades adicionales en el futuro, lo que indica un progreso prometedor en la lucha en curso contra las enfermedades infecciosas. **Objetivos**: Este trabajo analiza el papel de Edward Jenner en la erradicación de la viruela y los posteriores desarrollos de vacunas, identificando hitos y tendencias importantes en la historia de la vacunación. Se centra en el estado presente y futuro del campo. **Materiales y métodos**: En el transcurso de nuestra investigación, se utilizaron sitios web de bases de datos acreditadas, como PubMed, Medline y Google Scholar. Además, se examinaron 57 artículos. **Resultados**: La historia de la vacunación se inició en 1796 cuando Edward Jenner descubrió que el material de la viruela bovina podía usarse para vacunar contra la viruela. Su descubrimiento probó que un patógeno debilitado podría desencadenar una respuesta inmune a uno más severo y ha influido en el estado actual y la dirección futura del campo. **Conclusión:** Desde la época de Jenner, varios métodos de vacunación han eliminado enfermedades. Pero aún hay un largo camino por recorrer. Los desarrollos recientes han sacado a la luz la importancia cada vez mayor de las vacunas para prevenir enfermedades y salvar vidas.

Palabras clave: odontología vacunación; Origen; Edward Jenner; viruela

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1. INTRODUCTION

Vaccination remain one of the foundations of modern medicine today and is one of the most important discoveries in medical science.
They are one of the pillars of the medical revolution and are frequently attributed with a large portion of the responsibility for the increase in life expectancy over the past 200 years(1).

The concepts of vaccination have been evolved over the years, starting with the first voluntary immunizations several centuries ago and continuing with Edward Jenner and Louis Pasteur who created the first vaccines that are still used today(1,2). As a result, the majority of the world has achieved control over more than ten main infectious diseases. However, only smallpox has been completely eradicated to date as a result of WHO global immunization programs. Other contagious diseases have decreased, have been eradicated in some regions of the world, and may do so in the next years(1,3).

According to estimates from the World Health Organization (WHO), vaccinations avert 3.5 to 5 million deaths annually. Similar to this, the measles vaccination alone is thought to have prevented 23 million deaths between 2000 and 2018 according to UNICEF's estimations(4) .
The intricacy of some infectious diseases, such as tuberculosis, malaria, and HIV infection, as well as the development or reemergence of new infectious organisms, continue to present significant hurdles. The goal of vaccination is to provide long- lasting immunity against a pathogenic agent (often a virus or bacteria) that causes an infectious disease, without resulting in clinical signs or adverse reactions(4,5) .

In order to prevent the start of a disease or to lessen its clinical signs, vaccinations are antigenic formulations that can trigger an active immune response in a person(1,2,4).
When a sufficiently large percentage of the population is immunized, this individual protection, which is based on the immune system's ability to recognize, memorize, and optimize the immune response, specific to an antigen during a second encounter with

the latter, allows a collective protection that is crucial to the success of vaccination and that must be encouraged(1,6).

Smallpox, a disease that had ravaged humanity for the entirety of recorded history, was mostly prevented by inoculation until the end of the Eighteenth Century.
By utilizing the substance derived from cowpox lesions, Edward Jenner pioneered the practice of vaccination as a more reliable and effective means of preventing smallpox(3,5,7).

Vaccine technology has dramatically improved since Edward Jenner's discovery. The late 19th century saw the advent of killed/inactivated and attenuated cell vaccines, marking the start of a new chapter in the history of vaccinations. These breakthroughs enabled the expansion of vaccine usage beyond smallpox to combat a wide range of hazardous bacteria and viruses(8). On the other hand , technological innovations have made it possible for immunization to spread more quickly and effectively throughout the world(1,2). Genetic advancements have lately pushed vaccination research in a novel and exciting direction, making it possible to quickly and affordably develop vaccines against emerging dangers like COVID-19(9,10) .

As a result, the current standing of the field has been defined by these various advancements, spanning from mRNA vaccines developed to counter COVID-19 to the initial application of cowpox in providing immunity against smallpox(11,12). These developments have often been provoked by periods of crisis in which progress in science, research and medicine in general have followed. Despite these numerous advances, smallpox remains the only disease that has been completely eradicated with a vaccine(13–15).
Although vaccines have, since their invention, saved and protected millions of lives, considerable progress must be made to eradicate diseases(1,7). Thematic of vaccination is particularly relevant for all of us today. Indeed, since November 2019, we have been facing a global pandemic, where vaccination has played a major and essential role in slowing down and weakening the pandemic(9,10).

The rapid spread and mutability of the virus responsible for COVID-19 has underscored the critical role of vaccination in safeguarding public health(16), while also highlighting the imperative to explore novel vaccine technologies that are both affordable and more effective(17).

This project will examine vaccine development from the time of Edward Jenner to the present day, examining milestones and tendency in this long and complex history. It will then analyze different vaccination programs and discuss their successes and weaknesses.

2. OBJECTIVES

2.1. Primary objectives

1. To describe Edward Jenner's life and his role in the fight to eliminate smallpox.

2.2. Secondary objectives

2 To identify significant turning points in the evolution of vaccinations from Edward Jenner to the current time.

3 To analyze the smallpox eradication campaign's results and compare them to other measures to determine whether or not they were successful.

4 To highlight major developments in vaccine research while predicting where the field is pushed in the future.

3. MATERIAL AND METHODS

3.1. Keywords and search equations

The aim of this work was to examine the beginning of immunization, starting from the time of Edward Jenner.

For this aim, electronic databases such as Medline, Academic search ultimate, Google Scholar, and PubMed were employed to search scientific publications, as well as journals from the year 1881 to 2023. The keywords and Boolean operators used for this research were the followings: “Edward Jenner” AND “origin” AND “vaccination”, “smallpox” AND “cowpox”.

3.2. Inclusion criteria

- Language : English, French, Spanish
- Year of publication: From 1881 to 2023
- Type of sources: Scientific articles, textbooks, journals
- Relevance: Only articles that matched the searches were selected
- Availability: Only complete articles were used

3.3. Exclusion criteria

To ensure the accuracy of the results, the study's exclusion criteria consisted of articles that only contained abstracts, outcomes that were not relevant to vaccination or its origin, articles written in languages other than English, French, and Spanish, articles that did not match the search criteria, and incomplete articles.

4. RESULTS

4.1. Study selection process

Figure 1 depicts the study selection procedure. Database screening provided 523 records, of which 350 remained after duplicates were eliminated. Following the reading of titles and abstracts, this number was decreased to 100. For eligibility, the text of these 100 papers was reviewed. 43 of the 100 studies were eliminated because they did not meet the inclusion criteria. As a result, 57 articles were included in the final bibliography.

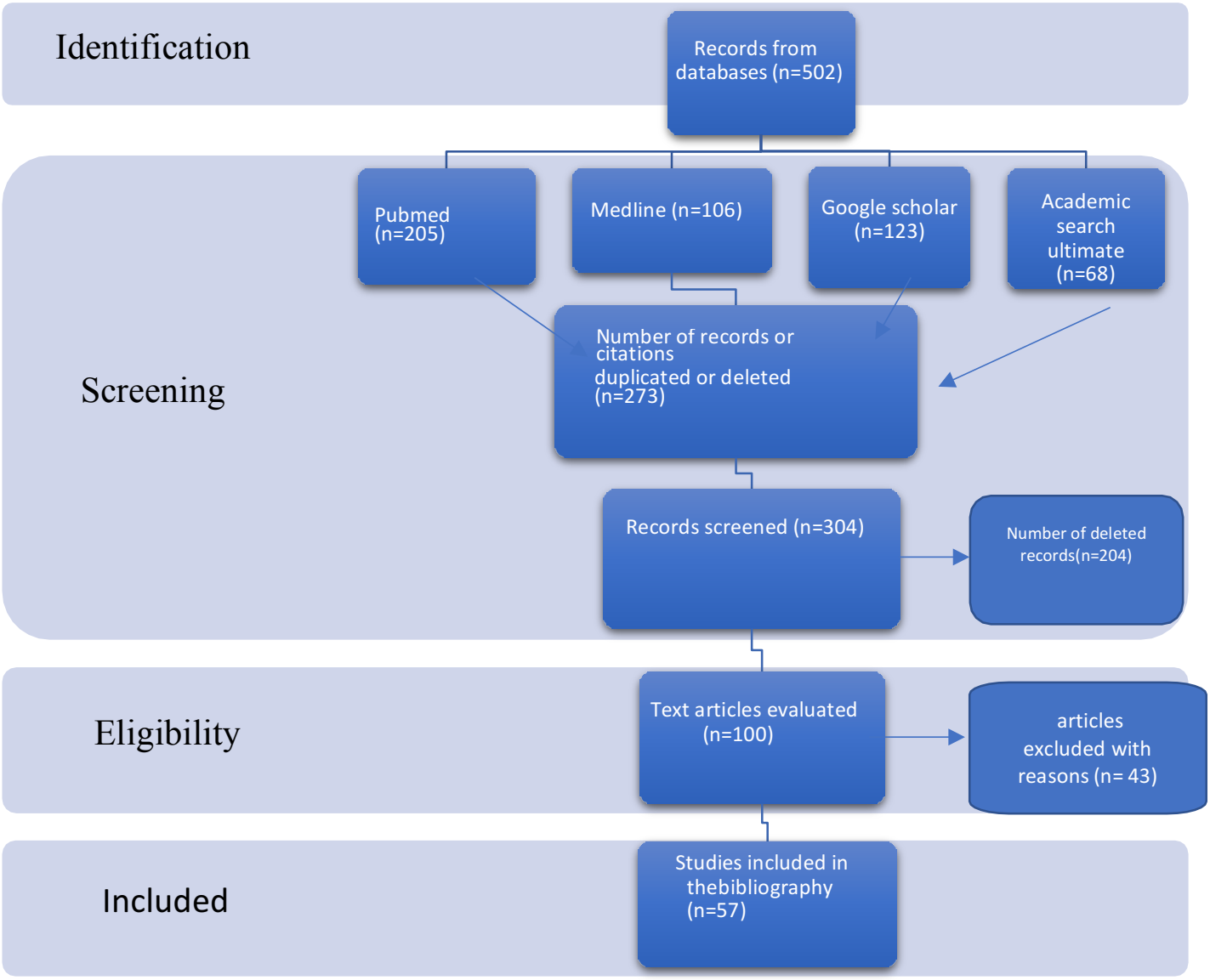

Figure 1: Flowchart of the records selection process

4.2. The smallpox and inoculation

The immunization of 8-year-old James Phipps by Edward Jenner in May 1796 was a major breakthrough in immunology. It played a crucial role in the eradication of smallpox, a disease that had been causing devastation in civilizations for at least 3,000 years, which was confirmed by the discovery of smallpox-like lesions on Ancient Egyptian mummies.(3).

Smallpox had spread to Europe by the 6th century and was believed to have contributed to the death of Marcus Aurelius and the decline of the Roman Empire(3,5). The disease had a significant impact on the Americas, where it was introduced by conquistadors and contributed to the decline of the Aztec and Inca empires(3). Smallpox was also used as a biological weapon in war, such as when British armies in North America distributed smallpox-infected blankets to Native Americans in an attempt to reduce their population(3,18).

The disease was highly contagious and transmitted mainly through face-to-face contact, with initial symptoms including high fever, shaking, and discomfort, followed by the development of vesicles, pustules, and scabs(7). Survivors often experienced blindness and scarring, with case fatality rates varying from 20% to 80% (3,7). Smallpox has since been eradicated, and Jenner's contributions to immunology have led to the development of vaccinations for 17 potentially fatal diseases(4).

Variolation or inoculation, which involved deliberately infecting people with smallpox to provide immunity, was the primary strategy for fighting smallpox before vaccines became available(3). The practice was introduced to Europe by Turkish travelers in the early 18th century and was met with skepticism by medical professionals(3,18). It was only through the advocacy of Lady Mary Wortley Montague, who had contracted smallpox herself and witnessed her brother's death from the disease, that the practice was eventually adopted in England (19).

Inoculation was a risky procedure, as it carried the potential for death or transmission of the disease. Nonetheless, it was a widely used practice by the mid-18th century, and

the Sutton family developed a less intrusive protocol that made it less expensive and safer (20). The goal of inoculation was to provide immunity to smallpox by exposing a person to the disease in a controlled manner, usually by scratching a smallpox lesion under the skin. Some people even ingested ground-up smallpox scabs through a method called insufflation (7,21).

Smallpox was an ideal disease for testing immunization because it was easily transmitted and had distinctive symptoms, including a characteristic rash. Variolated individuals had a lower case-fatality rate than those who contracted smallpox naturally. Despite its risks, inoculation played a significant role in the fight against smallpox before vaccines became available (21).

4.3. Relation between smallpox vaccine and Edward Jenner

Jenner, who was born in 1749 in the English town of Berkeley, developed an interest in science at an early age. He began an apprenticeship with a local surgeon in Bristol at the age of 13. At the age of 21, he moved to London and studied under John Hunter, an experimental scientist, biologist, and anatomist at St. George's Hospital (22). Jenner and Hunter became friends and worked together for two years until Hunter's death(3,21). Jenner's passion for science also led him to assist Captain James Cook in categorizing species, although he declined an invitation to join Cook's second voyage. Jenner continued to explore various fields in science, including geology, blood experiments, hot air balloons, and cuckoos, which led to his election to the Royal Society. His last published study was on bird migrations (3,21).

In 1796, Edward Jenner began to eradicate smallpox by using cowpox virus, which is milder than smallpox but belongs to the same family (5). Jenner heard a dairymaid say that she would never get smallpox because she had cowpox, and this inspired him to investigate the matter. In May 1796, he found a dairymaid named Sarah Nelmes with cowpox and inoculated an 8-year-old child named James Phipps with her pustules (3). Phipps recovered after a few days of fever and discomfort. A few months later, Jenner

re-inoculated Phipps with material from a smallpox lesion, and Phipps did not get sick, proving that protection was complete. Jenner repeated the process on other people, and after inoculating 13 people who had been resistant to smallpox after cowpox infection, he reported his observations to the Royal Society. However, the society rejected his report due to insufficient evidence, so Jenner added 25 case studies to his report (3,21,23). In recognition of Phipps' bravery, Jenner granted him a cottage near his Berkeley home(21).

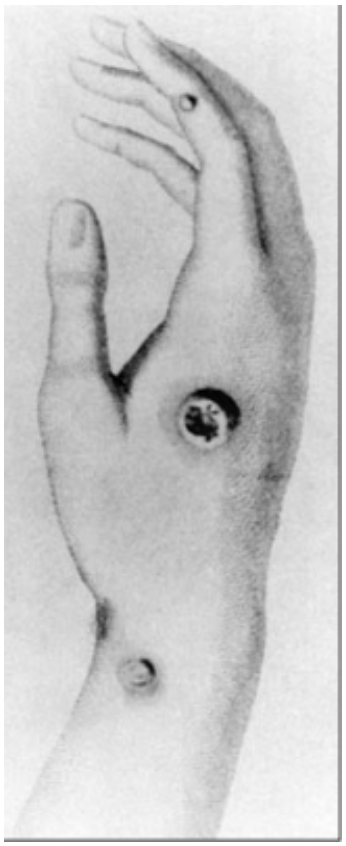

Figure 1 : The hand of Sarah Nelms (3).

Jenner wrote "An enquiry into the causes and effects of Variolae Vaccinae, a disease identified in several of the Western Countries and England, particularly Gloucestershire, and known by the name of cow pox" in 1798. It had three parts. Jenner initially explained that horses spread cowpox to cows. Jenner hypothesized that horsepox, which harmed horses' hooves, was the origin of cowpox because farms included horses and dairy cows (21). Although this notion was disproven, Jenner hypothesized that cowpox infection conferred smallpox protection. The second portion tests this idea, and the third part discusses smallpox results (3).

Jenner published “Further observations of the Variolae Vaccinae” in 1799. He describes cowpox lesions and distinguishes them from other pustule-causing infections (23).

Jenner shared cowpox samples with other physicians like Henry Cline to vaccinate people in their communities. In 1800, he published a report about the findings in "A continuation of facts and observations relative to the Variolae Vaccinae or Cow pox." By then, vaccination had spread widely across most European nations (3,23).Benjamin Waterhouse introduced vaccination in New England and persuaded Thomas Jefferson to implement it in Virginia, marking a significant step forward in the history of vaccination in the United States. Jefferson appointed Waterhouse to lead the National Vaccine Institute because of the experiment's effectiveness(3). During this time, Jenner focused on vaccinating the underprivileged for free in Cheltenham(23).

Jenner created the smallpox vaccine through this discovery. Unlike variolation, vaccination employed cowpox virus instead of smallpox. Jenner coined the name "vaccination" from "vacca" (cow) and "vaccinia" (cowpox) (3). Vaccination was finally accepted and variolation was outlawed in England in 1840 after much medical debate. In 1853, infants had to be smallpox-vaccinated (14). Edward Jenner was neither the first to link cowpox infection to smallpox protection, nor was he the first to vaccinate with it. John Fewster, who was a surgeon and a friend of Jenner, ran a clinic for inoculation. He noticed that individuals who had contracted cowpox were not affected by the smallpox inoculation. A farmer called Benjamin Jesty, used this information to vaccinate his wife and two sons with cowpox. Some European doctors have noted the link between cowpox and smallpox and vaccinated (15,21,24). Yet, Edward Jenner advocated for this information to be generally accepted and recognized. He proved that those afflicted with cowpox were immune to smallpox (24). For his vaccine research, Jenner received £10,000 from the British Parliament in 1802. He got £20,000 in 1807 (3,23).

In 1810, he lost his son due to tuberculosis, and in 1815, he also lost his wife to the disease. He retired from medicine and died in 1823 at his Berkeley house. Alongside his wife, kid, and parents, he was buried in Berkeley (24).

4.4. The elimination of smallpox

Smallpox is the only disease that has been completely eradicated through vaccination, a remarkable feat accomplished through global cooperation between the World Health Organization (WHO) and Member States. The WHO was founded in 1948, and in 1958, Viktor Zhdanov, a representative from the Soviet Union, urged the WHO to launch a worldwide campaign to eliminate smallpox. The request was approved in 1959, and over the next seven years, several countries strengthened their vaccination programs, leading to the successful eradication of smallpox. However, smallpox epidemics continued to occur even after the request was approved, making the global eradication efforts even more critical.

In 1966, new actions actions were taken to step up the fight against smallpox, and in 1967, these new actions were initiated when the project received an injection of additional money totaling $2.4 million(25).

The World Health Organization (WHO) announced their intention to eradicate smallpox by the year 1977 with the launch of this new program (25,26). Smallpox was still endemic in 31 countries when the WHO introduced its eradication program.

Each year, there were 10-15 million cases of smallpox, which resulted in the deaths of 1.5–2 million people. The bulk of these 31 countries were seen to be developing at a slower rate, which made the humanitarian and environmental crises that plagued them considerably more difficult (25,26).

Figure 2 : Smallpox in India, 1970s. Photo of the World Health Organization (3).

The WHO launched a campaign that resulted in two major technological improvements in the field of medicine that made it easier to administer the vaccine. These advancements were the bifurcated needle and freeze-dried vaccine. Benjamin Rubin is credited with inventing the bifurcated needle in 1961 while working at Wyeth Laboratories (25). The initiative revolutionized the vaccination process by simplifying the training and sterilization requirements, reducing the amount of vaccine needed, and making it reusable(25,26). Only a fourth of the dose previously necessary could be administered with the needle because of its bifurcated design (27). Since its introduction in the 1970s, the bifurcated needle quickly established itself as the industry standard (26). For this campaign, Wyeth Laboratories developed fifty million bifurcated needles(25).

The smallpox vaccine was a liquid that, once manufactured, had to be administered within a few weeks. On the other hand, the development of freeze-dried vaccines made it possible to store the vaccine for a much extended period of time, making it much

simpler to vaccinate people in isolated regions(25). 62 countries and 64 laboratories were involved in producing the freeze-dried vaccine by 1967. Out of the total 62 countries, 27 were situated in Europe, 19 in Asia, 9 in the Americas, and 9 in Africa(27). Due to these two developments in technology, the process of giving the vaccination became so simple that it was even possible to recruit locals to carry it out. Each individual was capable of administering up to 1500 shots in a single day with just very brief training. The total number of vaccinations administered during the duration of the campaign reached 2.4 billion(25).

Yet, there were some challenges associated with administering vaccinations on such a massive scale. The cases of post-vaccinal encephalitis and Vaccinia necrosum were the most severe, despite the fact that they were quite uncommon. In a study that included more than 14 million participants, it was discovered that post-vaccinal encephalitis affected 16 persons, resulting in 4 deaths, and that vaccinia necrosum affected 11 individuals also resulting in 4 deaths. Complications related to the first vaccination were responsible for around one death per millions, while revaccinations were responsible for approximately one death per four millions(27).

The level of vaccination coverage was subject to debate. What proportion of the population must be immunized for there to be no trace of the disease? It was determined that a vaccination coverage of at least 80% was adequate for eradication and that a coverage of 100% was unnecessary. Vaccination coverage was fraught with complications, and the youngest population was most frequently overlooked. Several factors impeded the success of the vaccination campaign, such as religious beliefs, superstition, opposition from minority groups towards the vaccinators and the challenges posed by accessing isolated populations(27).

The elimination of smallpox was made possible by a number of factors, including:
First of all, because the only way for the smallpox virus to live is inside a human host, reducing the amount of human-to-human transmission will result in the disease being eradicated. This presents a significant advantage as opposed to diseases like Ebola, which can remain in non-human animal hosts, rendering it much more challenging to

fight the propagation of the disease. Additionally, the soil can serve as a reservoir for the bacteria that causes tetanus, further complicating efforts to control the disease.

Second, because those infected with smallpox had a distinctive rash, it was simple to separate them from those who were not infected with the disease. As a result, laboratory tests were not required to verify the diagnosis of smallpox infection. Thirdly, the development of an efficient vaccine that could confer protection for a period of 5-10 years with just a single dosage meant that controlling the spread of smallpox was both achievable and effective(26,27).

The final occurrence of widespread smallpox took place nearly 11 years after the implementation of the eradication campaign, and over 175 years after Jenner's discovery that the cowpox virus provided immunity against smallpox (15), and the smallpox eradication was announced by the World Health Assembly in 1980 (14).

4.5. Louis Pasteur contribution to vaccination

Louis Pasteur, a French scientist, began the process of producing an anti-anthrax vaccine by drawing on the research of Edward Jenner and his own work on the theory of germs. Recent developments in the discipline of bacteriology have made this outcome achievable. For instance, the discovery of Bacillus anthracis in the 1860s and 1970s defined the first time that a specific microorganism could be attributed to a disease (28). In a similar manner, Robert Koch's discovery of Bacillus anthracis spores assisted in explaining how the disease might spread through airborne spores even in the absence of bacteria (29). Pasteur was able to create the first zoological anthrax vaccine as a result of his better understanding of how germs function and how they cause disease. In the same way that Jenner's smallpox vaccine used a weakened form of the virus (cowpox) to create the body's immune defense, Pasteur's anthrax vaccine utilized a weakened or attenuated form of anthrax (28).

In the year 1879, Pasteur made the observation that bacterial cultures over time became less infectious. Pasteur mistakenly left a culture unattended for some time after isolating the bacteria that causes chicken cholera. Injecting chickens with this culture elicited little response, indicating that the bacteria had been weakened. After this, Pasteur discovered that these chickens were less likely to become infected with a strain of chicken cholera that was particularly dangerous (30). These findings were utilized by Pasteur in the development of the live, attenuated vaccine for anthrax in the year 1881 (28,31). The *Bacillus anthracis* had been weakened by being cultivated at a particular temperature and under aerobic circumstances, both of which prevented the development of spores. This allowed the bacteria to be used safely. As a result of the attenuated germs, the body would be able to generate an immune response without being infected.

Pasteur notably showed the efficacy of his new vaccine in front of a crowd at Pouilly-le-Fort, France , following which it was rapidly adopted (28).
In the course of his research on anthrax, Louis Pasteur came up with the idea for a live, attenuated vaccination against rabies.

Rabies, in contrast to cholera and anthrax, is contagious and rapidly mutates because it is caused by a virus. As a result, Pasteur enabled the disease to evolve and become adapted to the body of a specific animal host by injecting it into rabbits. This attenuated version was taken from the spinal cords of the rabbits, and when it was administered to the dogs, it had a lower infectious potential, and it protected the dogs from rabies without producing infection(8,32).

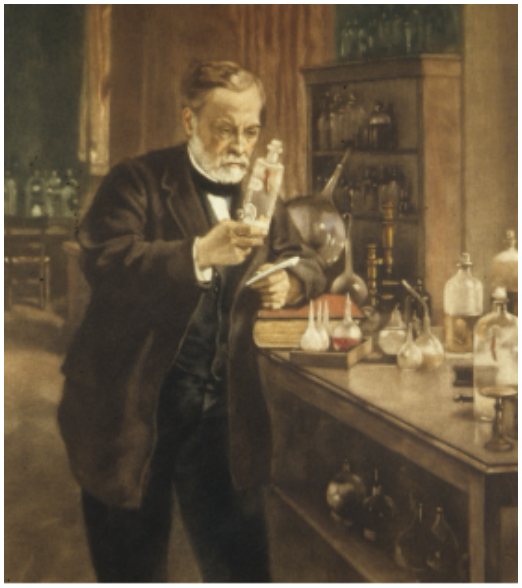

Figure 3 : Louis Pasteur holding a jar with a rabbit's infected spinal cord, used to create the rabies vaccine(30).

In 1885, Louis Pasteur successfully administered the rabies vaccine to a human for the first time, this was the starting point for the application of live, weakened vaccines in humans(28). The creation of Albert Sabin's polio vaccine in 1956 was made possible due to this advancement, which laid the foundation for the development of the next generation of weakened live vaccines(32).

4.6. The polio vaccine

The poliovirus is a type of enterovirus from the Picornaviridae family. It causes polio, also known as poliomyelitis, and can be spread through infected droplets in the air, contaminated food or water, and direct contact with infected feces. It affects the intestines and reproduces there after entering through the mouth or nose. Contrary to popular belief, most people who contract the virus do not experience any symptoms(33).

The poliovirus destroys the nerve cells in the brain and in the spinal cord, which results in damage to the lower motor neurons, which in turn causes flaccid paralysis (33,34). Polio is a type of paralytic disease that can cause symptoms like fever, headaches, sore throat, and vomiting. There is a possibility of developing neurological complications that can result in stiffness of the neck and back, weakness of muscles, joint pain, and paralysis

of limbs or the respiratory muscles. The respiratory paralysis can be fatal in severe cases. However, most people infected with the virus do not show any symptoms. Only 5% of those infected have moderate symptoms, while paralysis occurs in fewer than 1 in 1,000 individuals. This suggests that 95% of those infected have a natural immunity to the virus(33).

The inactivated polio vaccine (IPV), which was created by Jonas Salk in 1953, and the attenuated polio vaccine given orally (OPV), which was produced by Albert Sabin in 1956, were both designed as vaccinations to prevent poliomyelitis (34).

In order to eradicate polio, Jonas Salk combined three distinct poliovirus strains that had been cultured in the kidney cells of a monkey and treated them with formalin (formaldehyde). Because the virus had been rendered harmless, it could be reintroduced into the body without causing the disease to manifest itself(33,34). This was made possible because the virus had been rendered inactive.
An extensive clinical trial was carried out to evaluate its effectiveness, and in 1955, the vaccine was approved for use over the entirety of the United States. The number of people who developed paralytic poliomyelitis dropped dramatically during the subsequent few years. Scientists discovered that the Salk vaccine was 90% effective against Types II and III poliovirus and 60% to 70% effective against Type I poliovirus (35). Regrettably, about 250 cases of paralysis were reported, and as a result, the vaccine was withdrawn from the market. Vaccine testing revealed that the virus had not been effectively neutralized. It was decided to rearrange the vaccine and put it back on the market (33,36).

Concerns were raised regarding Dr. Salk's vaccine's potential to confer immunity that would last for an extended period of time At that time, Albert Sabin was developing a live-attenuated version of the vaccine with the potential to provide longer-lasting protection(35). Trials for the live-attenuated form of the vaccine had to take place mostly in countries other than the United States because, at this point in time, the United States had approved Salk's vaccine. The tests demonstrated that Sabin's vaccine did, in fact, confer immunity that lasted for a longer period of time and had the potential

to produce herd immunity(36). The vaccine could be given orally, either in the form of a sugar cube or mixed with a drink, which made it a more convenient option. Additionally, it was less expensive to manufacture, and in 1963, Sabin's live-attenuated vaccine was authorized for use in the United States.
The oral vaccine developed by Sabin started to replace the injectable vaccine developed by Salk, and by 1968, the United States had stopped producing and administering the Salk vaccine (33,35).

There were reports of cases of the attenuated virus regaining its virulent capacity as early as 1962, which was one of the concerns associated with Sabin's OPV. This risk was known as Vaccine-Associated Paralytic Poliomyelitis, or VAPP. An advisory group in the United States conducted an investigation into these instances in 1964 and reported that Sabin's attenuated vaccination was responsible for 57 of the cases that occurred between 1961 and 1964. In spite of the nearing eradication of polio on a global scale, the United States continued to use Sabin's vaccine since switching back to Salk's would incur enormous expenses and run the danger of undermining public trust in vaccinations(34,35).

During the 1970s, Sabin's OPV was being utilized in the majority of the world due to the fact that its immunity lasted for a longer period of time and that its production costs were lower. The Netherlands was one of the few countries that continued to manufacture and use Salk's IPV while also working to enhance it (35). In 2000, The GDC updated its polio vaccine guidelines to require children to receive Salk's IPV vaccine again, as the risk of VAPP associated with Sabin's OPV was no longer deemed acceptable(33,35).

Statistics show that between 1988 and 2014, the polio vaccine avoided an estimated 13 million cases of paralysis in children and 650,000 deaths (37,38). This is according to the Centers for Disease Control and Prevention (CDC) in the United States.

4.7. The Varicella-Zoster

Herpes Zoster, is a widespread disease marked by painful rashes and blisters on the face and/or body. Varicella zoster virus (VZV), a member of the herpesvirus family, is the causative agent of this disease, which is notoriously contagious(39,40).

Varicella, often known as chickenpox, is the outcome of an initial infection with the VZV virus and is characterized by fever, rashes, and blisters. Dormant in the body after the first infection, the VZV continues to exist. On the other hand, reactivation of the virus can take place, leading to herpes zoster. Millions of people are infected with herpes zoster (HZ) each and every year, and around 30% of the general population will get it at some point in their lives. There is a strong correlation between age and the incidence of herpes zoster; those over 60 years of age are approximately 8-10 times more likely to acquire HZ. In addition to getting older, other key risk factors include having a compromised immune system and being HIV positive. In addition to physical damage in the affected area, other risk factors include stress and being white(39,40).

The most concerning herpes zoster complication is postherpetic neuralgia (PHN). It is a type of neuropathic pain that occurs after the herpes outbreak has healed, and can persist for years in the worst cases. There are three stages in the progression of postherpetic neuralgia (PHN): acute herpetic pain, subacute neuralgia, and postherpetic neuralgia(40). PHN is more prevalent in people aged over fifty, and more than 40% of individuals aged 60 or older who have had herpes zoster have PHN (39).

In 1974, a live attenuated vaccine against varicella, popularly known as the chickenpox vaccine, was created in order to prevent initial VZV infection in youngsters who lacked the ability to mount an immune response. Varicella vaccine is now available as part of a combined measles-mumps-rubella-varicella vaccine, facilitating the process for children's immunization programs, or as a monovalent vaccine, such as Varivax(41).

In Europe, only 5 countries include chickenpox vaccine in their child vaccination program, while other countries may recommend it for vulnerable groups only. The WHO

recommends giving it to children between 12-18 months in places where chickenpox is a concern. However, the vaccine may increase the risk of herpes zoster by reactivating latent herpes or reducing immune boosting from exposure to chickenpox patients(41).

It is imperative to have a high level of VZV-specific T-cell immunity in order to defend oneself from Zoster later in life. Because of this, a vaccination that protects against zoster was eventually created. The varicella vaccine is essentially the basis for the zoster vaccine; however, the concentration of the vaccine is increased. Varivax, a monovalent varicella vaccine, comprises 1,350 plaque-forming units (PFUs), Zostavax, a vaccine developed specifically for preventing Zoster, comprises 19,400 PFUs (39,41). However, Varicella vaccines like Varivax are inadequate as a prophylactic measure against zoster in individuals aged over 60 due to insufficient levels of live-attenuated virus titers required to enhance VZV-specific T-cell immunity(39).

According to a United States cohort study, vaccination with Zostavax, the Zoster vaccine, resulted in a 55% reduction in the occurrence of Zoster among individuals aged over 60 who were vaccinated(41). Zostavax is an efficient and effective immunization against the zoster virus. Shingles Prevention Study Group did a big study, and their findings showed that the incidence of Zoster reduced by 51%, while the incidence of postherpetic neuralgia fell by 67% in those who were vaccinated (39). When administered to people over the age of 70, the Zostavax vaccine is only 38% effective in preventing herpes zoster(42).This is due to the fact that the vaccine's effectiveness declines significantly with age.

In the United States, healthy patients over the age of 60 are encouraged to use Zostavax, whereas in the United Kingdom, healthy patients over the age of 70 are encouraged to take the vaccine(41). The vaccine is not a cure for herpes zoster or postherpetic neuralgia Rather, this is a technique or preventive measure that aims to prevent the onset of herpes zoster(39).

4.8. An introduction to Hepatitis B

Hepatitis B (HBV) is a DNA virus that can only be transmitted through contaminated blood or bodily fluids. It spreads during pregnancy and early childhood and has infected over 2 billion people, with 360 million chronically infected, which increases the risk of death by up to 25%(43). The virus caused an estimated 887,220 deaths in 2015 due to liver-related illnesses(44). The first HBV vaccine was introduced in 1982, which uses purified HBsAg from asymptomatic carriers and does not contain any genetic information from the virus, making it non-infectious but still able to trigger an immune response. This new type of vaccine differs from those made for diseases like smallpox, polio, and varicella-zoster, which use either full or partial viral cells. Overall, HBV is a global health issue of significant magnitude(43,45).

However, the early HBV vaccines were derived from blood plasma, which raised concerns about the possibility of containing other infectious agents, and they were expensive to produce(44). Despite proving to be safe, there was still some reluctance to use them. Furthermore, if everyone were vaccinated, there would no longer be enough infected blood to produce plasma-derived vaccines. In 1986, a second generation of HBV vaccines using recombinant HBsAg was developed, which was cheaper to produce and made use of genetically modified yeast cells to produce the antigen(43,44). Although these new vaccines are not significantly more effective than the older ones, their cost-efficiency has allowed the World Health Organization to expand their vaccination programs(46).

Additionally, it has been proposed that recombinant vaccines utilizing HBsAg generated in mammalian cells may offer an even greater level of immunogenicity compared to those generated in yeast cells. This is because the HBsAg produced in mammalian cells contains both the S antigen and the pre-S region, whereas yeast cell-produced HBsAg only contains the S antigen(43,45). Including the pre-S region in vaccines may increase coverage to people who do not respond well to the S antigen alone, such as smokers, obese individuals, and those living with HIV(44,46,47). However, producing HBsAg in mammalian cells is too expensive for universal immunization programs.

Early efforts to immunize high-risk populations were difficult due to logistical challenges and high rates of HBV infection in those communities. Selective vaccination of at-risk individuals was not effective, and the WHO has since shifted towards mass vaccination campaigns. In places like Singapore and Alaska, early HBV vaccination programs effectively reduced the carrier rate to zero(44,48).

At present ,the World Health Organization (WHO) recommends that all member states incorporate the HBV vaccine into their immunization programs (49). The first dose should be given within 24 hours of birth, followed by two or more doses(49,50). This is because chronic HBV infection is most common in neonates, either during pregnancy or childbirth. The WHO reported that globally, as of 2013, hepatitis B vaccination had averted 14.2 million instances of chronic HBV infection among children under the age of five(49). Vaccination has been critical in reducing the incidence of chronic HBV. However, coverage remains inadequate, with only 39% of neonates having received the HBV vaccine dose at birth as of 2015, according to the WHO(49). Global efforts are still needed for eradication, but HBV is highly eradicable, similar to the successful eradication of smallpox, because it is primarily carried by humans and has very few animal reservoirs(48).

However, it is important to note that vaccination alone cannot fully eliminate HBV transmission from mother to child during pregnancy. Therefore, in addition to expanding vaccination programs, it is essential to increase efforts to screen pregnant women for HBV and administer prophylactic treatment to their newborns (50).

Nonetheless, the development of vaccines to protect against HBV has resulted in significant advancements in vaccine technology. For instance, the first use of subunits in vaccines by Merck and the Institut Pasteur in 1982 marked a shift away from using whole or partial cells and paved the way for the development of various subunit vaccines in a cost-effective and safe manner(44,51). Similarly, the recombinant vaccines developed in 1986 made use of gene modification technology to create a safer and more cost-effective alternative, and were the first to use virus-like particles(44). The HBV response

has achieved two significant landmarks in the vaccination field and paved the way for the creation of conjugate, subunit, and recombinant vaccines.

4.9. The Coronavirus Disease 2019 (COVID-19)

By June 2022, COVID-19 had infected over 544 million individuals and caused more than 6.3 million deaths. This respiratory disease, caused by the SARS-CoV-2 virus, was first identified in Wuhan, China in December 2019. The virus is closely linked to the one responsible for SARS and less closely related to the one that causes MERS (52).
Nevertheless, SARS-CoV-2 differs from these in several significant respects.
In 2002 and 2003, SARS was responsible for two major epidemics, while MERS caused an outbreak in 2012. However, these epidemics subsided rapidly, so no vaccine against these diseases was ever developed (9,53).

Efforts to improve public health have not been very effective in eliminating COVID-19, likely due to SARS-CoV-2's high reproduction rate, longer incubation period, and high rate of mild or asymptomatic infections, making it difficult to detect and control. This highlights the importance of vaccination, as other control measures have been ineffective and costly compared to previous outbreaks of SARS and MERS(52).

COVID-19 was important for mRNA vaccine development. Traditional vaccines use inactive viral cells or proteins to stimulate immunity, but mRNA vaccines instruct human cells to generate SARS-CoV-2 antigens, leading to antibody production(54,55).

As a rapidly spreading and global disease, COVID-19 necessitated a swift and collaborative response from scientists around the globe. Authorities in China released the SARS-CoV-2 genetic code online, prompting researchers all over the world to begin developing a vaccine (12). This was made feasible because mRNA vaccines do not contain actual virus material, so they can be derived from a digital transcription of the virus's RNA (12).The results of approximately thirty years of study into the potential of mRNA as a vaccine were accelerated as a result of this combined effort, and the first

vaccination against COVID-19 was licensed before the year 2020 came to a close. In this way, the COVID- 19 pandemic accelerated mRNA research (54).

The breakthrough in mRNA vaccine technology is crucial for two reasons: it enables the rapid development of vaccines without the need for viral cells, and it allows for the standardized and scalable production of vaccines(11,56). mRNA vaccines can be easily modified to code for antigens for new viruses, making mass production faster and more efficient(56). This means that vaccine manufacturers can respond quickly to emerging threats by producing vaccines on a large scale. Additionally, research suggests that mRNA vaccines may be more adaptable to account for virus alterations(11).

mRNA vaccines could improve our response to viruses like SARS-CoV-2 by adapting antigen design and combining multiple variants for protection against new strains(11). mRNA vaccines are fast and adaptable, but their long-term effectiveness remains unknown (11). mRNA vaccines require very low temperatures for storage, which could limit their use in certain areas (57). Some experts question whether manufacturers can keep up with new strains and mutations of diseases like SARS-CoV-2, as seen with HIV (57). It's unclear if mRNA vaccine producers will focus on developing new vaccines for emerging strains, multivalent vaccines, or a pan-coronavirus vaccine to protect against all coronaviruses(10,57).

5. DISCUSSION

5.1. Historical patterns of vaccination trends

Among the 57 sources utilized to compile this analysis, the history of vaccination is characterized by a number of prominent trends.

This paper illustrates that major accomplishments in the field of vaccination often stemmed from the integration of the findings of others and were prompted by significant breakthroughs in other scientific areas. Vaccination was discovered by accident by Edward Jenner, who had no clear idea of how it worked at the time (3).
Due to an enhanced understanding of microbiology, Louis Pasteur was able to extend and expand Jenner's work, building on the work of Robert Koch in finding the anthrax spore-producing bacterium(28,29).
Therefore, it is evident that Louis Pasteur built upon the discoveries of Edward Jenner, ushering in the era of modern vaccination. Pasteur built on Jenner's discovery that a weakened virus may provide protection by doing his own experiments and coming to the same conclusion(28). Consequently, Louis Pasteur extended the purview of vaccination to encompass viruses and bacteria that lacked inherent weaker strains, such as smallpox. Despite the widespread attribution of the title "Father of Immunology" to Edward Jenner, it is justifiable to bestow the same recognition upon Louis Pasteur(32).

Despite his achievements, Pasteur didn't fully comprehend the mechanism behind his rabies vaccine. It wasn't until the discovery of viruses that we realized how effective it was. Similarly, advances in DNA research and genetic engineering enabled the 1986 development of the first recombinant vaccine(51). Likewise, the advent of mRNA vaccines for COVID-19 was achievable due to the identification of mRNA and over thirty years of research into its applications.
Thus, this report discovered that every accomplishment in the history of vaccination, which may seem to emerge unexpectedly, owes its debt to the previous one and is a response to recent advancements in other scientific disciplines.

Moreover, this report's findings suggest that many of the major developments in the field of vaccination have occurred in response to a shared sense of urgency and in combination with the efforts of others. Our research indicates that the worldwide campaign to eliminate smallpox led to the development of the freeze-dried vaccine and bifurcated needle, enabling vaccines to be administered to a larger population with greater efficiency(25,27). Similarly, the COVID-19 pandemic necessitated international cooperation and knowledge-sharing, prompting a shift of focus and resources towards mRNA research. This impetus has positioned us to employ mRNA technology to tackle various illnesses that have previously proved difficult to vaccinate against(54).

Through the collection of data from various vaccination initiatives, we can identify shared patterns among them. For instance, the reluctance and doubt towards vaccines are not novel occurrences that arose during the COVID-19 immunization campaign. In reality, vaccine hesitancy presented a significant challenge in eradicating smallpox(27). Moreover, we have witnessed that Hepatitis B vaccines produced from plasma faced significant setbacks as a result of a lack of faith and misconceptions regarding their safety(44) .

The development of vaccines has undergone significant changes from Edward Jenner's smallpox vaccine to the present day. Jenner's vaccine used matter from cowpox pustules to protect against smallpox, whereas later vaccines developed by Pasteur used attenuated cells for the same purpose (28,30,31). Subsequently, the first subunit vaccine appeared in 1982, which moved away from using whole or partial cells (44). Similarly, the first recombinant vaccine in 1986 still used the antigen of the virus but grew it in yeast or mammalian cells. The emergence of the first mRNA vaccine in 2020 marked a significant departure from earlier vaccines, with the use of mRNA to prompt the body to create antigens without using any part of the pathogen itself(54).

5.2. Present situation and ongoing significance

During the history of vaccinations, this study has identified major trends that have profoundly influenced the present state of the field. We can observe, for example, that we are shifting away from whole cell or subunit vaccinations and toward mRNA vaccines. Additionally, the report highlights that the current vaccine distribution challenges, including logistical problems and hesitancy, are part of a broader trend that has persisted throughout the history of vaccination.

The COVID-19 pandemic has demonstrated the urgent requirement for enhanced vaccine technology to tackle rapidly spreading and mutating viruses that cannot be contained by conventional methods. The application of mRNA in vaccines has facilitated the swift development of novel vaccines, utilizing online platforms to exchange information on pathogen genetics, and potentially enabling modifications to vaccines(11,12,47,56). Despite significant advances in the field, there remains a critical necessity for sustained progress to combat future threats of this nature.

Smallpox is the only disease to have been eradicated entirely by vaccination thus far. The absence of the virus in non-human reservoirs and the obviousness of its symptoms made this achievable(15).

While other vaccines have had significant benefits for human health, they have not achieved complete eradication of their respective diseases. For instance, in utero transmission of HBV has limited the effectiveness of the vaccine against this virus(50). Nevertheless, the absence of animal reservoirs for HBV suggests that eradication is achievable in the long run(48). Likewise, it is evident that there is a scope for enhancing the efficacy of HBV vaccines and ensuring their widespread applicability, but it is crucial to weigh the costs and benefits prudently to achieve optimal global vaccine coverage(44).

5.3. Expectations regarding the future

Drawing on the conclusions derived from this report's analysis of the history and present state of vaccines, we can anticipate the field to manifest certain significant trends in the coming years.

Vaccines have been moving away from using whole or partial cells over the last 200 years, and mRNA technology is a major advance. mRNA is expected to have a more significant role in future vaccines as it enables rapid development by altering the mRNA code. However, viruses that mutate quickly like COVID-19 require vaccines to keep up with them(57). The efficacy of mRNA vaccines in adapting to new pathogen strains and overcoming logistical barriers is yet to be determined. There is also scope for progress in developing pan-coronavirus vaccines to avoid adapting to specific species of coronavirus(10). Although mRNA vaccines are promising, being the future of vaccines, their potential is still uncertain in the early stages.

Although the elimination of SARS-CoV-2 is improbable, hepatitis B and polio appear to be strong candidates for eradication. The elimination of smallpox taught us valuable principles applicable to the treatment of other illnesses, but additional effort will be required to overcome both economic and logistical obstacles. Hepatitis B and polio may be eradicated in the foreseeable future, given both illnesses have no known animal reservoirs(48).

Despite significant progress in vaccine development, Scientists still face distinctive challenges when it comes to diseases like HIV, indicating that there is a considerable distance yet to be covered in the future of vaccination.
However, advancements in other areas of science have historically coincided with improvements in vaccine technology, leaving the future direction of vaccines to be determined.

6. CONCLUSIONS

1 Edward Jenner's invention of vaccination in 1796, when he inoculated James Phipps with cowpox, is arguably the most significant discovery in medical history. This led to the eradication of smallpox and laid the foundation for further scientific advancements, including those made by Louis Pasteur.

2 The history of vaccination has been influenced by several significant events since Jenner's initial vaccines. One major milestone was Louis Pasteur's creation of live, attenuated vaccines, which enabled vaccines to target a wider range of diseases beyond smallpox. Another key development was the worldwide effort to combat smallpox, which led to technological advancements that increased the affordability and accessibility of vaccines. The development of subunit and recombinant vaccines marked a crucial moment, as it significantly increased the affordability and safety of vaccines, driving progress in the field. Furthermore, the latest breakthroughs in mRNA technology have fundamentally transformed the vaccination field, potentially leading and shaping its future trajectory.

3 The effectiveness of vaccination campaigns can vary depending on multiple factors, such as the characteristics of the targeted diseases and other circumstances. Challenges related to logistics, costs, and vaccine hesitancy have been identified as major obstacles to achieving disease eradication. Consequently, ongoing efforts to develop innovative solutions in vaccine design, vaccination strategies, and distribution methods will remain necessary to overcome these challenges.

4 Key historical trends in vaccination include the emergence of advancements during periods of crisis and cooperation, as seen in the smallpox and COVID-19 campaigns. Scientific innovations in related fields have also played a significant role, such as microbiology enabling live, attenuated vaccines and genetic modification leading to recombinant vaccines. Additionally, vaccines have progressively shifted from whole cell use to subunit-based vaccines, with mRNA

vaccines now being the most recent development. It is anticipated that future vaccines will further incorporate mRNA technology and build upon relevant scientific breakthroughs as they arise.

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8. ANNEXES