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Biotechnology and vaccines

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Abstract: Biotechnology has demonstrated its importance for health development, especially in the discovery of new drugs and production of vaccines. On account of the occurrence of many diseases that have killed millions of people in the world, vaccines were developed to control infections and prevent diseases caused by viruses, bacteria, protozoans and fungi, and even eradicate them, as is the case of smallpox. Vaccines can be of first, second and third generation. Currently, vaccine manufacturing can be directed to the use of DNA containing the gene that encodes an antigenic protein. The present work is a literature review, with the objective to present the first-, second- and third-generation vaccines, as well as to make an analysis of the use of these vaccines in Brazil.

Keywords: Biotechnology; Medicine; Immunology; Vaccines.

Introduction

Biotechnology, according to the Office of Technology Assessment (OTA),[1] can be defined as any technique that uses living organisms (or their parts) to obtain or modify products, improve plants and animals, or develop microorganisms for specific uses. Modern Biotechnology has a wide application in the health industry, attracting interest from scientists for production of drugs and vaccines, thus contributing to the economic development and, especially, to growth of pharmaceutical industry.[2]

Science and technology complement each other, integrating basic and applied sciences with other technologies such as molecular biology, cellular biology, immunological techniques, biochemistry and microbial fermentation processes.[3]

Advances in the industrial sector has brought many benefits to society, but it is worth saying that, among several consequences, massive migration of the population from countryside to urban centers has occurred, diminishing quality of life due to lack of basic sanitation and, consequently, causing more diseases for people and animals. In the 19th century, 80% of children died of various diseases before their 10th birthday.[3] In addition, millions of deaths have been recorded as a result of human contamination by viruses and bacteria, causes of diseases such as yellow fever, pertussis, smallpox, tetanus, diphtheria, measles, polio, rubella, hepatitis, bubonic plague, cholera, rabies, chickenpox, and mumps, which are among the most well-known diseases.

In order to control and prevent infections and diseases, scientists discovered vaccines, which were based on the principle that the individual's contact with the antigen produced an immune response.[4] As a result, several studies have been conducted to develop more effective vaccines. Genetic manipulation established by modern Biotechnology has modified in different ways research and development of these vaccines, which have been classified as first second and third generation.[5]

First generation or traditional vaccines are produced with live attenuated microorganisms, i.e., the weakened pathogen itself is inoculated into the patient. Vaccines against smallpox, polio, measles, rubella, adenovirus and tuberculosis can be included in this type. Second-generation vaccines arose from the idea that vaccines can be obtained by toxins produced by microorganisms that cause diseases. These toxins, called toxoids, can be inactivated and become recognized by the host's immune system. They can also be produced with purified polysaccharides. The recombinant proteins are used as a source for the antigens to be incorporated into the formulations.[5] In the 1990s, third-generation vaccines emerged, in which the material inoculated into the patient is not the attenuated or dead pathogen, but its DNA containing the gene that encodes an antigenic protein. However, it is necessary to have an agent that introduces DNA into the patient's cells, which are called DNA vectors, for the vaccine to present any effect.[6]

The history of vaccine, from its discovery by Edward Jenner in the late 18th century[7] until the present day, has provided the world's population with greater safety, health, and has undoubtedly saved billions of people from various diseases. Vaccine production in Brazil deserves special consideration, as the country is a global reference due to the efforts of the National Immunization Program, Butantan and Fiocruz Institutes.[8,9]

It is important to remember that the first vaccine reported was for smallpox, discovered in 1789. This vaccine arrived in Brazil almost one century later, in 1887, and, only in 1922, the Oswaldo Cruz Institute began to produce it. Smallpox eradication became a goal by the World Health Organization from the 1950s onwards, but it was eradicated only in the 1970s. The BCG vaccine was discovered in 1909 and only began to be used in Brazil in 1925. Production and use of the vaccine against yellow fever started to be produced in 1937 in Brazil. Currently, Fiocruz is the largest producer of this vaccine. The vaccine against poliomyelitis, discovered in 1949 by Jonas Salk, was later developed for oral application by Albert Sabin and started to be used in 1961. The discovery of the vaccine against rubella occurred in 1969. In 1963, the vaccine against measles was developed. In Brazil, this vaccine was effectively implemented in 1973 with the National Immunization Plan (NIP), but only in 1992 the fight against this disease was defined as a public health policy priority. The second dose of the triple viral vaccine (measles, rubella and mumps) was introduced in 2004.[10]

In addition, Brazil has adopted a successful vaccination strategy.[8] Brazil's National Immunization Program (NIP) is considered one of the most comprehensive among developing countries. For example, Brazil received the poliomyelitis eradication certificate in 1994 and also pioneered the introduction of rotavirus, conjugate pneumococcal, meningococcal meningitis, and conjugate C serogroup vaccines in 2007, and vaccination against the H1N1 pandemic influenza in the second half of 2010.[9] Tables 1, 2, 3 and 4 show the vaccination calendar in Brazil for children, teenagers, pregnant women, and travelers, respectively. Table 5 shows the calendar of national vaccination campaigns.

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Child			
Age	**Vaccine**	**Avoidable diseases**	**Dose**
At birth	BCG–ID	Prevents severe forms of tuberculosis (miliary and meningeal)	Single dose
	Hepatitis B		Single dose
2 months	Pentavalent (DTP + Hib + Hep. B)	Prevents diphtheria, tetanus, pertussis, hepatitis B, meningitis and Hib infections	1st dose
	Inactivated polio (VIP)	Prevents polio (infantile paralysis)	
	Pneumococcal 10–valent (conjugated)	Prevents pneumonia, otitis, meningitis and other diseases caused by Pneumococcus	
	Human rotavirus (VORH)	Prevents rotavirus diarrhea	
3 months	Meningococcal C	Prevents pneumonia and meningococcemia (generalized infection)	1st dose
4 months	Pentavalent (DTP + Hib + Hep. B)	Prevents diphtheria, tetanus, pertussis, hepatitis B, meningitis and Hib infections	2nd dose
	Inactivated polio (VIP)	Prevents polio (infantile paralysis)	
	Pneumococcal 10–valent (conjugated)	Prevents pneumonia, otitis, meningitis and other diseases caused by Pneumococcus	
	Human rotavirus (VORH)	Prevents rotavirus diarrhea	
5 months	Meningococcal C	Prevents pneumonia and meningococcemia (generalized infection)	2nd dose
6 months	Pentavalent (DTP + Hib + Hep. B)	Prevents diphtheria, tetanus, pertussis, hepatitis B, meningitis and Hib infections	3rd dose
	Inactivated polio (VIP)	Prevents polio (infantile paralysis)	3rd dose
12 months	Triple Viral (SCR)	Prevents measles, mumps and rubella	1st dose
	Meningococcal C	Prevents pneumonia and meningococcemia (generalized infection)	Reinforcement
	Pneumococcal 10–valent	Prevents pneumonia, otitis, meningitis and other diseases caused by Pneumococcus	Reinforcement
15 months	Triple Bacterial (DTP)	Prevents diphtheria, tetanus and whooping cough	1st Reinforcement
	Oral poliomyelitis (OPV)	Prevents polio (infantile paralysis)	1st Reinforcement
	Hepatitis A	Prevents hepatitis A	Single dose
	Tetraviral (SCRV)	Prevents measles, mumps, rubella and chickenpox	Single dose
4 years	Triple Bacterial (DTP)	Prevents diphtheria, tetanus and whooping cough	2nd Reinforcement
	Oral poliomyelitis (OPV)	Prevents polio (infantile paralysis)	2nd Reinforcement
9 years*	Human Papillomavirus (HPV)	Prevents papilloma, human virus that causes cancers and genital warts	Two doses in a period of six months

* It may be applied up to 14 years 11 months and 29 days

Table 1 – Vaccination calendar for children.Source: Adapted from the Brazilian Ministry of Health's website.[11]

Adolescent			
Age	**Vaccine**	**Avoidable diseases**	**Dose**
11 to 14 years (boys)	Human Papillomavirus (HPV)	Prevents papilloma, human virus that causes cancers and genital warts	Two doses six months apart
11 to 14 years (boys and girls)	Meningococcal C	Prevents meningitis and meningococcemia (generalized infection)	A booster or single dose
11 to 19 years	Hepatitis B (recombinant)	Prevents hepatitis B	Three doses**
	Adult double bacterial (dT)	Prevents diphtheria and tetanus	One dose every ten years**
	Triple viral (SCR)	Prevents measles, mumps and rubella	Two doses**

** According to the vaccination situation

Table 2 – Vaccination calendar for teenagers.Source: Adapted from the Brazilian Ministry of Health's website.[11]

Pregnant		
Vaccine	**Avoidable diseases**	**Dose**
Hepatitis B (recombinant)	Prevents hepatitis B	Three doses**
Adult double bacterial (dT)	Prevents diphtheria and tetanus	Two doses**
Triple acellular bacterial (dTpa)	Prevents diphtheria, tetanus and whooping cough	One dose with each pregnancy (from the 20th gestational week)

** According to the vaccination situation

Table 3 – Vaccination calendar for pregnant women.Source: Adapted from the Brazilian Ministry of Health's website.[11]

Traveler		
Vaccine	**Avoidable diseases**	**Dose**
Hepatitis B (recombinant)	Prevents hepatitis B	Three doses**
Adult double bacterial (dT)	Prevents diphtheria and tetanus	Two doses**
Yellow fever	Prevents yellow fever	Single dose (9 months to 59 years of age)***
Triple viral (SCR)	Prevents measles, mumps and rubella	Two doses (1 to 29 years) and one dose (30 to 49 of age)**

** According to the vaccination situation
*** Only applied to residents and/or travelers to areas with vaccination recommendation (ACRV)

Table 4 – Vaccination calendar for travelers.Source: Adapted from the Brazilian Ministry of Health's website.[11]

Traveler		
Vaccine	Priority Groups	Period
Influenza	Children (6 months to under 6 years of age)	April 10 to May 31
	Elderly people (60 years of age or older), those who have recently given birth (up to 45 days after birth), health workers, teachers in public and private schools, indigenous peoples, groups with chronic noncommunicable diseases and other special clinical conditions, adolescents and young people between 12 and 21 years of age under social and educational measures, people deprived of their liberty and prison system employees	April 22 to May 31. D" day of mobilization: May 4th

Table 5 – Calendar of the vaccination campaign. Source: Adapted from the Brazilian Ministry of Health's website.[11].

Objectives

The objectives of this work are to present the first–, second– and third–generation vaccines as well as to make an analysis of the use of these vaccines in Brazil.

Methodology

For this review work, a survey of the articles with the highest number of accesses and easy acquisition within databases such as Google Scholar and PubMed was carried out. The method of bibliographic research related to the subject was used and then the most relevant data of the main themes related to Biotechnology and vaccines were collected. The keywords used were: biotechnology, medicine, immunology and vaccines.

Development

Biotechnology

Biotechnology has contributed to a number of significant changes in the area of biology and health, especially in the field of genetics. Gene manipulation techniques, such as gene sequencing, have altered scientific research for the health sector in different ways. Some areas to which research is currently focused are: synthetic biology (creation of "customized" organisms), three–dimensional bioprinting and uses and applications in the area of neurotechnology.[12]

The insertion of Biotechnology in the pharmaceutical industry has enabled an increase in the number of therapeutic compounds, greater knowledge of the processes causing diseases, more accurate diagnoses and more efficient delivery mechanisms, such as recombinant DNA for therapeutic protein production, hybridization for monoclonal antibody production and techniques for cloning and manipulation of stem cells.[2]

Another area of health that has benefited from technological advances is the area of vaccines. Biotechnology has brought changes in the way vaccines are produced, such as the discovery of new antigens, adjuvants, vectors or delivery systems. The production process of a drug or vaccine can be briefly divided into three stages: a) production of the active ingredient, which is the substance responsible for the therapeutic action; b) formulation, a phase in which the active ingredient is mixed with other substances (adjuvants) in order to adapt characteristics of the final product, such as solubility, effect duration, stability, and absorption and elimination by the body; and c) packaging, i.e., the packaging of the finished product in quantities for final consumption.[5]

Many vaccines are still administered by methods created in the past centuries. It is expected from biotechnological advances that safer and more effective vaccines will be produced and made available to an increasing number of people.[5]

The development of the third–generation vaccines (called DNA vaccines) was possible due to technological advances in Biotechnology. Although their use in humans is not yet approved, such vaccines have been applied against diseases such as cancer.[4]

Vaccine concepts

Vaccination or immunization is the process of developing the body's immunity or defense against infections with antigens (substances that stimulate the body to produce antibodies against the infectious agent – viruses, bacteria or parasites). Vaccines can be produced from dead or attenuated microorganisms or from their components (first generation). However, in some cases, the disease may occur due to a toxic substance produced by the microorganism. Then, the vaccine needs to neutralize this toxin (second generation). In other cases, however, the problem is not the virus or the bacteria, but the quantity of them inside the host. Therefore, its multiplication must be controlled.[13] Figure 1 shows the three generations of vaccines.[14]

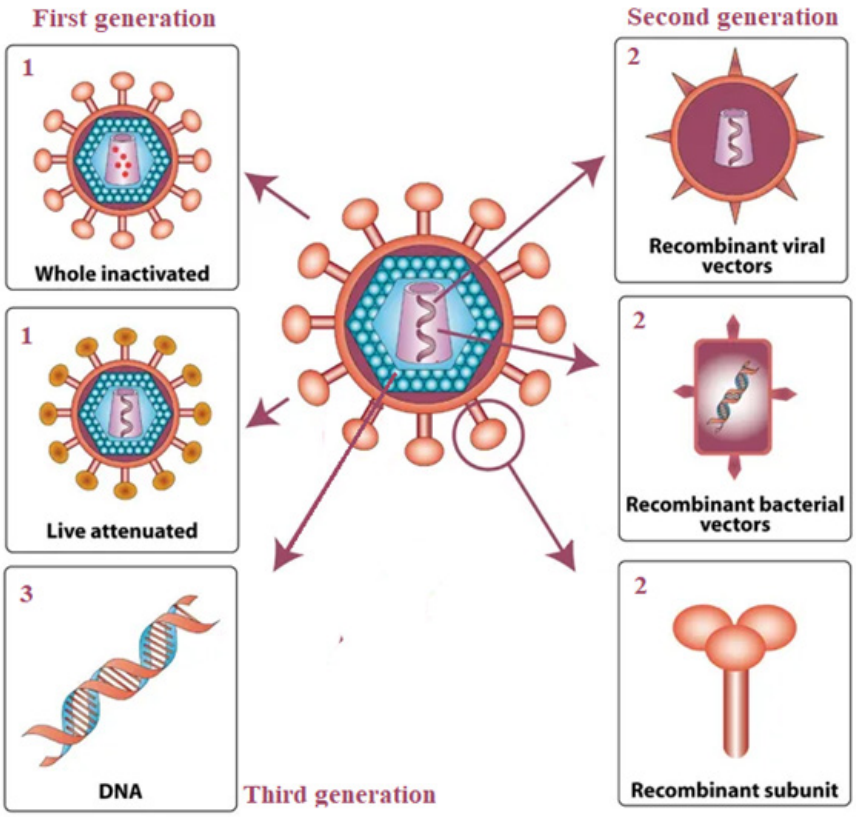

Figure 1 – The three generations of vaccines. **Source:** Adapted from Gorry et al. (2017).

The three generations of vaccine

First generation

First–generation vaccines are produced with antigens of only one infectious agent, which produces protective antibodies only for that agent, such as the diphtheria vaccines. They can also be combined, which are those that have two or more agents, such as diphtheria–tetanus or triple viral (against measles, mumps and rubella). Vaccines can also be conjugated, i.e. bacterial antigens are bound to protein carriers (polysaccharides) generating a long–lasting antibody response, such as pneumococcal vaccines.[13]

One of the first–generation vaccine production techniques is the inactivation of microorganisms (dead and inactive), such as antipertussis, typhoid fever, bubonic plague, Salk (injectable poliomyelitis), hepatitis A, influenza, rabies, whooping cough, anthrax and cholera vaccines. First–generation vaccines can also be produced with live attenuated microorganisms, such as BCG against tuberculosis.[15,16]

Smallpox is a disease that has devastated populations for many years, but is no longer considered a concern for humanity. Its eradication was registered in 1977. Vaccine against smallpox is considered the basis of immunology, suggesting that virus infection conferred specific immunity to the disease.[17] Vaccine against smallpox is not available to the public and the virus no longer exists in nature. The vaccine is produced from the attenuated ***vaccinia virus***, a poxvirus similar to smallpox virus, but less harmful.[18]

Vaccine against yellow fever, produced in Brazil since 1937 and internationally recognized, also consists of attenuated viruses, more specifically from the attenuated strain of the 17D virus of the ***Flavivirus*** genus.[20]

Another disease against which an attenuated virus vaccine is used is measles. This is a highly contagious viral disease that occurs throughout the world. The infection is characterized by fever, malaise, cough, coryza and conjunctivitis, followed by exanthema.[20] Humans are the sole host.[21] In Brazil, the vaccine was introduced in 1960. It is contained in the triple viral (measles–mumps–rubella), which contains weakened measles, rubella and mumps live virus and is currently recommended for children aged 12 months, with application of the second dose between four and six years of age or in any consultation after 12 months of life, with a minimum interval of four weeks. The Ministry of Health reports that Brazil was awarded a certificate of measles elimination by the Pan–American Health Organization in 2016, but states that the country has struggled to maintain this certificate, since two outbreaks had already been identified in 2018.[22]

Rubella is a disease caused by viruses of the ***Rubivirus*** genus which is transmitted by direct contact through tiny drops of saliva released into the air when the infected person coughs, sneezes or talks, or from the mother to the fetus through blood circulation. The vaccine, which is part of the triple viral (measles–mumps–rubella), is a combination of live attenuated viruses.[23]

Poliomyelitis, also called infantile paralysis, is an acute contagious disease caused by poliovirus, which can infect children and adults through direct contact with feces or with secretions eliminated by the mouth of sick people and can cause paralysis. In Brazil, the last case of infection by the wild poliovirus occurred in 1989 in the city of Souza, in the state of Paraíba. The strategy adopted for the virus elimination in the country was centered on conducting mass vaccination campaigns with oral polio vaccine (OPV). Sabin attenuated virus strains types I, II and III was used.[19]

Another immunization obtained by an attenuated strain is the vaccine against tuberculosis. The BCG vaccine (Calmette and Guérin bacillus) originates from avirulent strains of ***Mycobacterium bovis,*** after genetic mutation and with immunogenic protective properties against tuberculosis. In Brazil, BCG was applied in 1925 and was orally used until 1973, when it started to be intradermally administered, as determined by the Ministry of Health. There is a consensus in the literature that intradermal BCG is effective against severe forms of tuberculosis, such as meningoencephalic and miliary.[25]

The third part of the triple bacterial vaccine was the result of immunizers developed in 1942 by Louis Sauer, Pearl Kendrick and Grace Eldering against pertussis. Sauer et al. found that the vaccine was most effective in uniting diphtheric and tetanic toxoids.[26] Thus, the triple

bacterial vaccine emerged. According to the Ministry of Health, pertussis is a respiratory infection, transmissible and caused by the bacteria ***Bordetella pertussis***, a Gram–negative and aerobic coccobacillus. Pertussis transmission occurs mainly by direct contact of the patient with an unvaccinated person through droplets eliminated through coughing, sneezing or talking. Pertussis is produced with dead and inactivated microorganisms.[27]

Second generation

After the emergence of attenuated and inactive vaccines, second–generation recombinant vaccines emerged, proving that for individuals to be protected against an infectious agent, it is not necessary for him/her to produce antibodies against all the antigens of the microorganism. Recombinant vaccines are obtained by genetic engineering, by inserting a gene that produces an immunogenic protein in a microorganism.[28] The identification of one or two proteins crucial for immune protection is sufficient to create a second–generation vaccine in which the immune response is induced by a specific isolate antigen. The antitetanic, antidiphtheric, antihepatitis B vaccines and those for the control of meningococcal meningitis and pneumonia are found in this group.[5]

The first approved recombinant vaccine was the vaccine against hepatitis B, which only began to be produced in cell culture systems in 1986.[29] Among the second–generation vaccines there is the vaccine against meningococcal meningitis, caused by the bacteria ***Neisseria meningitidis***. The Cuban vaccine, the first in the world with proven efficacy against the disease caused by meningococci B, is based on proteins from the external membrane of this microorganisms capable of inducing antibodies against all tested ***Neisseria meningitidis*** pathogenic groups. To combat meningococcal meningitis, a conjugate vaccine is used, which is a differentiated type of vaccine because it was specially developed to combat encapsulated bacteria that have a protective membrane around their cell structure. These capsules are made of polysaccharides, which ensure a great resistance of the bacteria against the human immune defense system. Because of this, when producing a vaccine against encapsulated bacteria, it is necessary to wrap the protective capsule with a protein. So, the antibodies can penetrate the bacteria destroying and guaranteeing health for the vaccinated individual.[30]

Other second–generation vaccines that act against toxins are the antitetanic and antidiphtheric ones.[4] Diphtheria is a transmissible disease caused by bacteria that affect tonsils, pharynx, larynx, nose and occasionally other parts of the body such as skin and mucous membranes. The main form of prevention against the disease is through the pentavalent vaccine (diphtheria, ***tetanus***, pertussis, hepatitis B and ***Haemophilus influenzae*** type B). Since the 1990s, Brazil has shown an important reduction of the incidence of cases by expanding the vaccine coverage. In that decade, the incidence reached 0.45/100,000 inhabitants, decreasing as the coverage increased. Between 2008 and 2017, only 10 deaths caused by the disease occurred in Brazil[31]. The Butantan Institute reports that the antidiphtheric serum is the only effective drug for neutralization of toxins produced by the ***diphtheria*** bacillus (***Corynebacterium diphtheriae***). Serum, when applied to a patient diagnosed with diphtheria, acts by neutralizing the toxin produced by the diphtheria bacillus. By applying the antidiphtheric serum, the antibodies contained in the serum specifically bind to the toxin and thus neutralize its toxic actions in the body.[32]

According to the Butantan Institute, the antitetanic serum has the function of neutralizing the toxins produced by the tetanus bacillus (***Clostridium tetani***) and is intended for the treatment of patients with accidental or neonatal tetanus, for the prevention of tetanus in patients with injuries, not vaccinated, with uncertain vaccination or with less than three doses, or vaccinated with three doses, the last dose being for more than 10 years. The specific immunoglobulins (antibodies) generated by the immunization of horses produce the purified antitetanic serum that acts by neutralizing the tetanic toxins that are in the blood circulation.[32] ***Tetanus*** is a noncontagious acute infectious disease caused by fixation in the nervous system of exotoxins of ***Clostridium tetani***. Clinically, tetanus manifests by hypertonia of the jaw and neck muscles, and may reach progressive muscle stiffness and generalized muscle contracture, affecting the rectum–abdominal muscles and the diaphragm, leading to respiratory failure.[33]

Third generation

Gene (or third–generation) vaccines are so called because they are composed of DNA–coding plasma proteins of pathogens, allergens and tumors and encode potentially immunogenic antigens using gene fragments.[34]

DNA vaccines are so called because the antigen is synthesized ***in vivo*** after the direct introduction of their encoding sequences. They present a unique method of immunization that can solve many of the shortcomings of traditional vaccines. Other advantages are low cost, relative facility of manufacture, thermal stability, possibility of obtaining multivalent vaccines and rapid development of new vaccines in response to new strains of pathogens.[35] These vaccines are being evaluated as prophylactic and therapeutic treatments for infectious diseases, allergies and cancer. Plasmids that encode normal human proteins are also being tested as vaccines and treatments for autoimmune diseases.[36] Since cells do not accept receiving DNA from different cells, a vector playing this role is required, as is the case of DNA vectors. This must occur for DNA to encode an antigenic protein. The easiest method to produce and characterize gene transferring is the direct application of pure plasmid DNA. It is often applied by intramuscular injection, although it can be administered by several other routes such as oral mucosa, vaginal and epidermal layer by "gene guns".[35]

Although rodent research shows efficient immunogenicity. the lower efficacy of DNA vaccines in experiments on big animals, including humans, is due to the inefficient delivery of DNA plasmid to cells.[37] Ulmer et al. found it was sufficient to transplant stably transfected myoblasts expressing the influenza nucleoprotein to induce cell–mediated protective immunity. The mice used in the test produced high titer antibodies and cytotoxic T lymphocytes, which protected them from a lethal cross–strain test with influenza A virus. The authors concluded that the expression of the antigen by muscle cells is sufficient to confer protective immunity mediated by cells.[38]

Plasmid DNA vaccine has also been widely explored for immunization against tuberculosis. Zhang et al. produced a plasmid DNA vaccine that encodes Ag85A and GM–CSF genes and provides immunological protection against the ***Mycobacterium tuberculosis*** bacillus in mice tests. The authors showed that the use of electroporation allows a single intramuscular injection of DNA to be as effective as repeated injections of DNA in activating Ag85A–specific T–cells.[39] Until 2015, four DNA vaccines have been licensed for veterinary uses. They are vaccines against West Nile virus in horses, against infectious hematopoietic necrosis virus in salmon and for the treatment of melanoma in dogs (malignant neoplasia).[40]

The biotechnological advance of vaccines, which were previously manufactured with inactivated, live attenuated and sub–unit (first and second generation) micro– organisms, is evident. By 2020, other technologies such as a better comprehension of the innate immune system and the development of new adjuvants should contribute to the improvement of existing vaccines and the development of new vaccines to prevent and treat many types of infections.[41]

While development brings benefits to society such as increased employment opportunities and a warming economy, human health is the first to suffer the malefic consequences of reduced quality of life due to a lack of basic sanitation in a scenario of mass migration to urban centers as a result of industrialization. Advances in Biotechnology have made it possible to develop new technological products, including vaccines, which are increasingly effective in protecting health.

Brazil is one of the countries with the highest coverage of infantile and adult vaccination, as it has presented successful vaccination strategies. The national immunization program is considered an example for the whole world.

Immunization by the attenuated pathogens discovered by Edward

Jenner has given the world's population more security, health and a long–life expectancy. Smallpox, poliomyelitis, rubella, measles, diphtheria and pertussis are examples of diseases that were, at some point in human history, pandemics or epidemics that ravaged continents for decades or even centuries, and today are eradicated or with regional foci and very low mortality rates. However, diseases such as tuberculosis, AIDS, Ebola, influenza, yellow fever and cholera continue to affect millions (if not billions) of people because first– and second–generation vaccine immunization methods are ineffective against the microorganisms that cause such diseases.

One of the areas in which Biotechnology has made a great progress is health. New technologies, such as gene sequencing, have made it possible to discover new routes to eradicate viruses and bacteria that are harmful to human health. Manipulation of DNA has led to an evolution in treatment and prevention of diseases, despite ethical questions that may be raised. DNA or third–generation vaccines, although currently ineffective, are promising in the fight against diseases such as cancer and AIDS. Many researches have been carried out in the area of Biotechnology with the objective of bringing more safety and efficacy in the combat and eradication of diseases considered today without cure.

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