Dengue vaccination in Brazil

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ABSTRACT
Since the establishment of vaccines as a preventive method for diseases, especially epidemic ones, science has always sought in them the solution to major public health problems such as Dengue, an endemic disease in several tropical countries with large populations. Brazil is one of the countries that seasonally suffers from an increase in cases every year. Many vaccine development techniques have emerged over the past few decades and have provided possibilities to build effective vaccines against diseases that always presented major prevention challenges. Several vaccines against dengue currently exist and among them, Dengvaxia®, from the company Sanofi Pasteur, was the first to prove effective without causing worrying side effects. Another vaccine that deserves to be highlighted is the Qdenga vaccine, the first approved in Brazil for a wider audience (from four to 60 years of age). Thus, the methodology applied for the present study was a bibliographic survey using available internet research tools, such as the bibliographic database of the Virtual Health Library (VHL/BIREME), Google Scholar, the epidemiological bulletins of the Ministry of Health and searches on the website of the National Health Surveillance Agency and the company Sanofi Pasteur. The data presented were on the Dengvaxia vaccine, the Qdenga vaccine and the promising vaccine produced by the Butatan Institute. Regarding the efficacy of vaccines, Qdenga is mainly supported by the results of a large-scale study and Dengvaxia through vaccination campaigns can be considered important in regions with a higher incidence of dengue. The objective of this paper is to report the vaccination against dengue in Brazil and to emphasize the efficacy of the vaccines currently applied.

Keywords: Vaccine, Immunization, Qdenga, ANVISA, Dengvaxia.

1 INTRODUCTION

The use of an administered immunobiological agent aims to provide the body with protection against diseases, depending on a seroconversion that can be achieved or not varying from individual to individual, but in general this objective is achieved in most administrations. This process, called immunization, is classified in two ways: active and passive. The use of immunoglobulins, indicated for situations of early or urgent protection, characterizes passive immunization and provides only temporary protection. The use of agents that stimulate the body to produce an immune response and consequently an immunological memory is the process of active immunization and the administration of vaccines is part of this process (MALAGUTTI, 2011). Vaccines are among humanity's major achievements. Thanks to them, we have been able to eradicate smallpox, a disease that has killed millions of people throughout history, and we are close to eradicating polio worldwide. In this regard, we were also able to celebrate in 2015 the elimination of

rubella, congenital rubella, and maternal and neonatal tetanus in the Americas. In addition to the lives preserved, these advances can be translated into a reduction in hospitalizations and a reduction in the high social cost resulting from illness due to vaccine-preventable diseases. Positive results that will certainly be amplified with the development of new vaccines and with the increasing engagement of the population (BRAVO & BALLALAI, 2016). Dengue is the most prevalent urban arbovirus in the Americas, including Brazil, and is an important suspect in patients with acute fever. Its occurrence is widespread, mainly affecting tropical and subtropical countries, where climatic and environmental conditions favor the development and proliferation of *Aedes aegypti* and *Aedes albopictus vectors* (BRASIL, 2021). Thus, the importance of a dengue vaccine in Brazil is due to the fact that the country has a predominantly tropical climate, totally prone to the proliferation of *Aedes aegypti*, the mosquito that transmits the virus that causes dengue. The disease can have a fatal evolution and, therefore, Dengue is considered a notifiable disease (BRASIL, 2011) due to its magnitude, potential for dissemination and its social relevance and other criteria for inclusion in the list of compulsory notification of the Brazilian health authorities. Therefore, the objective of this study is to report the vaccines that are currently present in Brazil and to highlight their efficacy.

2 MATERIALS AND METHODS

This is a narrative literature review. To achieve the objectives, a bibliographic survey was carried out using available internet research tools, such as the bibliographic base of the Virtual Health Library (VHL/BIREME), Google Scholar, the epidemiological bulletins of the Ministry of Health, as well as the website (http://www.dengue.info/) with the publications of the company Sanofi Pasteur, and the website of the National Health Surveillance Agency (ANVISA) (https://www.gov.br/anvisa) with information about the Qdenga vaccine from the company Takeda Pharma Ltda.

3 RESULTS AND DISCUSSION

Composed of a single strand of positive RNA (Ribonucleic Acid), the Dengue virus produces three structural proteins that make up the capsid, the premembrane and the envelope and seven non-structural proteins known as NS (Nonstructural protein) 1, NS2A, -2B, -3, -4A, -4B and -5. There are four antigenically different serotypes and all capable of causing diseases in humans, infection by one serotype induces the production of an immune response against that serotype and the severity of dengue is in the secondary infection by another serotype, since the established hypothesis is that the antibody generated in the first infection binds to the virus of a different serotype from the second infection, But it does not neutralize it and does not prevent its entry into the cells, generating a more robust immune response. This is the biggest dilemma to be faced in order to produce a dengue vaccine, as it is necessary for the vaccine to induce the production of antibodies against all four serotypes simultaneously (RAVIPRAKASH, 2009).

Thus, Dengvaxia was the® first vaccine that was successful in the face of this dilemma. According to the researchers, the vaccine proved to be quite stable in the preclinical phase in vitro, and the recombinant strains were tested in human dendritic cells, which are the cells that first have contact with the virus, usually phagocytizing and presenting their antigens (GUY et al., 2010), comparing the immunological effects of the vaccine strains in relation to the parental ones, they observed that the recombinant viral strains CYD1, 2, 3 and 4 induced maturation of these cells and controlled immune response, as well as cytokine production and uniform INF1 (DEAUVIEAU et al., 2007), also studied the hypothesis that CYD viruses have the same tropism as yellow fever virus due to protein E being responsible for this preference of Flaviviruses for liver cells, the concern is due to the fact that studies show that both the dengue virus and the yellow fever virus can cause liver damage in susceptible people, through tests with cells of the liver lineage they observed the replication of the CYD viruses and according to them the viruses were not hepatotropic like the yellow fever viruses because they did not show high replication (BRANDLER, 2005). In vivo tests were also promising, animal models were used to test neurovirulence and compare neurotropism through intracerebral inoculation in mice, the researchers observed that the four CYD viruses were significantly attenuated (GUY et al., 2010) and to analyze viremia, with the use of NHPs (Non-Human Primates) rhesus monkeys, noticed that one dose of the vaccine had a low viremia, but showed an increase when more doses were administered, but it was proven to induce immunity against the four dengue serotypes when they did a challenge with wild DENV (GUIRAKHOO, 2004). In order to evaluate the efficacy and possible adverse effects, reduce the number of cases of hospitalization due to dengue and severe and hemorrhagic cases of the disease, studies of the clinical phases in adults and children, mainly from endemic countries, were initiated. The first clinical phase I study was carried out in the city of Springfield, state of Missouri, in the United States, and had the participation, at the beginning of the research, of sixty-six healthy men and women, who had not been in endemic regions, and in the case of women, were not pregnant or breastfeeding, aged between 18 and 45 years. everyone who had diseases that compromised the immune system was excluded, at the end of the study a total of 33 participants completed the entire research process (GUY et al., 2010). In clinical phase II, the first study was carried out with the aim of observing the reaction of the vaccine in children who had already been exposed to some *Flavivirus* and with a history of vaccinations, exploring and investigating whether there would be a need to reformulate the vaccine due to contact with other vaccines or even the scenario of the target population. As for phase III clinical evaluation, the trials studied the scheduling of vaccine doses and their effectiveness in children from endemic regions of Asia and Latin America. The results demonstrated in the final phase, clinical phase III, of the studies carried out in Asia and Latin America concluded that the vaccine has, in general, an efficacy of 60.8% in the population of Latin American countries in protecting against the four dengue serotypes because of the variation between age groups and countries, since the research took place in five different countries. But in specific aspects, the vaccine

candidate was effective in 64.7% in children or adults who received at least one dose of the vaccine, and in 83.7% in children who already had some antibody against dengue after the third dose of the vaccine, it was observed that against severe dengue the vaccine was effective in 91.7% after three doses of the vaccine and 90% against hemorrhagic dengue also after three doses. Adverse effects accounted for only 0.6% of the group that received the vaccine (VILLAR et al., 2015). The study carried out in Asia stated that the efficacy of the vaccine was 56%, there was a reduction in dengue cases admitted to hospitals, and it prevented an estimated 80% of dengue hemorrhagic fever cases, 75% of dengue cases caused by serotypes 3 and 4, 50% caused by serotype 1 and 35% caused by serotype 2, these differences were explained by the difference in serotypes circulating in each region. Adverse effects occurred in only 1% of the population in the group vaccinated with the tetravalent vaccine (CAPEDING et al., 2014). In Brazil, a vaccine against Dengue needs to prevent against the DENV-1 serotype as a priority. In 2016, of the 3,033 positive samples for dengue, 86.3% were positive for DENV-1, maintaining the predominance also observed in previous years (BRASIL, 2016), and then, in the case of vaccine adherence by a public health agency, attention should be paid to the efficacy of seroconversion to DENV-1 as an approval criterion. A relevant characteristic of Dengvaxia in its distribution to the population is that it is an attenuated type vaccine, and this is the weak point of the vaccine, people with compromised immunity due to immunological diseases, use of immunosuppressive drugs and diseases that lead to immunosuppression, pregnant women and also generally younger children, newborns, babies, who have lower immunity are not indicated to use this type of vaccine due to the possibility of spreading the virus. microorganisms, even attenuated, leading the individual to develop severe symptoms or even the disease, making this vaccine model contraindicated for these individuals (BRICKS, 1998), and ends up reinforcing the need to continue searching for another vaccine alternative that can better serve the population. Currently, ANVISA approved, through Resolution-RE No. 661, of March 2, 2023, the registration of a new vaccine for the prevention of dengue. The Qdenga vaccine, from the company Takeda Pharma Ltda., which is composed of four different serotypes of the virus that causes the disease, providing broad protection (BRASIL, 2023). The vaccine has been evaluated by the European Medicines Agency (EMA) and received a positive recommendation under the "EU Medicines for all" program. Its commercialization was approved in the European Union (EU) on 20/12/2022. The granting of registration by ANVISA allows the commercialization of the product in the country, as long as the approved conditions are maintained. The vaccine, however, remains subject to the monitoring of adverse events, through pharmacovigilance actions under the company's responsibility. The Qdenga vaccine is the first approved in Brazil for a wider audience (from four to 60 years of age). The previously approved immunizer (Dengvaxia) can only be used by those who have already had dengue. Efficacy against dengue for all serotypes combined among dengue seronegative individuals (no previous dengue virus infection) was 66.2% (95% CI: 49.1%, 77.5%). For seropositive individuals (individuals who had previous dengue virus infection), this value was

76.1% (95% CI: 68.5%, 81.9%). Individually, the calculated efficacy against the DENV-1 serotype was 69.8%, against the DENV-2 serotype 95.1% and against the DENV-3 serotype 48.9%. For the DENV-4 serotype, the small number of cases identified during the studies did not allow a statistically significant efficacy result to be established. In addition, in the specific case of DENV-3, the efficacy result for seronegative individuals was not satisfactory. However, the overall efficacy value of the vaccine, which is the primary objective of the clinical study presented, reached the level of 80.2%, calculated by comparing the results of the participants who received the vaccine and those who received placebo, for all four serotypes, and accounting for all identified dengue cases, whether in seropositive or seronegative individuals. The demonstration of the efficacy of Qdenga is mainly supported by the results of a large-scale, phase 3, randomized, placebo-controlled study conducted in dengue-endemic countries to evaluate the efficacy, safety and immunogenicity of the vaccine.

However, in Brazil, the institute responsible for producing the vaccines has developed a partnership with the National Institutes of Health of the United States to build a vaccine against the four dengue serotypes. The tetravalent Dengue Butantan vaccine is a vaccine with live attenuated viruses, weakened through the deletion of gene segments of the four types of viruses (BUTANTAN, 2016). A small-scale "human challenge" test carried out in the USA proved that the vaccine protected against the four serotypes of dengue virus without having side effects and especially against serotype two, which is the most difficult to develop protection against, corroborating the tests already carried out by the Butantan Institute (UNA-SUS, 2016).

4 CONCLUSION

Dengue can now be fought more effectively and efficiently with the help of the vaccines that are now being offered in Brazil, but this does not exempt the population or governments from maintaining their commitment to preventive measures against the vector of the virus. Dengvaxia®'s efficacy of around 60% is not considered a very relevant efficacy, given that many well-established vaccines have efficacy levels above 80% or even 90%. In view of the efficacy demonstrated by the Dengvaxia® vaccine against the most severe forms of the disease caused by the dengue virus, the implementation of the vaccine through vaccination campaigns can be considered important in regions with a higher incidence of dengue. The demonstration of the efficacy of Qdenga is mainly supported by the results of a large-scale, phase 3, randomized, placebo-controlled study conducted in dengue-endemic countries to evaluate the efficacy, safety and immunogenicity of the vaccine.

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