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Editorial

Latest advances in the development of a vaccine against malaria

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EDITORIAL

Latest advances in the development of a vaccine against malaria

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Malaria is a global health problem and is an important cause of disease in all the developing countries. Estimations are that approximately 3000 million people (almost half of the world population) live in areas where malaria is endemic[1]. This disease affects every year between 300 and 500 million persons and causes 1 to 3 million deaths in the world[2-4].

The most affected continent is Africa, and especially the region of the Sub Sahara. Estimations are that there are approximately 220 million cases a year and 30 % of all the hospital admissions are due to this infection in Africa. Calculations are that between 700,000 and 1.6 million persons die as a direct consequence of the disease, the majority children and pregnant women[5].

The disease is caused by the *Plasmodium* parasite that, by means of the sting of the infected female of the Anopheles mosquito, is capable of invading the blood stream of healthy persons.

The four types of parasites that infect humans are *Plasmodium vivax*, *ovale*, *malariae* y *falciparum*. The last one can be found in Africa and in Asia, and is responsible for 90 % of deaths; however, the most prevalent species is *Plasmodium vivax*[5].

During the first decades of the XXth century the areas with endemic malaria were reduced in 30 %. The first successes occurred in North America and most of Occidental Europe, due to the rapid socioeconomic development that allowed resources to be allocated to the fight in reducing the transmission of infection. These successes were followed by reductions in the prevalence of disease in India and the Soviet Union by means of insecticide dichloro-diphenyl-trichloroethane (DDT) during the decades of 1950 and 1960, and by campaigns against the vector of disease as part of a world program to control malaria. In Spain malaria was eradicated en the 1960s.

Once malaria was eliminated in industrialized countries, the world program for the control of this disease failed due to the reduction in interest, and a lack of economic resources directed to the control of the disease, as well as a lack of interest in developing new technologies.

In a short period of time, new strains of resistant parasites to the most frequently used antimalarial medicines, such as chloroquine, as well as to the insecticides used began to appear. This situation worsened due to a series of circumstances such as: the lack of interest of the pharmaceutical industry in the development of new medicines; the changes in the environment; overpopulation; the insufficient and inadequate distribution and implementation of means to control the disease; the collapse of the national programs for the control of the disease; the increase in tourism and migratory movements, with the subsequent movement of non immune populations to endemic areas[6]. As a consequence the cases of malaria have increased in the entire world and this disease has become one of the most important health problems in vast areas of Sub-Saharan Africa, Asia, Latin America and Oceania.

Today we have a series of tools to control the disease, from which we can point out the following: the quick diagnosis and treatment of cases with effective and appropriate antimalarial medicines, taking into account their availability, validity and cost-effectiveness; the reduction of contact between the vector and humans (basically by means of mosquito nets impregnated with insecticide); intermittent preventive treatment in pregnant women and children; and an integrated system for vector control based on at home fumigation or with larvicides, as well as an effective communitarian and intersectorial participation.In many countries these mechanisms have not been implemented due to, economical, social and political reasons. Among theses it is important to mention great deficiencies in basic health services. An effective safe and of low cost vaccine, that protects children from endemic areas, plus other strategies of control already in existence, would be a key element to control the disease.

The development of a vaccine against malaria began in the XXth century, but did not materialize into a vaccine even though the biomedical advances and the studies in that period were important. At the beginning of the 1970s it was proved that sporozoites of *P. falciparum* and

P. vivax irradiated with ultraviolet rays and inoculated to healthy volunteers produced complete immunity in 90 % of them against the bite of infected mosquitoes[7,8]. The introduction of molecular biology techniques in the study of malaria, as well as the possibility of in vitro growth of *P. falciparum* and the greater mortality of infection caused by this species have turned it into a major objective of research. Advances have also been made in the development of a vaccine against *P. vivax* that has a much greater geographical distribution than *P. falciparum*. The difficulty of in vitro growth of this parasite is one of the drawbacks in the development of a vaccine against it. The *Plasmodium* genus parasites have a complex life cycle and grow through different stages, each one of which has multiple antigens that can be immunogenic.

The research in the development of a vaccine is centred in three different approaches:

• vaccines against the pre-erythrocyte stage that protect against the sporozooites (infectious form injected by the mosquito) or block hepatocyte invasion [9-13];

• erythrocyte vaccines or against the haematological stage of disease, that inhibit the multiplication of the parasite in the blood cells, preventing severe disease during the infection of the blood[14-16];

• vaccines for the sexual stage of the parasite, that try to prevent the development of sexual forms once the mosquito has ingested them, breaking in this way the cycle of the parasite[17].

The development of vaccines is much more complicated than what it seemed 30 years ago.

This is due to various factors, especially: the complex development and the high antigenic variability of the parasite (that convey it with an extraordinary mechanism for avoiding the infected organisms defences), the lack of immunological markers that correlate with protection against malaria and the lack of animal models.

Plasmodium presents multiple antigens that vary during the different stages of its vital cycle and against which chained sequential immune responses are required. In this manner, an antibody that protects against the initial period of infection will not protect against posterior periods of infection.

Furthermore, many of the parasites proteins exhibit many different forms, and the same parasitic clone can have up to 50 different copies of the gene that codifies an essential protein for its mechanism of action, expressing a different version of the protein in each successive invasion of parasites in the blood. This variability is critical for the survival of the parasite and unfavourable for the infected individual.

The only way that the efficacy of a vaccine can be known is by clinical essays of the candidate vaccines in endemic zones of malaria. Theses studies are always very complex logistically. The total costs for the development of a vaccine are very high; the process that leads from the commercialization of a vaccine till the investment is returned after it has been registered can take up to 30 years. This is one of the reasons why the pharmaceutical industry has had such a low interest in developing a vaccine for this disease.

In the last years a vaccine has been developed that offers a significant progress in the lasting protection against this disease in African children after clinical essays. Many different formulas have been used in the search for a good candidate for vaccine and until now, only RTS,S has proven to induce a protective response in humans. Consensus exists on the fact that adjuvants like AS02 are essential to promote the development of elevated antibody titles.

The RTS,S/AS02A vaccine developed by GSK (Glaxo Smith Kline Biologicals) is made up of the C-terminal part of the CS protein (aminoacids 207 to 395) joined with the hepatitis B surface antigen expressed in a virus-like form. The adjuvant is known as AS02 and is made up of two immunoactivating substances: MPL and QS21 in an emulsion of water and oil. This vaccine was tried first in non immune voluntary adults demonstrating a protection of 41%[18]. In other studies made in Gambia a 71 % protection during the first 9 weeks and a 34% reduction of infection during a period of 15 weeks, was shown, with a reduction of efficacy that disappeared on the long run[19]. In both studies it was shown that the vaccine was immunogenic.

After these studies a randomized,double blind,controlled, clinical essay was undertaken in Mozambique in 2,022, 1 to 4 years old children to determine the efficacy, immunogenicity, and reactogenicity of the vaccine. The primary purpose of this study was to evaluate the efficacy against malaria caused by *P. falciparum* at 6, 18 and 45 months of follow-up[9,10]. Two cohorts were included with different types of controls. In cohort 1, the principal purpose was to evaluate for the efficacy of the vaccine against the episodes of malaria (considering episode as an axillary temperature of 37,5ºC and more than 2,500 asexual parasites per microliter of blood). In cohort 2, the main purpose was to determine the efficacy of the vaccine against new infections. The participants were randomized to receive the RTS,S/ASO2A vaccine or the control vaccines (heptavalente pneumococcal vaccine alternated with the vaccine against *Haemophillus influenzae* or the Hepatitis B vaccine). The results showed at 6 months after the vaccination an efficacy of the vaccine against the first episode of clinical malaria of 29.9% (CI 95%: 11-44.8; p=0.004), an efficacy against the first infection of 45% (CI 95%: 31.4-55.9; p<0.0001) and against severe malaria of 57.7% (IC95%: 16.2-80.6; p=0.019)[9]. Recently it has been proven that efficacy is mantained up to 45 months of

follow up with percentages of 30.5% (95% CI 18.9–40.4; p=<0.0001) against a first infection and 38.3% (95% CI 3.4 - 61.3; p=0.045) for severe malaria.

Essays have also been made with this same vaccine in children from Mozambique with ages less than 6 months to evaluate its security, immunogenicity efficacy, and non inferiority in immune response, when administered with the vaccines included in Expanded Program of Immunisation (EPI). In these the study vaccine was administered between other vaccinations of the EPI (diphtheria, tetanus, pertussis and *Haemophillus influenzae type b*). The results in this study have shown an efficacy of 65,9% (95% CI 42.6 – 79.8; p<0.0001)[20]. This article is evaluated in the present number of "Evidencias en Pediatria" [21].

Multiple candidate vaccines exist in the present time, and are in different stages of development, the majority of them being in preclinical phase. More than half of the 90 candidate vaccines that are being developed are based only in three antigens, that were cloned more than twenty years ago: the circumsporozoite protein (CSP), and the surface protein of the merozoit (MSP) and the apical membrane antigen 1 (AMA-1).

After this historical review, and thanks to the significant advances of the last years, we can conclude that there are good reasons to be optimistic. Even though the scientific task has to confront future difficulties, we believe that a register of a first generation of vaccines against malaria is a very real possibility. We need more research to develop a definitive vaccine that can avoid many deaths in the most vulnerable population of all: children. The register of this candidate vaccine is not the final stop, but only an intermediate station, in the global effort to develop the best tools for the control and eventually the eradication of malaria.

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