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The world's first malaria vaccine – promising clinical results

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Abstract

Work on the malaria vaccine has been going on since the early 20st century. The RTS,S/AS01 (Mosquirix) vaccine is the first and only in the world that has shown action against Plasmodium falciparum, a germ that contributes to the highest number of deaths from malaria. After passing the three phases of clinical tests positively, the fourth phase was launched in 2019 - the MVIP program (The Malaria Vaccine Implementation Program). It covers three African countries: Kenya, Ghana

and Modawi. Around 360,000 children are expected to receive the vaccine from these countries annually. The third phase of Mosquirix vaccine testing lasted five years (2009-2014) and was based on the extraction of 15 459 children and infants from seven African countries, followed by the administration of four doses of each medicine. In four years, among children aged 5-17 months who received 4 doses of Mosquirix, 4 out of 10 (39%) managed to prevent the development of malaria. The number of hospitalizations for malaria and severe anemia, which is one of the consequences of this disease, has also decreased significantly. In the fourth phase of the study, the role of the vaccine in reducing the number of deaths in children and its safety will be assessed in the context of routine, global use. Data from the MVIP program will include WHO recommendations on the wider use of the vaccine.

Keywords: malaria, the MVIP programme, vaccine

Introduction

Malaria is a serious parasitic disease caused by five types of malaria germs. It is transmitted by the bite of an infected female Anopheles mosquito. Nearly 70% of cases are concentrated around 11 countries, of which 10 are African ones. According to the WHO annual report, there were 219 million new malaria cases in 2017, of which 435,000 died as a result of the disease [1]. Some groups of the population are particularly at risk: malaria mainly affects infants, children under 5 years of age, pregnant women and people with HIV/AIDS. The treatment is based on the combination of artemisinin or its derivatives with pharmaceutical agents belonging to other groups of drugs (ACT, Artemisinin-based combination therapy) [2]. Even though previous preventive and curative measures have caused a decrease in malaria incidence over the past 15 years, a well-tolerated and effective vaccine would be a valuable tool to control the disease. RTS,S /AS01 (trade name Mosquirix) is a vaccine that was created by genetic engineering in 1987. [3] The vaccine is selective for the protozoan Plasmodium falciparum, which is associated with severe malaria and causes the highest mortality from this disease. [1] It consists of a subunit containing CSP (circumsporozoite protein), which is present on the surface of Plasmodium falciparum sporozoites [4]. This subunit is also connected to the HBV surface antigen (HbsAg) and induces the production

of anti-HBs antibodies, which may be important for the epidemiology of hepatitis type B. [5] The name RTS,S was created from the first letters of the ingredients of the vaccine, while the abbreviation A01 is the name of the adjuvant system. [6] The vaccine elicits a response from CD4 + T cells and induces the production of antibodies against sporozoites that have been introduced into the human body along with a bite by an infected mosquito. [7] The safety of Mosquirix has been confirmed in three phases of clinical trials.

Description of the state of knowledge

RTS's was created in 1987 by scientists working in the GKS laboratory. Early clinical development was conducted in conjunction with the Walter Reed Army Institute for Research. In January 2001, GSK and PATH's Malaria Vaccine Initiative (PATH/MVI), using a grant from the Bill & Melinda Gates Foundation to PATH, introduced a joint partnership to invent RTS,S for newborns and young children living in endemic malaria countries in Africa Sub-Saharan. [8]

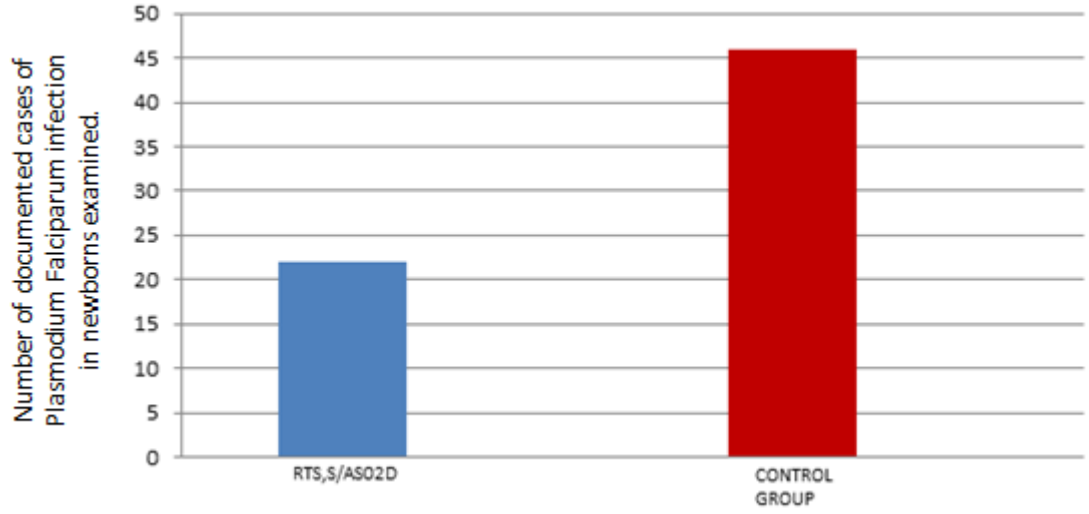
The first major human study concerning RTS'S was a double-blind, phase IIb randomized study conducted on 2022 children aged 1-4 in Mozambique in 2004. [9] The RTS,S/AS02A vaccine in which the surface antigen Plasmodium falciparum of the pre-erythrocytic phase is present was used.

The focus was on assessing the efficacy, immunity and safety of the vaccine in African children. The study included two cohorts of children living in two separate areas for which two different end goals were identified. In each of the separate cohorts, some study participants received three doses of the RTS'S/A02 vaccine, while the rest were in the control group. The primary end point set in cohort 1 (n = 1605), was time to first clinical episode P. falciparum malaria (axillary temperature ≥37,5 ° C and P. falciparum asexual blood parasitemia >2500 uL) over a 6-month observation period. The effectiveness of preventing new infections was determined in cohort 2 (n = 417).

The vaccine's effectiveness in the first clinical episodes was 29.9%. At the end of the 6-month observation period, the incidence of P. falciparum infection was 37% lower in the RTS,S/AS02A group compared to the control group. The effectiveness of the severe malaria vaccine was 57.7%. In cohort 2, the vaccine's effectiveness in extending the time to first infection was 45%. Formulated conclusions, which stated that the RTS,S/AS02A is safe, well tolerated and immunogenic.

On October 17, 2007, a Phase I/IIb double-blinded study was published in concerning 214 neonates from Mozambique. [10] Children were randomly assigned to two groups - the first group received

the RTS,S/AS02D vaccine, while the second hepatitis B vaccine, Engerix-B. Subjects received 3 doses - at 10, 14 and 18 weeks of age. The effectiveness was assessed within 3 months after the last dose of vaccine. In the study group receiving RTS,S/AS02D, the number of detected cases of Plasmodium Falciparum infection was 22. Among children who received 3 doses of Engerix-B, the number of documented sickle cell infections was higher - 46 cases were reported.



Graph 1. The number of documented cases of Plasmodium falciparum infection in newborns examined.

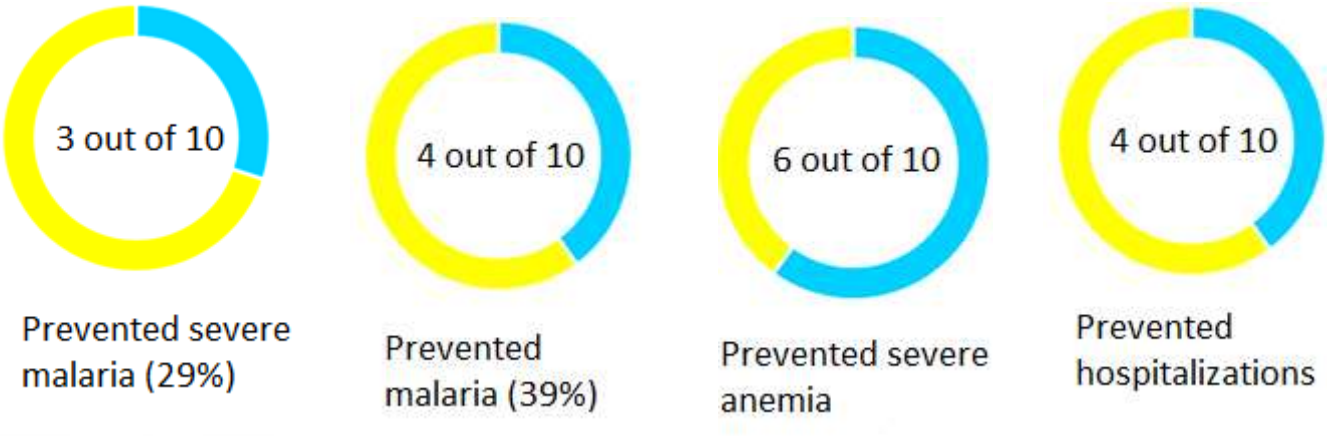
The third phase of clinical trials was conducted in seven sub-Saharan African countries in 2009-2014. It was a double-blind, randomized trial, which included 15,459 children aged 5-17 months. Participants were randomly assigned to the following groups:

- 3+1 scheme: three doses of primary vaccination and a booster dose of RTS'S/A01 vaccines (0, 1, 2, 20 months)

-3+0 scheme: three doses of RTS,S/A01 vaccine and control vaccine dose at 20 months (0, 1, 2 months)

- a control vaccine at similar intervals.

Patients were followed for approximately 48 months. The 4-dose regimen was found to be more effective than the 3-dose regimen on which previous studies were based. In the 4-year follow-up period for children aged 5-17 months who were vaccinated according to the 3 + 1 scheme, the effectiveness of RTS,S in preventing the occurrence of clinically symptomatic malaria was 39%, while in the prevention of severe malaria 29%. [11]



Graph 2. Results of clinical phase III studies ongoing in the years 2009-2014 on a group of children aged 7-15 months.

In 2015, the European Medicines Agency issued a positive scientific opinion on RTS,S, indicating that the benefits of the vaccine in preventing malaria outweigh the potential risks. [12]
Due to the above and promising results of the third phase of clinical trials, the beginning of the fourth phase was announced at the beginning of 2019. Three out of 10 African countries were selected because of: satisfactory levels of other vaccinations, moderate or high levels of malaria transmission, an adequate level of other malaria prevention methods and a sufficient number of young children living in malaria areas. [13] These countries are Malawi, Ghana and Kenya, of which clinical trials in Malawi began in April 2019. [14]

Summary

The possibility of preventing diseases through preventive vaccinations is a huge medicine achievement. It allowed the elimination of many infectious diseases, which often grew to the rank of epidemics. Malaria is one of the diseases that currently requires special attention as a cause of high mortality of people in the territories of the protozoa P. falciparum. In this regard, scientists are trying to invent a way to prevent infection. However, this is more difficult than one might expect. Until now, all vaccines available have been directed against bacteria or viruses. RTS,S directed against protozoa is an innovation in this respect. Because eukaryotes have a more complex structure and cell cycle, the invention and implementation of the P. falciparum vaccine program

remain a challenge. [15] The cited results of clinical trials have shown the effectiveness of RTS,S. The ongoing phase IV testing will allow for even more accurate observation and assessment of safety of use. However, it should not be forgotten that despite promising results, the effectiveness in preventing malaria is about 40%. Therefore, there is a need for further research into measures that could potentially reduce morbidity. Currently, researchers at the Center for Infectious Disease Research (CIDR) in Seattle, WA, USA are researching the new GAP3KO vaccine, which may be more effective. [16] For now, however, we are waiting for new reports in this field.

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