



Critically Appraised Article

Promising results in the research for a vaccine against malaria: effective and secure, not only in children, but also in infants

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Promising results in the research for a vaccine against malaria: effective and secure, not only in children, but also in infants

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Structured abstract:

Objective: to study the security, immunogenicity, and initial efficacy of a vaccine against malaria in African infants.

Design: randomized, controlled, double blind phase I/IIb clinical essay.

Location: Mozambique rural area.

Study population: two hundred and fourteen infants, with ages from 6 to 12 weeks of life, enlisted during one year. Conditions for study inclusion were a normal gestation, lack of illness and maternal consent was obtained. Exclusion criteria were: sons of mothers who were either hepatitis B or HIV positive, that had not received vaccination for polio or BCG at least one week before the study vaccination or those that received other vaccines in study period. The sample size was calculated based on the security of the vaccine. The study was undertaken between august 2005 and september 2006.

Intervention: the patients were randomly allocated to two groups: one group received the malaria vaccine (GM: 0.5 ml IM of RTS,S/AS02D vaccine; n = 107 patients) and the other received the Hepatitis B vaccine (GH : 0.5 ml IM of Engerix-B vaccine; n = 107 patients). Three doses of the vaccine were applied at ages 10, 14 and 18 weeks of age (two weeks after the routine vaccination with DTP/Hib/polio at 8,12 and 16 weeks, respectively) by a team that was not blinded, but did not participate in any other phase of the study.

Outcome measures: the principal variable of the study was the security of the RTS,S/AS02D vaccine in the first six months of the study, through an exhaustive clinical and analytic follow up undertaken by a trained team (and that included a daily home visit in the six days after the vaccination). The secondary variables included the immunogenicity (basal and 1 and 3.5 months after the third dose of vaccine) and the estimation of efficacy (active and passive detection of the infection by malaria). The analysis was made by intention to treat: of the 107 patients in each group 94 children in each group received three doses of vaccine, and of those who ended the follow up: 87 in the GM and 89 in the GH.

Main outcome measures: no significant differences with respect to adverse effects between the groups were detected (by order of frequency: pain, irritability, somnolence, loss of appetite, fever and local inflammation).

These were similar to those detected with the vaccination DTPw/Hib. Serious adverse effects were detected in 15.9 % of cases (CI 95% 9.5-24.2) in each group and two deaths in each group, none of them related to the vaccine. No differences were found in the analytical controls either.

In group GM 99% of children had anti-circumsporozoite antibodies that were detectable one month after the third dose of RTS, S/AS02D vaccine. During the follow up period 68 new cases of malaria were detected: twenty two in the GM and 46 in the GH group. The crude efficacy estimate was 62,2% (CI 95% 37.1%-77.3% p=0.0002) during the three months of follow up after completing the vaccination. Adjusted by the distance to the health centre and community of residence, the vaccine efficacy was 65.9 % (42.6%-79.8%, p< 0.0001)

Authors Conclusion: the RTS,S/AS02D vaccine against malaria is safe, well tolerated and immunogenic in infants.

Competing interests: several members (seven out of 22) work for GSK, five have equity Investments in the company. Two are the inventors of patented vaccines against malaria, even though none of them is the owner of the patent. The rest do not declare any conflict of interest.

Financial source: Malaria Vaccine Initiative, funded by the Bill & Melinda Gates Foundation.

Critical commentary:

Justification: malaria causes 1-3 million deaths yearly around the world (together with AIDS and tuberculosis they make up a triangle of co-infection of enormous sanitary impact), the majority in children under five years of age¹. Mortality has changed little, even though important efforts have been made to reduce the transmission and for better treatments. This stresses the importance for research on this vaccine: In the year 2004, several RCTs proved that the RTS,S/AS02D vaccine reduced infection and disease by *P. falciparum* in 2-4 years old African children² and that this protection lasted for at least 18 months³. But the control strategy that has proved most effective against malaria consists in having vaccines that can be applied to lactating infants and can be incorporated to a vaccine program; this is the purpose of this phase I/IIb RCT.

Validity: this RCT is of high quality based on the criteria established by Jadad (5 points). The question in this RCT is well defined in terms of population, intervention and result variables. It has been adequately randomized (with adequate masking of the randomization), blinding (double blind for patients and researchers; only the team that applied the vaccine was not blind to the procedure, but they did not participate in any other phase of the study), and the results were analyzed based on intention to treat.

Clinical relevance: even though this RCT has been designed to study the security of this vaccine, it has also been possible to study the efficacy (given the elevated rate of transmission of malaria in the area where the study was undertaken), taking care to interpret the conclusions with caution: the number needed to treat to avoid one infection by *P. falciparum* is 4.5 (CI 95% 2.9-9.7) in the analysis by Intention to treat and 3.8 (CI 95% 2.5-8.0) in the analysis by protocol*. Even though the efficacy of the RTS,S/AS02D vaccine in infants at three months after the last dose (65.9%; CI 95%: 42.6-79.8%) seems greater than that obtained by the RTS,S/AS02A vaccine in children 1 a 4 years old (45%; CI 95%: 31,4-55,9) in the initial RCT², this result must be interpreted with caution since the follow up time has been different and the confidence Intervals overlap.

Applicability in clinical practice: the phase I (or tolerance phase) and phase II (or immunogenicity and initial efficacy phase) of this RDA has allowed the authors to obtain information on dose, security, immunogenicity and efficacy of the RTS,S/AS02D vaccine in a limited group of infants. It must be taken into account that these are exploratory studies awaiting phase III (or efficacy phase) and IV (or postcommercialization pharmacovigilance) results. If the results are confirmed they will open a new road to obtaining a vaccine against malaria applicable in small infants in the affected areas. The authors acknowledge that vaccination against this disease must be integrated in a complex strategy that includes the reduction of the number of vectors or the possibility of being infected.

***Calculated using the data from the study.**

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