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Prevention of malaria in children: malaria vaccine RTS,S/AS01 (RTS,S) ; assets and limits.

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Résumé

Malgré les progrès réalisés, les efforts de lutte contre le paludisme se heurtent à de nombreux défis. La Région africaine reste la plus touchée par la malaria, on y enregistre en effet 95 % des cas et 96 % des décès dans le monde. Les enfants sont particulièrement vulnérables ; près d'un demi-million d'enfants africains meurent du paludisme chaque année.

En conséquence, la stratégie de lutte contre cette maladie endémique dans plusieurs régions africaines passe nécessairement par une intensification des moyens de prévention contre le paludisme en accompagnement des principes actifs existants pour guérir la maladie et d'autres moyens aussi de prévention telle que dormir sous la moustiquaire imprégnée d'insecticide.

Parmi ces moyens de prévention, il y a les vaccins antipaludiques parmi lesquels nous citons le RTS,S/AS01 (RTS,S) dont les atouts et limites sont abordés dans la présente revue de la littérature.

L'efficacité et le fait d'être sûr dans la réduction du nombre d'hospitalisations pédiatriques pour paludisme grave et de la mortalité infantile constituent les atouts majeurs du vaccin RTS,S/AS01 (RTS,S). Alors que ses limites telle qu'un approvisionnement en vaccins limité qui selon des prévisions actuelles pourrait bienheureusement être comblées par la production du nouveau vaccin antipaludique, le R21 en l'occurrence.

Et donc de nos jours, le vaccin antipaludique RTS,S/AS01 (RTS,S) reste un moyen efficace et sûr de lutte contre le paludisme ou la malaria chez les enfants.

Mots clés : Prévention, malaria, pédiatrie, atouts et limites, vaccin RTS,S.

Summary

Despite the progress made, efforts to combat malaria face many challenges. The African region remains the most affected by malaria, with 95% of cases and 96% of deaths worldwide recorded there. Children are particularly vulnerable; nearly half a million African children die from malaria every year.

Consequently, the strategy to combat this endemic disease in several African regions necessarily involves an intensification of the means of prevention against malaria in conjunction with the existing active ingredients to cure the disease and also other means of prevention such as sleeping under the mosquito net impregnated with insecticide.

Among these means of prevention, there are anti-malaria vaccines, among which we cite RTS,S/AS01 (RTS,S), the assets and limits of which are discussed in this review of the literature. Efficacy and safety in reducing the number of pediatric hospitalizations for severe malaria and infant mortality constitute the major advantages of the RTS,S/AS01 (RTS,S) vaccine. While its limitations such as a limited supply of vaccines which, according to current forecasts, could fortunately be filled by the production of the new anti-malaria vaccine, R21 in this case.

And so today, the RTS,S/AS01 (RTS,S) malaria vaccine remains an effective and safe means of combating malaria in children.

Key words: Prevention, malaria, pediatrics, assets and limits, RTS,S vaccine.

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Introduction

The names given to this pathogenic complex, malaria, come from the fact that the swamps with their stagnant waters constitute a biotope favorable to its development. For a long time, it was even thought that the disease was caused by the fetid fumes from the marshes, breathed by local residents, hence the name malaria which means bad air. (1)

Already around 1600, the testimonies of certain Jesuits indicated that the Peruvian Indians fought fevers caused by this condition by using cinchona bark. Around 1820 we managed to isolate quinine, that is to say the alkaloid contained in this bark, which constitutes a powerful febrifuge. (1)

However, we had to wait for the famous experiment of Doctor Donald Ross in 1897 to know that malaria is transmitted by the bite of a dipteran insect from the mosquito family, the anopheles (a term which means harmful). About ten years later, Laveran discovered the infectious agent, a plasmodium, in the blood of malaria patients. (1)

To fight malaria, insecticides and drugs have been developed but their ineffectiveness has been highlighted by the resistance of the parasite to these active ingredients. A vaccine against malaria was therefore necessary to accompany the measures taken previously in the fight against the parasite.

Thus, in 1983, researchers managed to precisely establish the structure of the surface proteins of Plasmodium knowlesi (a disease of primates), which constitute the immunoprotective antigens of the parasite. They then attempted to synthesize these proteins in the laboratory, by polymerization of amino acids into polypeptides of identical structure. These chemically produced antigens were injected into mice and rabbits to make them produce antibodies.

Furthermore, progress in molecular biology over the past ten years has enabled decisive progress in the field of genetic engineering. Some teams of researchers have embarked on this new path. After determining the structure of the antigen, they attempted to identify the coding gene, isolate and clone it (vegetative multiplication), then introduced it into the genetic heritage of certain bacteria so as to produce these antigen proteins in appreciable quantities, an essential condition for the manufacture of the vaccine. The proteins thus

produced by the manipulated bacteria were then injected into laboratory animals to induce the latter to produce specific antibodies. (1)

The first application trials of the vaccine containing these antibodies were attempted in vivo on liver cells in 1986. They were crowned with success; under the effect of antibodies, these liver cells then proved impervious to the action of sporozoites. It was then decided to test the vaccine on human volunteers in order to measure its effectiveness. (1)

Despite the progress made, efforts to combat malaria face many challenges. In 2021, there were an estimated 247 million cases of malaria and 619,000 deaths from the disease worldwide. The African region remains the most affected by malaria, with 95% of cases and 96% of deaths in the world recorded there. Children are particularly vulnerable; nearly half a million African children die from malaria every year. (2)

The same year i.e. 2021 (2), a first vaccine – called RTS,S/AS01 (RTS,S) and the result of 30 years of research and development carried out by the British pharmaceutical giant GlaxoSmithKline (GSK) (3) – has been approved by the WHO. With an effectiveness rate of around 75% when administered, this vaccine acts against Plasmodium falciparum, the deadliest malaria parasite in the world and the one most present in Africa. It was first recommended by WHO to prevent malaria in children in October 2021 in areas with moderate to high malaria transmission. It should be administered in a 4-dose schedule to children from 5 months of age. (Vaccination programs may decide to administer the first dose at an older or slightly earlier age based on operational considerations.). A fifth dose, administered one year after the fourth dose, may be considered in areas where there remains a significant risk of malaria in children one year after receiving the fourth dose. In areas where malaria is highly seasonal or in areas where malaria transmission is perennial with seasonal peaks, countries may consider administering the vaccine according to age and seasons or a combination of these approaches. (2)

The WHO recommendation for this malaria vaccine is based on the results of the Malaria Vaccine Implementation Program, which the Organization coordinates. Pilot introduction programs have enabled nearly 2 million children to be vaccinated in Ghana, Kenya and Malawi under the Malaria Vaccine Implementation Program (MVIP) since 2019 and more than 4.5 million doses of the vaccine have been administered through routine

immunization programs implemented by countries. The introduction of the RTS,S/AS01 (RTS,S) malaria vaccine by the ministries of health in the territories of the three participating countries, with the support of WHO and international and national partners, including PATH, GSK and the UNICEF has had a significant impact, reducing the number of pediatric hospitalizations for severe malaria and saving lives. The populations are in great demand for this vaccine, which is well accepted in African communities. (2)

The RTS,S/AS01 (RTS,S),S malaria vaccine was prequalified by WHO in July 2022. (2)

Cycle of the plasmodium (1)

When an infected female anopheline is about to bite a man, it generally chooses a space of tender, thin skin covering a superficial blood vessel to insert its proboscis, which functions like a tube. Hypodermic syringe with two channels. The mosquito's upper lip is rigid, while the lower lip is soft and flexible; they serve as a sheath for the mouthparts. The two mandibles, ending in a point, serve to pierce the skin and the two maxillae ending in sawtooth widen the wound. Parallel to the proboscis lies a very fine canal which communicates with the salivary glands.

During a sting, the insect begins by injecting a droplet of saliva; this exerts a dual function, anticoagulant and anesthetic. The absorbed blood remains fluid and the sting is not immediately felt; it's only after a short time that blood appears through the pharynx which expands and contracts rhythmically. The suction ends when the mosquito is engorged with blood; it then remains practically immobile for two or three days, the time to digest, at a short distance from the place where it feeds.

When the insect is infected, it injects, with saliva, plasmodia in the form of sporozoites. After just a few minutes, some of these sporozoites reach and penetrate the liver where they multiply and acquire new antigenic characteristics, forming schizonts. Then, after about five days, these multinucleate schizonts (measuring 30 to 60 nanometers) divide into uninucleate merozoites (hematozoa). These are then released a few days later into the blood circulation system and invade red blood cells (red blood cells) where they feed on hemoglobin. They evolve into schizozoites or erythrocytes. They multiply rapidly (virulence) and this proliferation leads to the bursting of red blood cells. The toxins are

then released into the blood serum causing, through a sort of allergic defense reaction, sudden attacks of fever. The schizozoites thus released rush to invade and parasitize other red blood cells and continue to multiply. There comes a time when some of these schizozoites undergo sexual differentiation, forming gametocytes or gamontes. The male, banana-shaped, and female, crescent-shaped gamontes no longer multiply and remain in the red blood cells.

If a healthy Anopheles insect bites a sick person at this stage in the evolution of the infectious agent, it absorbs, with the blood, these gametocytes.

During the digestion of red blood cells in the mosquito's stomach, the gamontes are released. They then evolve into true male and female gametes. The first die quite quickly, after having fertilized the females. This fertilization takes place in the mosquito's intestine. The fertilized egg settles in neighboring tissues where it encysts (oocyst) and divides to form numerous sporozoites. These are then released into the Anopheles body and some end up in the salivary glands. When it bites again to feed, it will inject, with saliva, a certain number of these sporozoites into the human body. The cycle then begins again.

Human blood becomes contaminated approximately ten days after being bitten by an infected mosquito. When a healthy Anopheles insect bites a malaria sufferer, sporozoites are found in the saliva approximately twelve days later and the insect then becomes contagious.

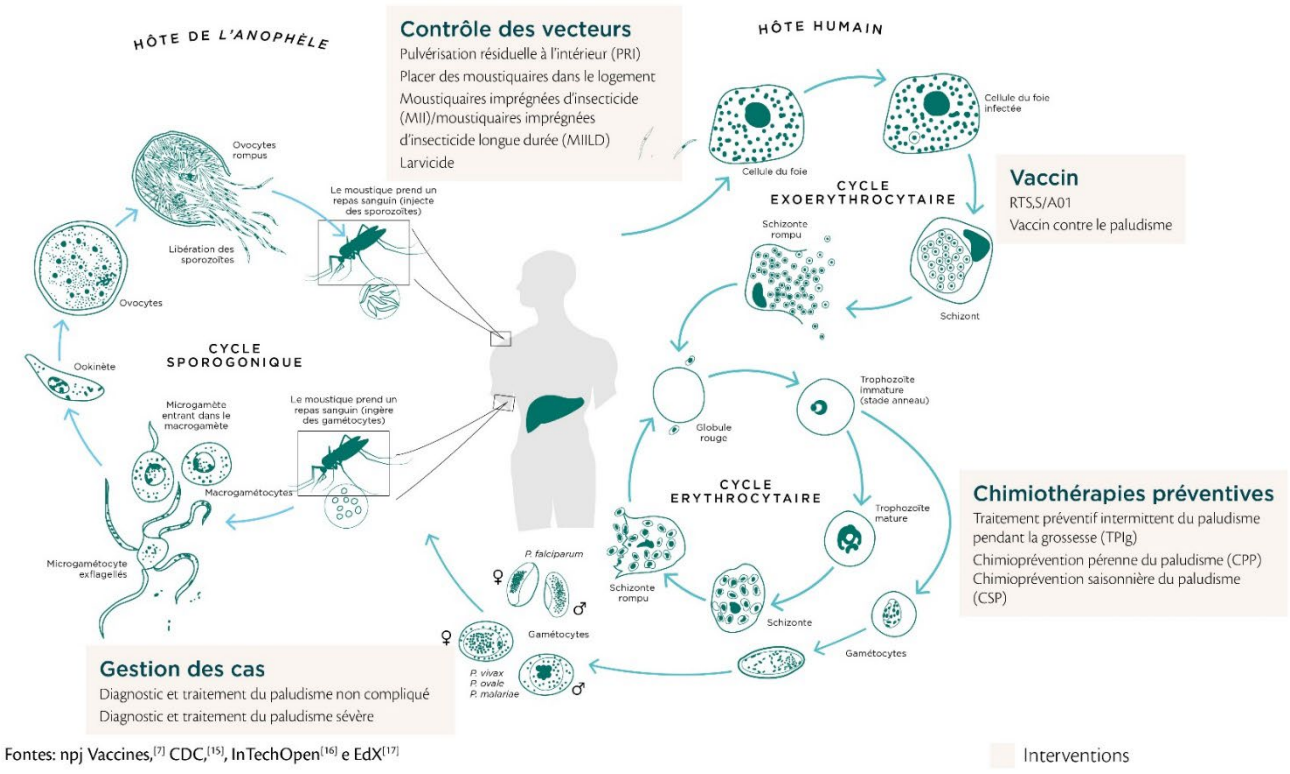

Figure 1: Life cycle of the malaria parasite and current tools for prevention and control of malaria (4)

Incubation time and general symptoms (1)

After twelve to fourteen days of incubation, after the bite by an infected Anopheles insect, the first symptoms appear in the form of sudden bouts of violent fever. In the case of Plasmodium falciparum, the attacks follow one another at an average interval of 48 hours (third-party fever). These attacks accompany the bursting of red blood cells and the release of toxins into the blood serum. The interval between bouts of fever is approximately 72 hours for Plasmodium malariae (quarter fever).

Mechanisms of action of an anti-malaria vaccine (1)

An anti-malaria vaccine can be:

- **Antisporozoidal:** it aims to neutralize sporozoites when they penetrate the human body and to prevent them from parasitizing liver cells.
- **Antimerozoites:** in order to neutralize the plasmodium in the already infected organism.

- **Antigametocyte:** which aims to prevent contamination of the Anopheles mosquito biting a malarial patient and therefore the spread of malaria by the vector. In this case, in fact, the anopheles would ingest the antibodies at the same time as the gametocytes contained in the red blood cells. When these gametocytes were then released into the mosquito's stomach, they would immediately find themselves neutralized.

Description of the vaccine

The anti-malaria vaccine RTS,S/AS01 (RTS,S), which targets the pre-erythrocytic stage of Plasmodium falciparum, induces a humoral and cellular immune response against the circumsporozoite protein present on the surface of sporozoites and schizonts at the hepatic stage (5). A detailed description of the final and previous formulations of the vaccine, as well as an analysis of studies in adults and phase I and II trials in children, have been published previously (6). In short, the vaccine consists of a recombinant protein that spontaneously forms viral pseudo-particles, called RTS,S ; associated with the patented AS01E adjuvant system. The RTS,S antigen contains a portion of the P. falciparum circumsporozoite (CS) protein fused to the amino terminus of the hepatitis B virus surface antigen (HBsAg), which is also used in approved hepatitis B vaccines. To stabilize the recombinant particles, the fusion protein is co-expressed with the HBsAg(S) protein in Saccharomyces cerevisiae. AS01E consists of 3-O-desacyl-4'-monophosphoryl-lipid-A (MPL ; produced by GSK), QS-21 (Quillaja saponaria Molina, fraction 21 ; licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA company) and liposomes.

The RTS,S/AS01 (RTS,S) vaccine consists of a powder (lyophilized RTS,S) and a suspension (AS01E) the powder with the suspension to give 1mL of opalescent, colorless to pale brown liquid. Presented in 2 separate bottles without preservative. The final vaccine is obtained by reconstituting a dose of vaccine is obtained by taking 0.5mL from the vial after reconstitution. Each dose contains 25 µg of RTS,S antigen ; as well as 25 µg of each immunomodulatory molecule MPL and QS21.

The vaccine is administered intramuscularly (7).

Figure 2: RTS,S/AS01 (RTS,S) vaccine

Assets and limits

1. **Assets :**
   - ✓ Reduces the number of pediatric hospitalizations for severe malaria and pediatric mortality. Malaria cases fell by more than half in the first year after vaccination and by 40% during the 4 years of follow-up from 2009-2014. (2)
   - ✓ Just like the last vaccine recommended in October 2023 against malaria by the WHO (R21), RTS,S/AS01 (RTS,S) prevents around 75% malaria attacks when administered seasonally in areas of highly seasonal transmission where chemoprevention of seasonal malaria is ensured. The vaccine therefore has the same as R21. (2)
   - ✓ Good safety profile: The safety of the vaccine was demonstrated after the administration of more than 4.5 million doses to nearly 1.7 million children as part of the pilot introduction programs. (2)
   - ✓ The RTS,S/AS01 (RTS,S) vaccine has had a significant impact in high, moderate and low transmission areas. (2)
   - ✓ Possibility of adding this vaccine to routine vaccination: The high and equitable vaccination coverage obtained during the pilot introduction programs showed that communities were very demanding of the vaccine,

that it enjoyed good acceptance by health workers. Health and that countries were capable of administering it effectively. (2)

- ✓ Equity: The vaccine improves equity in access to malaria prevention tools (under pilot introduction programs, more than two-thirds of children who do not sleep under an insecticide-treated mosquito net have been vaccinated). (2)
- ✓ Both vaccines use similar technologies and target the same stage of the malaria parasite life cycle. (8)

2. **Limits :**
   - It is estimated that the vaccine saves one life for every 200 children vaccinated. (2)
   - RTS,S/AS01 (RTS,S) is more expensive than R21 : The WHO said the new R21 vaccine would be a "vital additional tool". Each dose costs between 2 and 4 dollars (between 1.65 and 3.30 euros) and four doses are needed per person. This is about half the price of the RTS,S/AS01 (RTS,S). (8)
   - Extremely limited vaccine supply : So far, there are only 18 million doses of RTS,S/AS01 (RTS,S) while the world's largest vaccine manufacturer, the Serum Institute of India, is already ready to produce more than 100 million doses of the R21 vaccine per year and plans to increase to 200 million doses of the same vaccine per year. **(**8)
   - Compared to RTS,S/AS01 (RTS,S), the new vaccine, R21, is easier to manufacture, as it requires a lower dose and uses a simpler adjuvant (a chemical substance contained in the vaccine that stimulates the immune system). (8)

Conclusion

Having regard to the assets and limits listed in the point 'Assets and limits', we conclude the following : the RTS,S/AS01 (RTS,S) antimalaria vaccine as a means of prevention accompanying other measures to combat malaria or malaria such as insecticide-treated mosquito nets, are safe and effective. However, it presents some limitations such as a limited supply of vaccines which, according to current forecasts, could fortunately be filled

by the production of the new anti-malaria vaccine, R21 in this case. The latter, R21, will have as its next important step the conclusion of the WHO prequalification process which is currently underway. This prequalification is a prerequisite for the international purchase of the vaccine by United Nations organizations such as UNICEF, and by the Gavi Alliance, among others.

We also suggest the manufacture of a vaccine which would be an amalgamation of the three main mechanisms of action mentioned in the point 'Mechanisms of action and general symptoms', namely a vaccine: Antisporozoidal, Antimerozoite and Antigametocyte. This would be an ideal vaccine.

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