Efficacy and safety of malaria vaccines: can Ethiopia introduce them?

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ABSTRACT

Malaria is causing significant health problems across the world. Sub-Saharan Africa is among the parts of the world which are significantly affected. Ethiopia is one of the countries where malaria remains a major public health concern, despite ongoing efforts to eliminate the disease in high-burden districts. The World Health Organization (WHO) has recommended RTS,S/AS01 for use in combination with other malaria control interventions in children living in areas with moderate to high malaria transmission. This vaccine has demonstrated reasonable effectiveness against clinical malaria and has demonstrated acceptable safety. The malaria vaccine is 26.7% effective in children aged 6–12 weeks and 45.7% effective in children aged 5–17 months. This effectiveness was measured 18 months after they received the third dose. R21/Matrix-M is the second malaria vaccine that was recently recommended by the WHO. It has shown high efficacy (74% with a low dose and 77% with a high dose of adjuvants) and a favorable safety profile. It is also recommended by the WHO for routine childhood immunization. The introduction of WHO-recommended malaria vaccines into national routine immunization programs is crucial to reduce the incidence of malaria cases and deaths among children in endemic areas.

Keywords: Malaria, Parasitology, Vaccination, Immunization

Background

Malaria continues to cause ill-health and mortality across the world, with over 262 million cases and more than 600,000 deaths every year (1). Despite considerable progress in controlling the disease through available public health interventions, malaria continues to affect millions of people worldwide (2). Specifically, it affects the highest proportion of people living in sub-Saharan Africa (1). The WHO African Region accounted for 94% of all global malaria cases and 95% of all global malaria deaths in 2023 (1). Children in the African Region are significantly affected by malaria infection, and 76% of all malaria deaths in the region are among children under five years old (1).

Despite the implementation of a malaria elimination program, Ethiopia is significantly affected by malaria outbreaks in multiple parts of the country (3). Over 7.3 million malaria cases and 1157 deaths were reported in Ethiopia between 1 January and 20 October 2024 (4). The recent estimated pooled attack rate in current malaria outbreak in Ethiopia was 3% , which is the highest in recent year (5).

The two malaria vaccines (RTS, S/AS01, and R21/Matrix-M) have shown efficacy against malaria in children under five years old (6). They have also demonstrated a favorable safety profile (6). The two vaccines are recommended by the WHO for use in children living in areas with moderate to high malaria transmission (1,6).

The WHO has allocated the limited malaria vaccine supply to roll out the two vaccines in African countries with a high malaria burden that have shown interest in introducing them as part of their national malaria control strategies (7). Despite other challenges, the efficacy and safety of the vaccines are the two primary concerns highlighted in the literature when considering their introduction (8). Thus, this editorial aimed to provide an overview of the efficacy and safety of the two malaria vaccines and draw conclusions regarding their inclusion in the national malaria elimination program in Ethiopia.

Efficacy of RTS, S/AS01 vaccine

The RTS,S/AS01 vaccine has shown a moderate efficacy against malaria with 46% efficacy against clinical malaria over 18 months (9). It has also shown 34% efficacy against severe malaria, malaria-related hospital admissions, and all-cause hospital admissions (9). However, the impact of the vaccines on the burden of malaria is significant when they are combined with other existing malaria control strategies (10). It is more protective in children aged between 5 and 17 months than in those aged 6–12 weeks, and a fourth dose at 20 months after the third dose also provides additional protection (10). Moreover, RTS, S/AS01 vaccine has 26.6% effectiveness against clinical malaria in children 6–12 weeks of age, and 45.7% in 5–17 months of age children after 18 months post dose 3 vaccination (11). In addition, effectiveness of the vaccine against clinical malaria was 26.7% in children aged 6–12 weeks for 38 months, and 39% in children aged 5–17 months for 48 months (10). However, beyond 18 months of vaccination (after third dose) the efficacy of the vaccine rapidly declined, which indicates the need of fourth dose (10). According to WHO recent global malaria report, RTS, S/AS01vaccine has prevented more than 1.2 million children in Ghana, Kenya and Malawi (12). Based on these findings, WHO has recommended the use of RTS, S/AS01 vaccine for malaria prevention in October 2021 (12).

Efficacy of R21/Matrix-M vaccine

Evidence from clinical trials depicted the efficacy and safety of R21/Matrix-M vaccine (13,14). The efficacy of R21/Matrix-M vaccine in the low-dose adjuvant group was 74%, while in the high-dose group, it reach 77% (14). It has also showed the possibility of maintaining immunity in vaccinated children for up to one year, indicating the need for annual vaccine boosters (14). The R21/Matrix-M vaccine has showed 75% efficacy at seasonal sites at 12 months, while 68% efficacy was observed at normal sites for time to the first symptomatic malaria episode (14). The efficacy of the vaccine is nearly similar against symptomatic malaria episodes at the seasonal and normal sites (75% versus 68%) (14).

Safety

Three safety concerns related to RTS, S/AS01 vaccine has been raised. The first was an increased number of meningitis cases in vaccinated group compared to the control group in older children. However, no excess meningitis cases were observed in vaccinated children in the lower age group. The second concern was the raise in the number of cerebral malaria cases in the older age group in the vaccinated group compared with the control group. However, no excess cerebral malaria was observed in vaccinated children in the lower age group. The third concern was that the risk of death was twice as high in girls who vaccinated compared to girls in the control group. However, analyses of pilot study data have not confirmed, any of the safety issues observed during the Phase 3 clinical trials of the vaccine. The R21/Matrix-M vaccine has demonstrated a favorable safety profile and is the minor adverse events are tolerable (15). Injection site pain and fever are generally well tolerated. No serious adverse events or treatment-related deaths were observed in the vaccine groups (15).

CONCLUSION

Based on the available evidence from Phase 3 clinical trials, reports, and position papers, RTS, S/AS01 demonstrates moderate efficacy against *Plasmodium falciparum*. However, it could provide substantial public health benefits and potentially prevent millions of malaria cases and deaths when used alongside other malaria interventions. RTS, S/AS01 is also considered safe for use in malaria control programs. The R21/Matrix-M vaccine is the first malaria vaccine to meet the WHO-specified efficacy recommendation of 75%. In addition, it is well tolerated and exhibits only minor adverse effects. Therefore, introducing of the R21/Matrix-M vaccine into the national malaria control program is crucial to prevent more malaria cases and deaths among children, compared to RTS, S/AS01. However, further study on safety and effectiveness of the R21/Matrix-M vaccine is necessary in Ethiopia because the *Plasmodium falciparum* strain found

in Ethiopia has unique genetic diversity compared to where the trial conducted. Vaccine acceptance studies and pilot implementation are also recommended before introducing the R21/Matrix-M vaccine in Ethiopia.

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