Summary of WHO Position Paper on malaria vaccines, May 2024

https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers/malaria

Background

Malaria is a vector-borne disease transmitted through the bite of infected anopheline mosquitoes. In many endemic areas, malaria transmission occurs throughout the year, often with seasonal increases. In areas of highly seasonal malaria, transmission may be primarily limited to several months each year.

In 2022, there were an estimated 249 million cases and 608 000 deaths globally. Approximately 95% of malaria cases and deaths occur in sub-Saharan Africa. Almost all malaria deaths are caused by *Plasmodium falciparum* and most occur in African children under 5 years of age with the highest burden concentrated in those under 3 years of age.

In areas of high transmission, young children often experience 4–6 episodes of clinical malaria each year, even when the most effective malaria control tools are used, such as insecticide-treated nets (ITNs) and diagnosis and treatment. Morbidity due to *P. falciparum* can range from mild febrile illness to life-threatening disease with coma, respiratory distress, severe anaemia or circulatory shock. Case fatality rates in severe malaria have been estimated at 13–20% for hospitalized children or >90% if the child remains at home. Severe malaria may present as life-threatening anaemia. More frequently in older children, severe malaria may present as cerebral malaria. The contribution of malaria to increased childhood mortality due to common childhood illness – such as pneumonia, diarrhoea and malnutrition (i.e. indirect malaria mortality) – is substantial.

The burden of malaria in Africa has been reduced substantially in recent decades due to the scale-up of malaria control measures. However, the rate of progress in reducing both malaria cases and malaria deaths has slowed since 2014 and, in some countries with the highest burden, the annual number of malaria cases has increased.

Vaccines

Two malaria vaccines, RTS,S/AS01 and R21/Matrix-M, are WHO-prequalified and recommended for use. Both vaccines prevent *P. falciparum* infection in children and subsequent illness and death; they are not designed to interrupt malaria transmission and there is no known cross-protection with other *Plasmodium* species.

The safety and efficacy for both vaccines, using a 4-dose schedule, have been demonstrated in phase 3 clinical trials. The safety and effectiveness of RTS,S/AS01 have also been evaluated as part of large pilot introductions into routine immunization systems in Ghana, Kenya and Malawi, showing a significant reduction in all-cause mortality and hospitalizations with severe malaria. There is a small risk of febrile seizures within 7 days (mainly within 2–3 days) of vaccination, which have been observed in clinical trials to resolve without long-term consequences.

WHO Position

WHO recommends the use of malaria vaccines for the prevention of *P. falciparum* malaria in children living in malaria endemic areas, prioritizing areas of moderate and high transmission.[1] However, countries may also consider providing the vaccine in low transmission settings.[2]

Malaria vaccines should be provided as part of a comprehensive malaria control strategy. All malaria control interventions, including vaccines, provide partial protection; the highest impact is achieved when a mix of interventions is used. Appropriate mixes of interventions (ITNs, preventive chemotherapies, vaccines etc.) should be identified for different subnational settings. These mixes are defined by national malaria programmes on the basis of the local malaria epidemiology (e.g. intensity of transmission, age pattern of severe disease, vector species and vector behaviour, insecticide and drug resistance patterns) and contextual factors (e.g. structure and function of the health-care system).

The additional visits needed to administer malaria vaccine are opportunities to provide other integrated malaria control and preventive health services,

Malaria vaccines should be provided in a 4-dose schedule in children from 5 months of age for the reduction of malaria disease and burden.[3] The minimum interval between any doses is 4 weeks; however, to achieve prolonged protection, the fourth dose should be given 6–18 months after the third dose.

To improve coverage, there can be flexibility in the timing of the fourth dose, including by aligning it with vaccines given in the second year of life. Alternatively, because vaccine efficacy is highest in the first months after vaccination, the fourth dose can be given just prior to seasonal peaks in malaria transmission to optimize vaccine efficacy.

A fifth dose, given one year after the fourth dose, may be provided in areas of highly seasonal transmission and may be considered in other areas where a significant malaria risk remains for children.

At the time of vaccine introduction, catch-up vaccination can be considered in children up to 5 years of age, subject to local epidemiology and age of high risk, feasibility, affordability and vaccine availability.

In areas with highly seasonal malaria transmission or perennial malaria transmission with seasonal peaks, countries may consider providing the vaccine using an age-based or seasonal approach. Alternatively, countries could consider a hybrid of these approaches, giving the first 3 doses through age-based administration and subsequent annual doses seasonally.

Both malaria vaccines are considered safe and well tolerated. On the basis of clinical trial data and pilot evaluation, the most serious adverse reaction associated with RTS,S/AS01 and R21/Matrix-M is febrile seizures within 7 days (but mainly within 2–3 days) post-vaccination, with an attributable risk of 2.5 per 1000 doses of RTS,S/ AS01 administered and 1 per 2800 doses of R21/ Matrix-M administered. The seizures resolved without long-term consequences. The most commonly reported adverse reactions were fever (27% for RTS,S/AS01 and 38% for R21/Matrix-M), followed less frequently by irritability, and injection site reactions such as pain and swelling.

Three safety signals were identified in the RTS,S/AS01 pivotal phase 3 trial. These safety signals were rigorously monitored prospectively as part of the pilot evaluations in Ghana, Kenya and Malawi. The safety signals were not found to be associated with vaccination, supporting the conclusion that they were chance findings. A statistically non-significant imbalance in deaths was observed in the R21/Matrix-M phase 3 trial; no deaths were assessed as being related to vaccination. As with any vaccine introduction, proper planning and training of staff to conduct appropriate pharmacovigilance should take place beforehand.

Malaria vaccines may be administered simultaneously with other childhood vaccines.

The choice of product to be used in a country should be based on product characteristics and programmatic considerations, as well as vaccine supply and long-term affordability.

The malaria vaccination series for each child should be completed with the same product whenever feasible. However, if the product used for a prior dose is unavailable or unknown, the series should be completed with either of the available WHO-recommended malaria vaccines. Restarting the vaccine series is not recommended.

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[1] Moderate and high transmission settings are defined as areas with *P. falciparum* parasite prevalence more than 10% *Pf*PR_{2-10} or an annual parasite incidence greater than 250 per 1000. These thresholds are indicative and should not be regarded as absolutes for determining the applicability of the malaria vaccine recommendation.

[2] Decisions on expanding malaria vaccination to low transmission settings should be considered at country level on the basis of the overall malaria control strategy, affordability, cost-effectiveness, and programmatic considerations such as whether the inclusion of such areas would simplify delivery.

[3] Countries may choose to give the first vaccine dose earlier than 5 months of age on the basis of operational considerations, to increase coverage or impact.