Malaria vaccines update

Eastern and Southern Africa National Malaria Programmes and Partners Annual Meeting 2023
3-6 October 2023
Updated WHO recommendation, including R21/Matrix-M as a second malaria vaccine
As a malaria researcher, I used to dream of the day we had a safe and effective vaccine against malaria. Now we have two.”

WHO Director-General’s opening remarks

WHO Press release: https://www.who.int/news/item/02-10-2023-who-recommends-r21-matrix-m-vaccine-for-malaria-prevention-in-updated-advice-on-immunization
WHO recommends the programmatic 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

- The malaria vaccine should be provided in a schedule of 4 doses in children from around 5 months of age\(^1\) for the reduction of malaria disease and burden

- A 5th dose, given one year after dose 4, may be considered in areas where there is a significant malaria risk remaining in children a year after receiving dose 4

- Countries may consider providing the vaccine using an age-based, seasonal, or a hybrid of these approaches in areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks

- Countries should prioritize vaccination in areas of moderate and high transmission, but may also consider providing the vaccine in low transmission settings

- Vaccine introduction should be considered in the context of comprehensive national malaria control plans

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\(^1\) Vaccination programmes may choose to give the first dose at a later or slightly earlier age based on operational consideration. Studies with RTS,S/AS01 indicated lower efficacy if first dose was given around 6 weeks of age. However, it seems unlikely that efficacy would be substantially reduced if some children received the first dose at 4 rather than 5 months, and providing vaccination at an age younger than 5 months may increase coverage or impact
WHO recommendation: malaria vaccine dose schedule and delivery

• In areas of perennial malaria transmission, the malaria vaccine should be provided as a 3-dose primary series, starting from around 5 months of age, with a minimal interval of 4 weeks between doses

• The fourth dose should be given to prolong protection. There can be flexibility to optimize delivery for dose 4:
  • Alignment with other second year of life vaccines
  • Administration prior to seasonal peaks in malaria transmission to optimize efficacy
  • The optimal interval between dose-3 and 4 has not been established

• If malaria remains a significant public health problem in children a year after the fourth dose, then a fifth dose might be considered, depending on a local assessment of feasibility and cost-effectiveness

This recommendation now includes two malaria vaccines:

• RTS,S/AS01
  WHO prequalified in 2022

• R21/Matrix-M
  Currently under WHO pre-qualification review
WHO recommendation based on full evidence review of R21/Matrix-M by expert advisory bodies SAGE and MPAG on 27 September 2023¹

R21/Matrix-M Phase 3 trial design:
Seasonal administration (n=2,400), ages 5-36 months at first vaccination
• 2 sites: Nanoro, Burkina Faso and Bougouni, Mali

Age-based (“standard”) administration (n=2,400), ages 5-36 months at first vaccination
• 3 sites: Dande, Burkina Faso; Kilifi, Kenya and Bagamoyo, Tanzania

Primary endpoint: 12 months post dose-3
Data available and reviewed through 18-months follow-up post dose 3

¹ SAGE (Strategic Advisory Group of Experts on Immunization); MPAG (Malaria Policy Advisory Group)
Meeting materials available from: https://www.who.int/news-room/events/detail/2023/09/25/default-calendar/sage_meeting_september_2023
Evidence on R21/Matrix-M (R21) malaria vaccine

- **High efficacy when given just before the high transmission season**: In areas with highly seasonal malaria transmission (where malaria transmission is largely limited to 4 or 5 months per year), the R21/Matrix-M vaccine was shown to reduce symptomatic cases of malaria by 75% during the 12 months following a 3-dose series. A fourth dose given a year after the third maintained efficacy
  - This high efficacy is similar to the efficacy demonstrated when RTS,S is given seasonally (73% during 12 months follow-up)
- **Good efficacy when given in an age-based schedule**: The vaccine showed good efficacy (66%) during the 12 months following the first 3 doses in moderate to low perennial transmission settings. A fourth dose a year after the third maintained efficacy
  - Although it has not been tested in areas of high perennial transmission, R21 expected have similar high impact as that seen with RTS,S
  - No data are available to directly compare the performance of R21 and RTS,S when given in an age-based strategy.
- **High impact**: Mathematical modelling estimates indicate the public health impact of the R21 vaccine is expected to be high in a wide range of malaria transmission settings, including low transmission settings
- **Cost effectiveness**: At price assumption of US$ 2 – US$ 4 per dose, the cost-effectiveness of the R21 vaccine would be comparable with other recommended malaria interventions and other childhood vaccines
- **Safety**: The R21 vaccine was shown to be safe in clinical trials. As with other new vaccines, safety monitoring will continue
- **Similarity of R21 and RTS,S vaccines**: The R21 vaccine is similar to RTS,S in construct, target population, and delivery strategy. There is no evidence that one vaccine performs better than the other
- **Price**: The initial price of R21/Matrix-M vaccine is expected to be considerably lower than that for RTS,S/AS01
Implications and next steps
Outlook of key next steps

• **Ongoing WHO pre-qualification review for R21/Matrix-M**
  • WHO PQ is a pre-requisite for UNICEF to procure and for Gavi to fund the vaccine

• **UNICEF to finalize supply agreement with Serum Institute of India (SII), manufacturer of R21/Matrix-M**
  • SII indicates to have established production capacity for 100 million doses per year

• **Cumulative supply availability of two malaria vaccines expected to meet the demand, starting in 2024**
  • Enabling more countries to introduce and scale up faster
Countries’ Gavi application status – as of 4 October 2023

- At least 28 countries in Africa expressed interest in introducing a malaria vaccine
- Since opening the funding window in mid-2022, Gavi approved applications from 18 countries to roll-out the vaccine
- **12 countries have RTS,S supply allocation confirmed** for introduction in Phase 1 (greatest need areas), starting in Q1 2024
- Guidance from Gavi forthcoming on how countries can access additional supply (once R21/Matrix-M is WHO pre-qualified)
Further information

- **WHO Press release on R21/Matrix-M recommendation:** [https://www.who.int/news/item/02-10-2023-who-recommends-r21-matrix-m-vaccine-for-malaria-prevention-in-updated-advice-on-immunization](https://www.who.int/news/item/02-10-2023-who-recommends-r21-matrix-m-vaccine-for-malaria-prevention-in-updated-advice-on-immunization)

- **SAGE meeting materials:** [https://www.who.int/news-room/events/detail/2023/09/25/default-calendar/sage_meeting_september_2023](https://www.who.int/news-room/events/detail/2023/09/25/default-calendar/sage_meeting_september_2023)
  - Full evidence report on R21/Matrix-M and additional background documents available in the SAGE «Yellow Book»; Session highlights; Presentation

- **Updates will be made to incorporate the updated WHO recommendation in materials available to support country vaccine introductions, including:**
  - Q4 2023: Update to *WHO Guidelines for Malaria (incl. MAGICApp)*
  - Q4 2023: Implementation Guidance for Malaria Vaccines
  - Guide to introducing a malaria vaccine
  - Generic training modules for health workers
  - WHO webpage on malaria vaccines and dedicated TechNet-21 page on the malaria vaccine (forthcoming)
  - Q1 2024: Revision to the Gavi application guidelines
Thank you

Contact:
Malaria Vaccines Team at WHO
malarialavaccines@who.int
Back-up slides
Summary findings from the Malaria Vaccine Implementation Programme (RTS,S/AS01 implementation since 2019) helped inform R21/Matrix-M vaccine consideration

- Feasible to introduce with high uptake
- High demand by community and acceptability by health workers
- Vaccine confirmed to be safe
- High impact: Vaccine introduction resulted in a substantial reduction in severe malaria and all cause mortality in children age-eligible to receive the vaccine, even when introduced in areas with good ITN use and access to care
- Equity: Vaccine delivery is equitable by gender or socioeconomic status and is reaching children who are not using other forms of prevention

Since 2019, over 1.8 million children vaccinated with RTS,S/AS01, over 5.4 million doses administered

Kenya, Ghana, Malawi
Estimated public health impact of R21/Matrix-M

Use the fitted, validated model to predict impact in non-seasonal and seasonal settings with different levels of transmission, over a 15-year time horizon.

<table>
<thead>
<tr>
<th>Seasonal setting</th>
<th>Perennial</th>
<th>Seasonal</th>
<th>Hybrid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementation method</td>
<td>Age-based</td>
<td>Age-based</td>
<td>Seasonal</td>
</tr>
<tr>
<td>Proportion of clinical cases averted in children younger than 5 years</td>
<td>41.6% [46.0; 30.6]</td>
<td>41.4% [47.2; 29.3]</td>
<td>43.4% [49.8; 29.4]</td>
</tr>
<tr>
<td>Proportion of malaria deaths averted in children younger than 5 years</td>
<td>34.3% [44.6; 21.4]</td>
<td>34.4% [45.3; 20.2]</td>
<td>35.0% [47.8; 18.9]</td>
</tr>
<tr>
<td>Clinical cases averted per 100,000 fully vaccinated children</td>
<td>190,602 [42,236; 330,866]</td>
<td>210,616 [32,428; 398,620]</td>
<td>225,428 [37,117; 391,277]</td>
</tr>
<tr>
<td>Malaria deaths averted per 100,000 fully vaccinated children</td>
<td>632 [268; 633]</td>
<td>663 [216; 719]</td>
<td>689 [236; 709]</td>
</tr>
</tbody>
</table>

Estimates represent median values at 20% PfPr2-10 and intervals median values at 3% and 65% PfPr2-10 for a four-dose schedule.

1 For full draft manuscript, see addition Background Document 7.7 (The public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine: a mathematical modelling study) included the “SAGE Yellow Book” for the September 2023 meeting, accessible here: https://www.who.int/news-room/events/detail/2023/09/25/default-calendar/sage_meeting_september_2023
# Estimated cost effectiveness of R21/Matrix-M

Use the fitted, validated model to predict cost effectiveness in non-seasonal and seasonal settings over a range of transmission levels.

<table>
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<tbody>
<tr>
<td><strong>Implementation method</strong></td>
<td>Age-based</td>
<td>Age-based</td>
</tr>
<tr>
<td>Cost per clinical case averted (USD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$2 per dose</td>
<td>$5 [33, 3]</td>
<td>$5 [43, 2]</td>
</tr>
<tr>
<td>Cost per DALY averted (USD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$3 per dose</td>
<td>$36 [126, 34]</td>
<td>$33 [158, 27]</td>
</tr>
</tbody>
</table>

Estimates represent median values at 20% $\text{Pr}_{2-10}$ and intervals median values at 3% and 65% $\text{Pr}_{2-10}$ for a four-dose schedule.

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