Clinical malaria cases averted/1000 vaccinees

WHO PQ and policy recommendation pending
- Ghana and Nigeria FDA approval in April, 2023

Status
- Deliverability improvements
- Lower sale price
- Larger manufacturing scale (x30 fold greater)
- More surfaced malaria antigen molecules

Key Findings from Pivots:
- Possible to avert malaria
- Reaching the unvaccinated
- Strong safety profile
- No negative impact on uptake of bednets, other childhood vaccinations, or health seeking behavior for febrile illness
- High impact in real-life childhood vaccination settings
- Highly cost-effective

WHO Recommendations (Oct. 2021)
- Prevention of malaria in moderate to high transmission settings (reduction in disease and burden)
- Children >5 months old, 4 doses regimen
- Three doses approx. 4 weeks apart with the fourth dose at 15-18 months
- Prevention of P. falciparum in moderately to high transmission areas (reduction in disease and burden)
- Children >5 months old, 4 doses regimen
- Prevention of malaria in low transmission settings (reduction in disease and burden)
- Children >5 months old, 4 doses regimen

R21/MATRIX-M™ Phase III Trial

Key Features about R21:
- More surfaced malaria antigen molecules
- Larger manufacturing scale (x30 fold greater)
- Deliverability improvements
- Lower sale price
- Status:
  - Ghana and Nigeria FDA approval in 2023
  - WHO PQ and policy recommendation pending

Malaria Vaccine Targets & Proposed Protective Immune Mechanisms

Pre-Erythrocytic Stage (anti-infection)
- Abs bind sporozoites to block infection of liver cells
- CD4 T cells block infection and pathology

Mosquito Sexual Stage (transmission-blocking)
- Abs prevent fertilization of gametocytes, interfering zygote or oocyst development

Asexual Blood Stage (anti-diseases)
- Abs opsonize, block invasion, prevent sequestration, recruit "innate"

Transmission Intensity

RTS,S/AS01 Performance by Sites in Children aged 5-17 months during 48 months of follow-up post-immunization

VE in Phase III Trial

Study Population

<table>
<thead>
<tr>
<th>Population</th>
<th>Efficacy vs. Clinical Malaria</th>
</tr>
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<tbody>
<tr>
<td>5-17 mo</td>
<td>45% (41-46)</td>
</tr>
<tr>
<td>6-12 mo</td>
<td>27% (21-33)</td>
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Clinical malaria cases averted/1000 vaccinees

WHO Strategic Priorities for Malaria Vaccines (to Address Control and Elimination)

- SP1: Malaria vaccines that prevent human blood-stage infection at the individual level
  - 1 blood stage infection (e.g., >90% over 12 months)
- SP2: Malaria vaccines that reduce morbidity and mortality in individuals at risk in endemic areas
  - 1-2 clinical malaria episodes (e.g., >90% over 12 months preferred or 45% over 32 months)
- SP3: Malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human infection in the community
  - Transmission leading to reduction of incident human infections or clinical malaria at the community level
NIAID Extramural Malaria Vaccine Preclinical Portfolio

**Strategies and Approaches**
- Structural based immunogen design
- Broaden antigen coverage
- Whole organism-based
- Combined antigens
- Technology platforms
- Adjuvants, VLPs, viral or bacterial vectors, nanoparticles, DNA/mRNA, etc.
- Novel vaccination regimen
- Prime/booster (Primechips)
- De-fractional dosing

**Recent Candidate Malaria Vaccines in Clinical Development**

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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</table>

**Blood Stage Antigens**

- PfG36
- PfG36/SpG36 (gamete surface antigen)
- PfAMA1-RON2/MatrixM (invasion molecule)
- PfAMA1-RON2L plus merozoite extract
- PfAMA1-RON2L (invasion antigen)
- PfAMA1-RON2L/VLP (invasion antigen)
- PfAMA1-RON2L (invasion antigen)

**Sporozoite Antigens**

- PfSPZ
- Sporozoites PfSPZ-LARC2
- Sporozoites PfSPZ plus T cell Ags
- Sporozoites "Mosaic" PfSPZ-LARC2
- Sporozoites adjuvanted PfSPZ

**DNA-ChAd63 PfCSP PfAMA1 ME-TRAP (prime-boost)**

**Prime/Trap PfSZP/DNA-CSP**

**Combinations**

- DNA: Pfs25, Pvs25, Pfs48/45, Pfv48/45, PfCSP
- CMV/MHC-E-restricted T Ags
- Nanoparticle and/or mRNA (CSP+DBP)
- Recombinant protein Pv48/45
- Nanoparticle SANP-CSP
- Recombinant protein PfSEA-1+CDPK5
- Recombinant protein MSP1/8
- Prime/Trap PfSZP/DNA-CSP

**Combination Vaccine Consideration**

**Plasmodium falciparum vaccines**
- Target to more than one life cycle stage to reduce "force of infection"
- e.g., R21 + Pf55, R21 + Pf230
- Combine multiple antigens of the same life cycle stage to overcome polymorphism/redundancy or achieve a functional complex
- e.g., multiple antigen alleles, multiple BS antigens
- e.g., AMA-1/RO2 and HRSV/RPA/RS complex
- Combine technologies to induce different immune mechanisms
- e.g., R21+PSPZ, RTS,S Prime/Ad35, CS boost

**Pan-Plasmodium vaccines**
- Multiple Pf strains
- Multiple species (e.g., Pf and Pv)
Clinical Development Pathway for Malaria Vaccines

<table>
<thead>
<tr>
<th>Phase I-IIa</th>
<th>CHMI Models</th>
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<tr>
<td>Phase I</td>
<td>Safety</td>
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<tr>
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Pivotal Licensure Studies

Post marketing Studies

Consideration for Late-stage Clinical Development

- Trial design
  - Comparator arms, superiority and non-inferiority trials
  - Drug pre-treatment has implication for safety and product labelling
- Standard of care: improvement for trial participants may limit detection of secondary outcomes including mortality
- Case detection system: PCD preferred in Phase III to measure public health impact and reducing burden on health facilities
- Other control interventions (ITNs, IRS, access to diagnosis and treatment, etc.) could be confounders
- Transmission intensity (incl. degree of seasonality) impacts vaccine efficacy
- Safety evaluation
  - Relevant populations and age groups (incl. special populations)
  - Absence of clinically relevant interference (safety and immunogenicity) with other vaccines (DPT), malaria or other chemoprevention strategies (e.g., anti-helminth)
  - Interference with development of naturally acquired immunity (“rebound effect”)