WHO/MPP mRNA Technology Transfer Workshop

Status of Malaria Vaccine R&D and Clinical Development Considerations

Annie Mo, PhD, Senior Program Officer
National Institute of Allergy and Infectious Diseases
NIH, DHHS

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Disclosure: The presentation is prepared as part of my official capacity as a U.S. government employee and I have no financial conflicts of interest.

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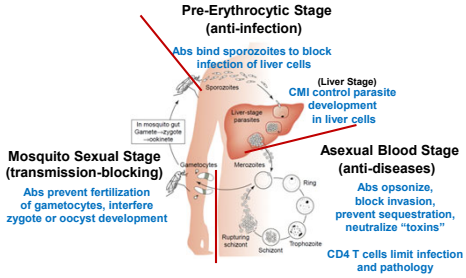
Malaria Vaccine Targets & Proposed Protective Immune Mechanisms



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WHO Recommendation of RTS,S/AS01

VE in Phase III Trial

	Intent-to-Treat (ITT) Analysis		
Study Population	Efficacy vs. Clinical Malaria		
	18 mo	Final Analysis (* w boost)	
5-17 mo; N=8923	45% (41-49)	28% (23-33)	36%* (32-40)
		1363	1774*
6-12 wk infants; N=6537	27% (21-33)	18% (12-24)	26%* (20-32)
		558	983*

Clinical malaria cases averted/1000 vaccinees

Key Findings from Pilots:

- Feasible to deliver
- Reaching the unreached
- 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 *P. falciparum* in moderate to high transmission settings (reduction in diseases and burden)
- Children >5 months old, 4 doses regimen
  - Three does approx. 4 weeks apart with the fourth dose at 15-18 months after dose three)

https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk

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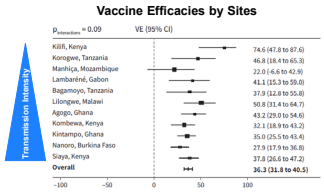
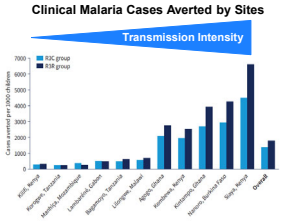
RTS,S/ASO1 Performance by Sites in Children aged 5-17 months during 48 months of follow-up post-immunization





RTS,S Clinical Trial Partnership, Lancet 2015
Bell et al., J Infect Dis, 2022

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R21/Matrix-M™ Phase III Trial

Key Features about R21:

- More surfaced malaria antigen molecules
- Larger manufacturing scale (x30 fold greater)
- Lower sale price
- Deliverability improvements
  - Multi-dose vialing of mixed antigen/adjuvant
  - Excellent product thermostability

Status

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

Interim Analysis: Modified Per-Protocol Analysis (first clinical malaria episode)		
Regimens	Sites/ Population	Unadjusted VE
Standard Perennial Regimen (Day 0, 28, 56, boost at 1yr) N=2315	Dande, Bagamoyo, Kilifi 5-30 mo. old	73% (64-79) (follow-up time 252 days) 246
Seasonal Regimen (Day 0, 28, 56, boost at 1yr) (started in April/May) N=2339	Bougouni, Nanoro 5-30 mo. old	75% (71-78) (follow-up time 344 days) 860

Clinical malaria cases averted/1000 vaccinees

Adrian Hill, ASTMH presentation, 2022

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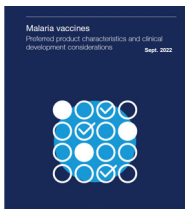
WHO Strategic Priorities for Malaria Vaccines (to Address Control and Elimination)



- **SP1:** Malaria vaccines that prevent human blood-stage **infection** at the individual level
  - ↓ blood stage infection (e.g., >90% over 12 months)
- **SP2:** Malaria vaccines that reduce **morbidity and mortality** in individuals at risk in endemic areas
  - ↓ all 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

https://www.who.int/publications/i/item/9789240057463

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NIAID Extramural Malaria Vaccine Preclinical Portfolio

Pathogen	Target Identification/Validation	Proof of Concept	Process Development, cGMP Production
Plasmodium falciparum	Pre-erythrocytic ▪ Sporozoite Ag (Ab-mediated) ▪ Exported protein (Liver stage) ▪ Protein+vide T cell Antigen Asexual Blood Stage ▪ PfSEA-1 TB agent ▪ Rh5 complex ch Sexual Stage ▪ Ag ID (differe Multi-stages ▪ Immunogen de	Pre-Erythrocytic ▪ Sporozoites PfSPZ-GAP ▪ Sporozoites adjuvanted PfSPZ	Pre-Erythrocytic ▪ Sporozoites PfSPZ LARC2 Process Improvement for sporozoite vaccines ▪ Cryopreserved manipulated mosquitoes ▪ Dissection ▪ Isolation
Plasmodium vivax	Asexual Blood Sta ▪ Ins DBPII Epito Sexual Stage ▪ Pvs48/45 Epito ▪ Ag ID (transfe ▪ Ag ID (System		▪ Live PvSPZ for Challenge
Pan-Plasmodium	Multi-species (Pf+Pv) ▪ Pan-Vax: VAR2CSA + Pf	▪ CMV/MHC-E-restricted T Age ▪ DNA: Pfs25, Pvs25, Pfs48/45, Pvs48/45, PfCSP	

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/boost (Prime/trap)
  - De-fractional dosing

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Recent Candidate Malaria Vaccines in Clinical Development

	Phase 1	Phase 2	Phase 3
Pre-erythrocytic	▪ BNT165b1 (CSP mRNA) ▪ rCSP/AP10-602 (FL-CSP) ▪ FMP013/ALFQ (FL-CSP) ▪ FMP014/ALFQ (CSP, nanoparticles) ▪ VLPM01 (CSP, virus-like particle) ▪ DNA-ChAd63 PfCSP (prime-boost) ▪ DNA-ChAd63 PfCSP PfAMA1 ME-TRAP (prime-boost) ▪ PfGAP3-KO (genetically attenuated sporozoite) ▪ PfSPZ-GA1 (genetically attenuated sporozoite) ▪ PvCSP/ISA51 (CSP) ▪ PvSPZ (attenuated sporozoite)	▪ PfSPZ (irr. attenuated sporozoite)	▪ R21/MatrixM
Blood Stage	▪ BK-SE36/CpG (PfSERA5 antigen) ▪ Rh5.1/MatrixM1 (invasion molecule) ▪ Pf7G8 (chem. attenuated parasite) ▪ PRIMVAC(targeting VAR2CSA, for Malaria in Pregnancy) ▪ PAMVAC(targeting VAR2CSA, for Malaria in Pregnancy)	▪ Rh5.1/AS01 (invasion molecule) ▪ ChAd63-MVARh5 (invasion molecule) ▪ ChAd63.MVA.PvDBP RII (invasion antigen) ▪ PvDBPII/MatrixM1 (invasion antigen)	
Sexual Stage	▪ Pfs25-IMX313/MatrixM (zygote/ookinete) ▪ Pfs25M-EPA/AS01B (zygote/ookinete) ▪ Pfs230D1-EPA/MatrixM (gamete surface antigen) ▪ R0.6C (Pfs48/45) (gamete surface antigen) ▪ AnAPN1/GLA-LSQ (mosquitos midgut antigen) ▪ Pvs25-IMX313/MatrixM (zygote/ookinete)	▪ Pfs230D1M-EPA/AS01B (gamete surface antigen)	
Multi-stages	▪ RH5.2-VLP plus R21 in Matrix-M (planning)		

Blue: Pv targets

Sources: https//www.who.int/data/gho, Clinicaltrials.gov, & personal communication

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PfSPZ Sporozoite Vaccine Candidates

PfSPZ Vaccine Features:

- **3-doses/DVI over 4 weeks (anti-malaria pre-treatment in endemic areas)**
- **Storage: LN2 vapor phase**
- **Manufacturing involves insectary**
- **Potential for prevention of infection & transmission**

Population	Vaccine Efficacy (vs. infection by parasitemia)	Reference
Naïve Adult CHMI (measured at 3 or 9-10 wks)	**79%** (heterologous) **77%** (homologous)	Mordmüller, *NPJ Vaccines*, 2022
Burk. Faso adults - natural exposure (over two transmission season)	**48% or 46%** (6 or 18 mos) (1-harzard ratio) **36%** or **15%** (6 or 18 mos) (1-risk ratio)	Sirima, *Science Translational Medicine*, 2022
Mali adult women - natural exposure	Promising data	Diawara & Healy, unpublished

An improved version in early development:
A genetically attenuated, late arresting PfSPZ-LARC2

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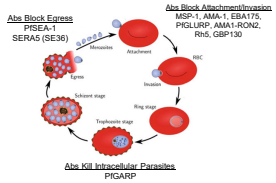
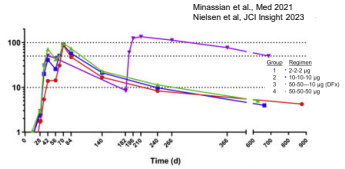
Blood Stage Immune Targets & Promising Adjuvanted PfRh5 Vaccine Candidate

Blood Stage Antigens



Phase I/IIa Trial of Rh5.1/AS01B in Healthy Adults



Modified from Vijayan & Chitnis, Methods Mol Biol. 2019;

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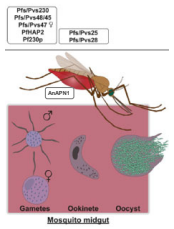
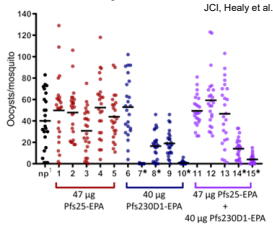
Transmission Vaccine Targets and Promising Candidate Pfs230-EPA

Major Sexual Stage Antigens



Pfs230-EPA Induces higher TBA than Pf25-EPA in a FIH trial
JCI, Healy et al., 2021



More potent adjuvants (Phase I or II in Mali) on-going

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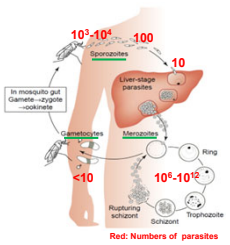
Combination Vaccine Consideration

***Plasmodium falciparum* vaccines**

- **Target to more than one life cycle stages** to reduce "force of Infection"
  - e.g., R21+ Rh5, R21+ Pfs230
- **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/RON2 or Rh5/CyRPA/Ripr complex
- **Combine technologies** to induce different immune mechanisms
  - e.g., R21+PfSPZ, RTS,S Prime/Ad35.CS boost

Pan-*Plasmodium* vaccines

- Multiple *Pf* strains
- Multiple species (e.g., *Pf* and *Pv*)



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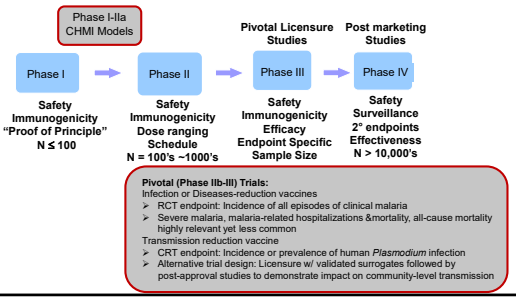
Clinical Development Pathway for Malaria Vaccines



Pivotal (Phase IIb-III) Trials:
Infection or Diseases-reduction vaccines
- RCT endpoint: Incidence of all episodes of clinical malaria
- Severe malaria, malaria-related hospitalizations &mortality, all-cause mortality highly relevant yet less common

Transmission reduction vaccine
- CRT endpoint: Incidence or prevalence of human *Plasmodium* infection
- Alternative trial design: Licensure w/ validated surrogates followed by post-approval studies to demonstrate impact on community-level transmission

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Consideration for Late-stage Clinical Development

- **Trial design**
  - **Comparator arm**, 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 (EPI), malaria or other chemoprevention strategies (e.g., anti-helminth)
  - Interference with development of naturally acquired immunity ("rebound effect")

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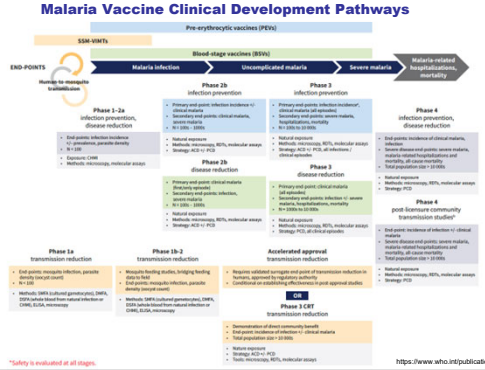
Malaria Vaccine Clinical Development Pathways



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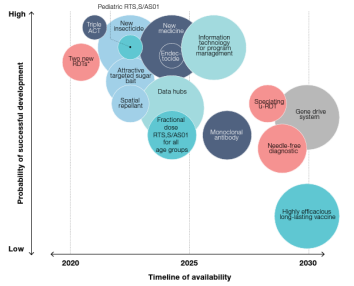
Research and Development Framework for Malaria Eradication



Lancet Commission, 2019

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