WHO update on malaria vaccines and monoclonal antibodies

PDVAC, 13 December 2023, 9:45-10:45am CET

Mary Hamel and Lindsey Wu
World Health Organization

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Credit: WHO/F.Combrink

WHO update on malaria vaccines and monoclonal antibodies

Topic	Presenter
Update on RTS,S/AS01 and R21/Matrix-M	Mary Hamel, WHO
WHO PPCs and R&D pipeline for malaria vaccines and mAbs	Lindsey Wu, WHO
Pre-erythrocytic and blood stage vaccines	Ashley Birkett, PATH
Transmission blocking vaccines	Patrick Duffy, NIH

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Update on RTS,S/AS01, R21/Matrix-M and WHO malaria vaccines recommendation

Mary Hamel

Credit: WHO/F.Combrink

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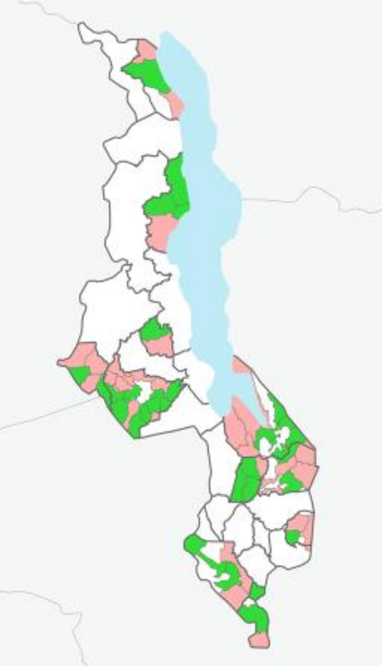
RTS,S/AS01 malaria vaccine implementation since 2019

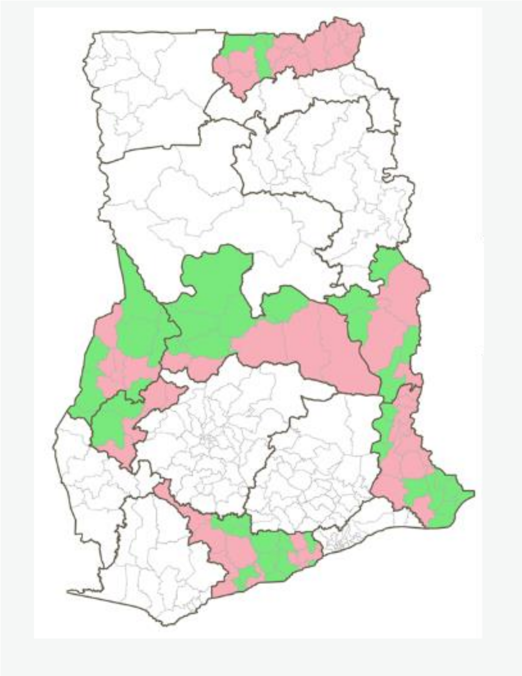
Expanded to comparator areas since Nov 2022 – March 2023

MVIP initial vaccinating district
MVIP comparator district
Non MVIP district

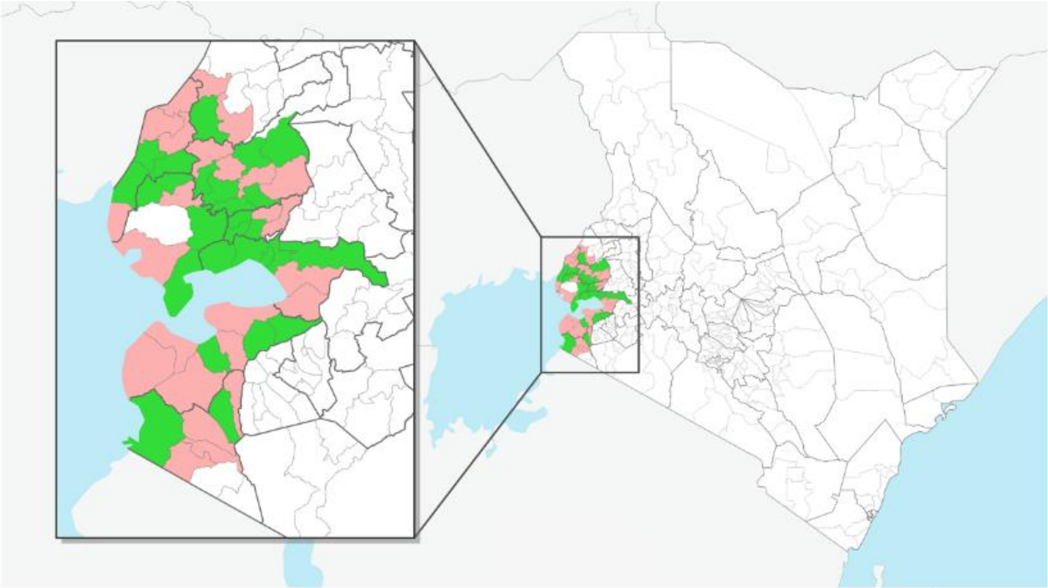
Malawi
First introduced: 23 April 2019
Expanded: 29 Nov 2022



Ghana
First introduced: 30 April 2019
Expanded: 20 Feb 2023

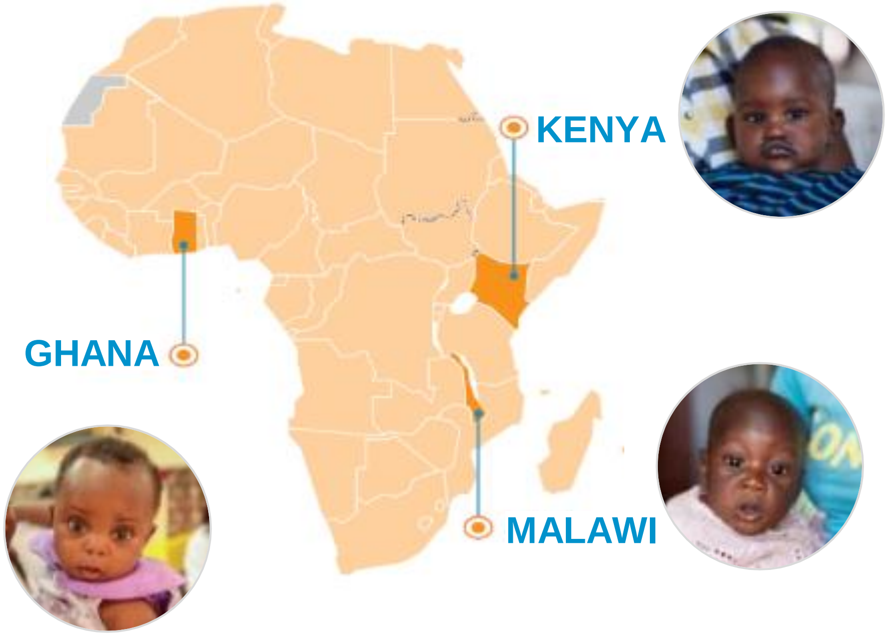


Kenya
First introduced: 13 Sept 2019
Expanded: 7 March 2023



Findings from the Malaria Vaccine Implementation Programme: 46 months of implementation showing good safety profile, high impact

Since 2019, over 2 million children vaccinated with RTS,S/AS01, over 6 million doses administered



Source: MOH monthly administrative data and MVIP projections, April 2019 to October 2023

- **Vaccine confirmed to be safe** with no evidence of the safety signals in Phase 3 trial, and no new safety signals
- **High impact during 46 months of vaccine introduction:**
  - **13% reduction in all-cause mortality** excluding injury [0.87 (95% CI: 0.78, 0.98)] additional impact on top of that provided by ITNs, IRS and other interventions in place

  Impact measured in children age-eligible to receive the vaccine (~64-75% dose 3 coverage, 33-54% dose 4 coverage)
- **Feasible to introduce with high uptake** and no reduction in ITN use, care seeking behavior or uptake of other vaccines
- **High demand** by community and acceptability by health workers
- **Equity:** Vaccine delivery equitable by gender or SES and extends reach of preventive tools

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WHO press briefing on SAGE meeting outcomes, 2 October 2023

WHO recommends R21/Matrix-M vaccine for malaria prevention in updated advice on immunization

2 October 2023 | News release | Geneva |Reading time: 5 min (1351 words)

The World Health Organization (WHO) has recommended a new vaccine, R21/Matrix-M, for the prevention of malaria in children. The recommendation follows advice from the WHO: Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Group (MPAG) and was endorsed by the WHO Director-General following its regular biannual meeting held on 25-29 September.

WHO also issued recommendations on the advice of SAGE for new vaccines for dengue and meningitis, along with immunization schedule and product recommendations for COVID-19. WHO also issued key immunization programmatic recommendations on polio, IA2030 and recovering the immunization programme.

The R21 vaccine is the second malaria vaccine recommended by WHO, following the RTS,S/AS01 vaccine, which received a WHO recommendation in 2021. Both vaccines are shown to be safe and effective in preventing malaria in children and, when implemented broadly, are expected to have high public health impact. Malaria, a mosquito-borne disease, places a particularly high burden on children in the African Region, where nearly half a million children die from the disease each year.

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

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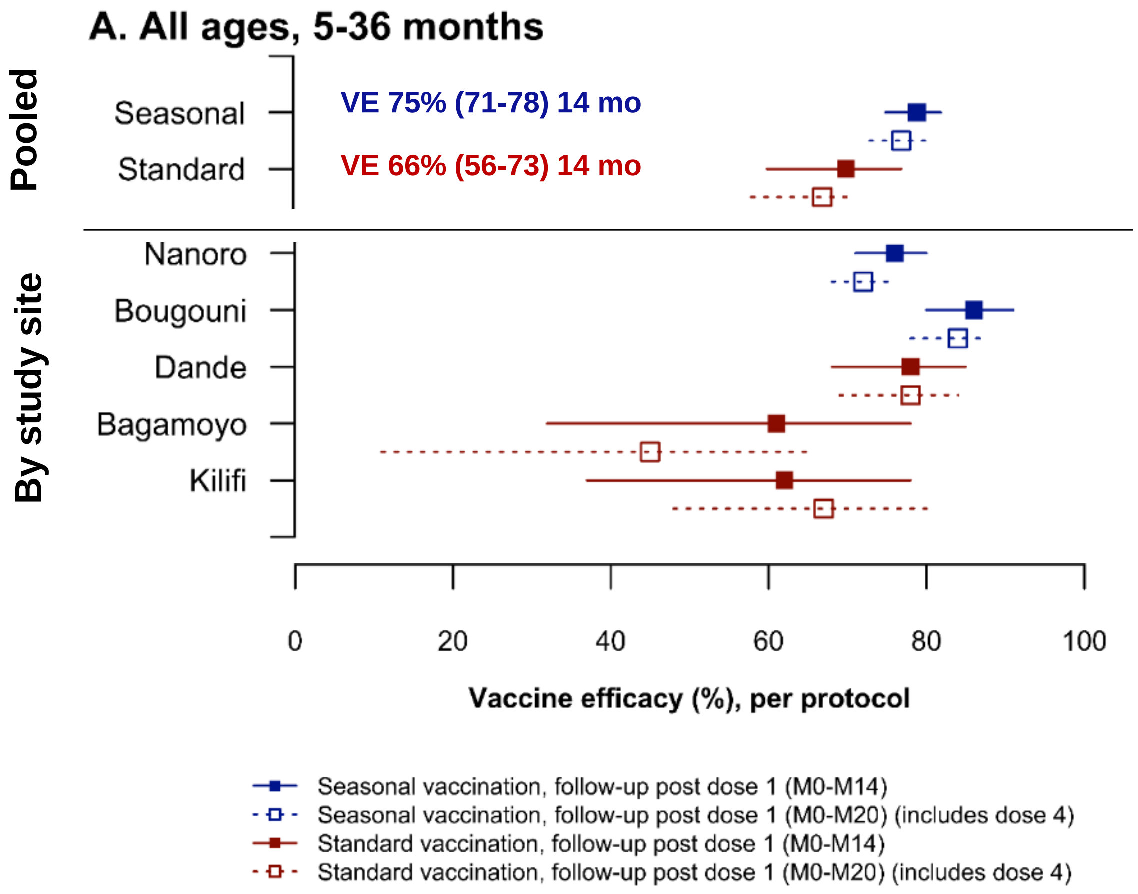
R21 vaccine efficacy against all episodes of clinical malaria, *per protocol*

Seasonal sites, 14- and 20-month follow-up post dose 1 (blue); Standard sites, 14-month follow-up post dose 1 (red)



- Efficacy similar 12 months after 3 doses and 6 months after dose 4
- Efficacy lower in East African sites (Bagamoyo, Kilifi)
  - Low transmission, age-based vaccination
- No significant differences in VE between boy and girls
- VE similar by number of rounds of seasonal malaria chemoprevention (SMC) received, but limitations to data*

*study not designed to measure SMC effect, SMC provided through MOH with varying coverage, ascertainment of SMC through home health cards, no written documentation of SMC given on health card interpreted as zero SMC received

Evidence on R21/Matrix-M malaria vaccine

- **High impact:** Initial 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
- **Cost effectiveness:** At a price range 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:** No major safety concerns were noted that would warrant a delay in recommendation of R21 malaria vaccine for public health use
- **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 has been announced at US$ 3.90 per dose, considerably lower than the initial price for RTS,S/AS01 (EUR 9.30 per dose)

WHO recommendation: malaria vaccines

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

This recommendation now includes <u>two</u> malaria vaccines:

- **RTS,S/AS01**
  WHO pre-qualified in 2022
- **R21/Matrix-M**
  WHO pre-qualification review ongoing

[1] Vaccination programmes may choose to give the first dose at a later or earlier age based on operational considerations. 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

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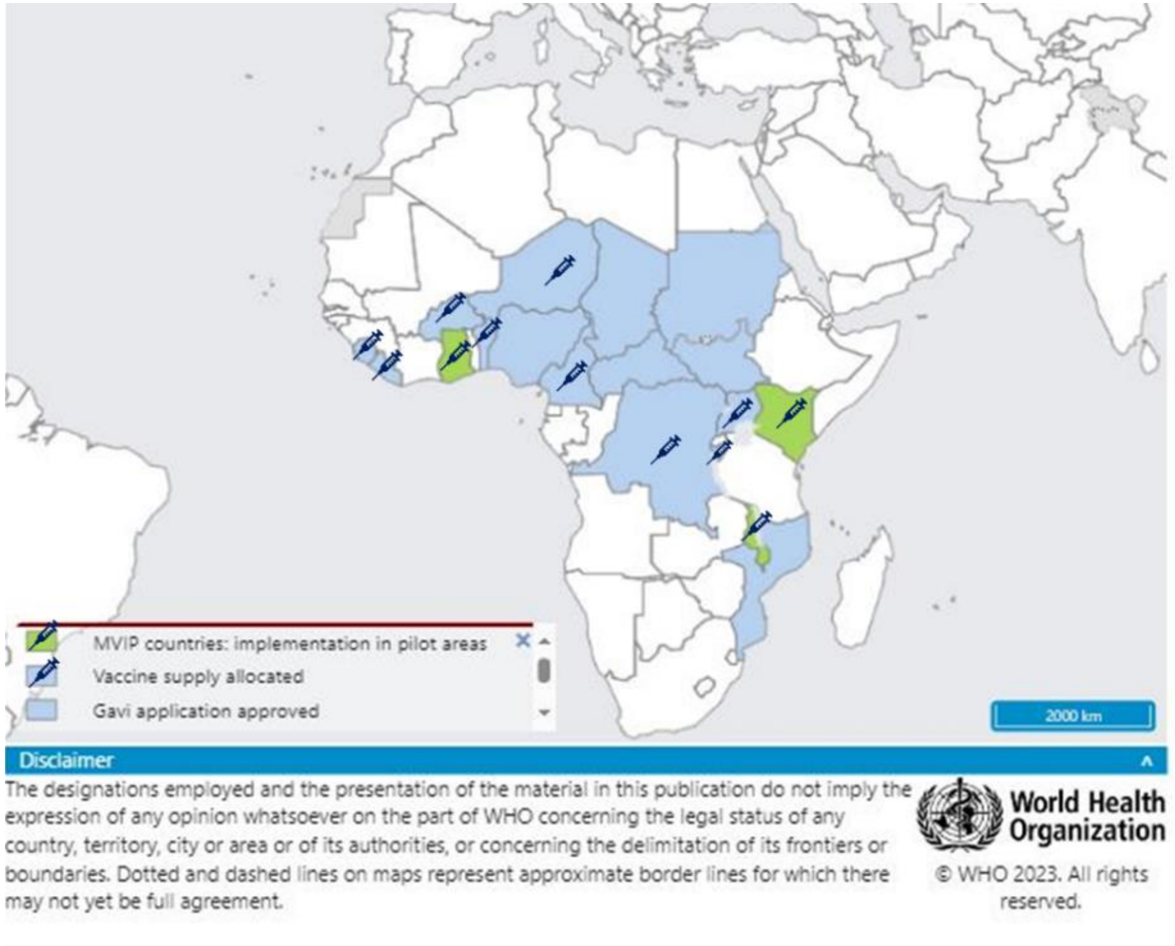
Countries' Gavi application status for malaria vaccines - as of 28 Nov 2023

- **>30 countries** in Africa interested in introducing
- Since opening the funding window in mid-2022, **Gavi approved applications from 18 countries** to introduce vaccine in routine immunization programmes:

  Benin, **Burkina Faso**, **Burundi**, **Cameroon,** Central African Republic, Chad, **DR Congo**, **Ghana, Kenya, Malawi, Niger**, Nigeria, **Liberia**, Mozambique, **Sierra Leone**, South Sudan, Sudan, **Uganda**

- First non-pilot countries to begin introductions in early 2024
- With two WHO recommended vaccines, supply expected to be sufficient to meet demand



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1 WHO/UNICEF/Gavi Joint News Release https://www.who.int/news/item/05-07-2023-18-million-doses-of-first-ever-malaria-vaccine-allocated-to-12-african-countries-for-2023-2025--gavi--who-and-unicef

WHO PPCs and R&D pipeline for malaria vaccines and monoclonal antibodies

Lindsey Wu, WHO

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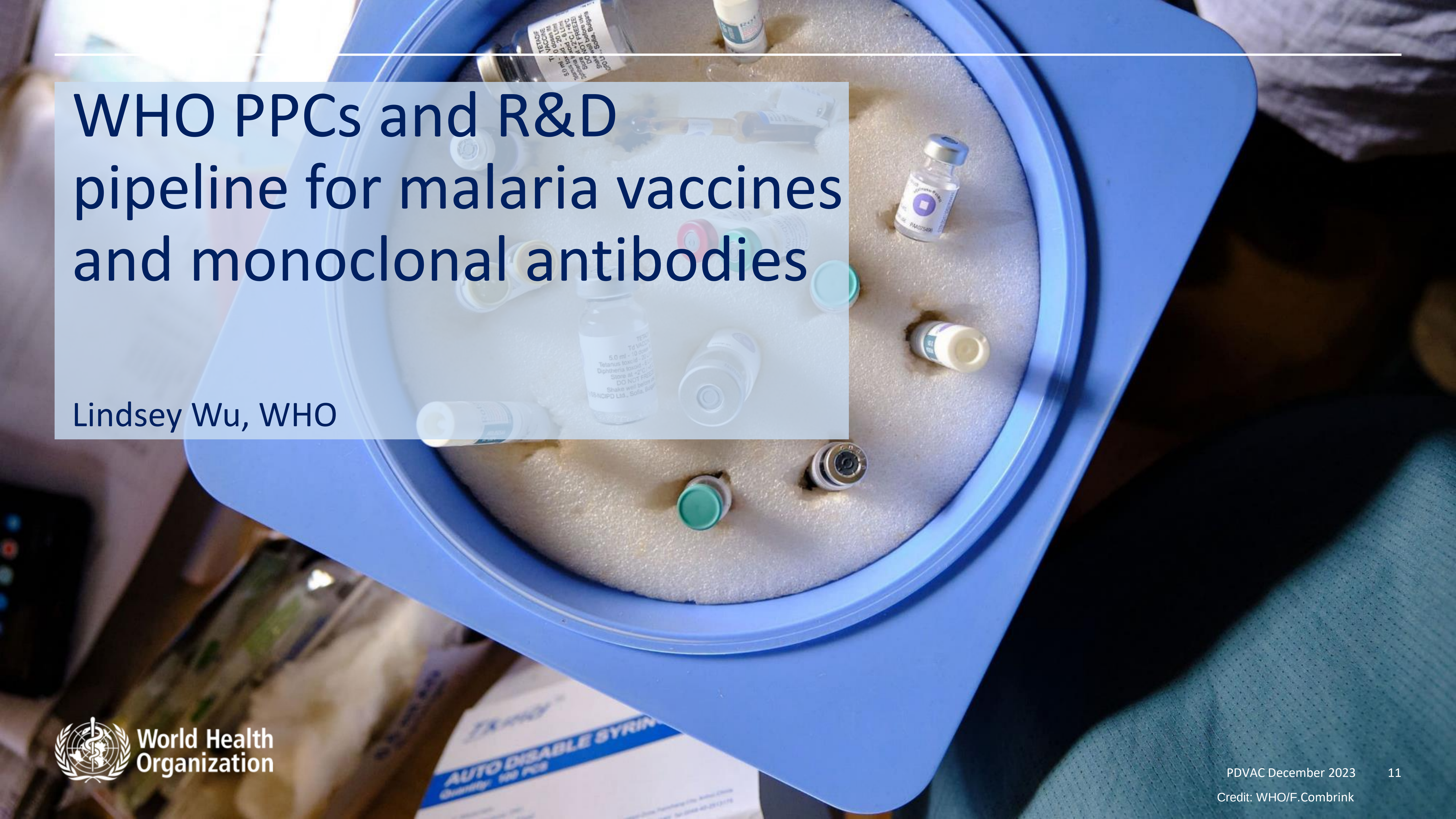

Credit: WHO/F.Combrink

Malaria vaccine PPCs updated in 2022

Expanded set of strategic goals

- Vaccines to prevent blood stage infection (new)
- Vaccines to reduce morbidity and mortality
- Vaccines to reduce transmission at the community level

Clinical development considerations

- Evaluation and harmonisation of endpoints, clinical development pathways

Update on the state of the art

- Functional assays, CHMI studies, adjuvants and delivery platforms

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WHO Strategic priorities for malaria vaccines

Strategic goal 1

- Prevention of human blood-stage infection at individual level
  - e.g., high efficacy PEV or combination PEV/BSV vaccines

Strategic goal 2

- Reduction of morbidity and mortality
  - e.g., PEVs (RTS,S/AS01 & R21) and high efficacy BSVs

Strategic goal 3

- Reduction of parasite transmission and reduction of the incidence of human infection in the community
  - e.g. TBVs, or very high efficacy PEV/BSVs

PEV: pre-erythrocytic stage vaccine
BSV: blood stage vaccine
TBV: transmission blocking vaccine

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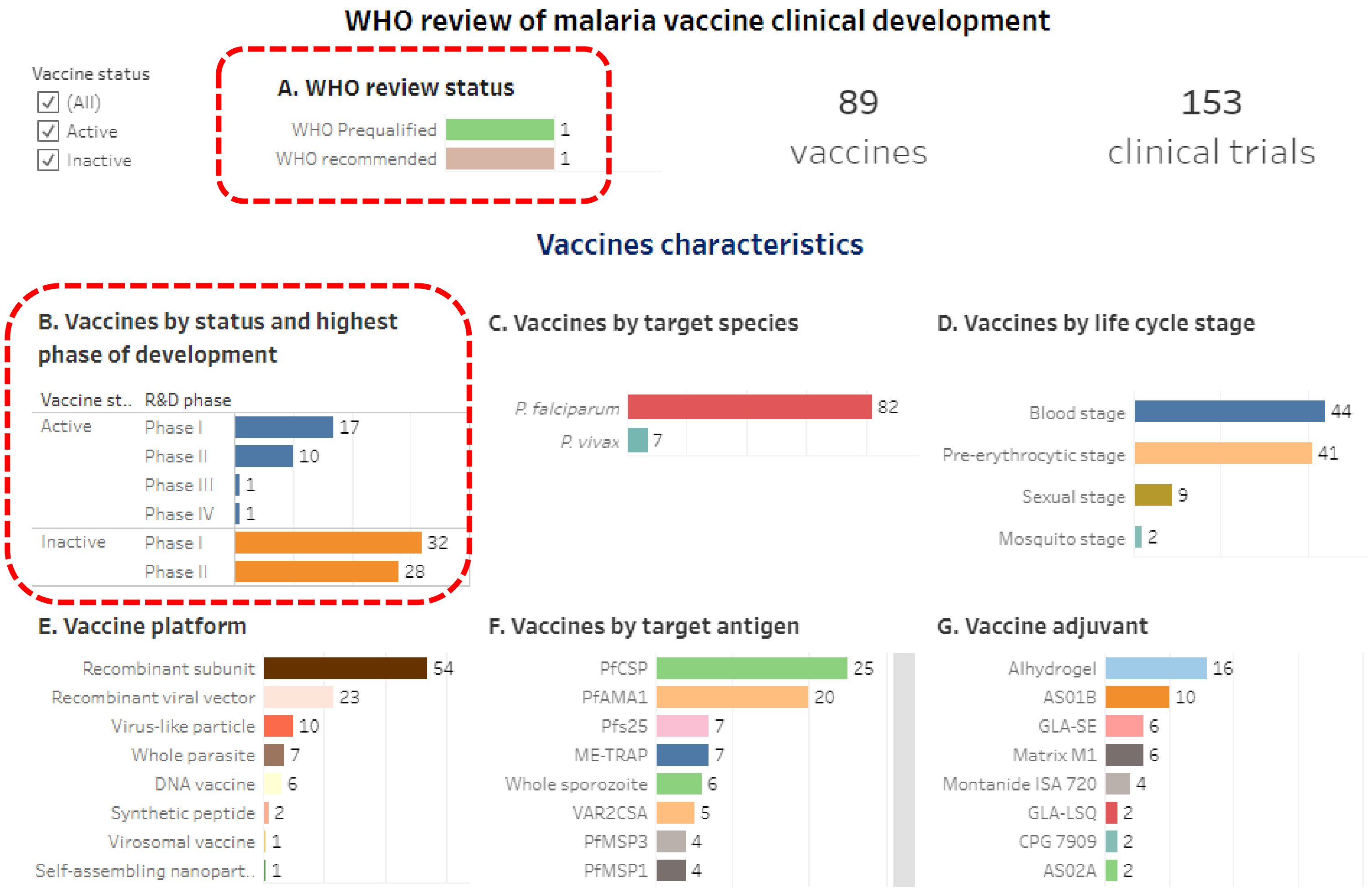
Malaria vaccine R&D pipeline

- Over 150 clinical trials and nearly 90 vaccine candidates tested
- However, only two vaccines (RTS,S and R21) are WHO recommended
- Both are moderately efficacious pre-erythrocytic vaccines to reduce clinical malaria in infants/children



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https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/who-review-of-malaria-vaccine-clinical-development

Pre-erythrocytic stage vaccines: *opportunities and challenges*

R&D status

- WHO recommended - RTS,S/AS01 and R21/Matrix-M
- Evaluation of safety and efficacy in Phase 3 (RTS,S/AS01 & R21/Matrix-M), pilot implementation (RTS,S/AS01)

Public health impact

- RTS,S/AS01 - demonstrated impact on malaria morbidity/mortality across transmission settings
- R21 – efficacy against clinical malaria in phase 3 in low to moderate transmission

Gaps/challenges

- Moderate efficacy; should be part of comprehensive malaria control strategies
- Operational challenges (delivery approaches, dose schedule)
- Target population - infants and young children (ages 5-36 months); efficacy not demonstrated in older children or adults
- Does not target gametocytes to prevent onward transmission

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Blood stage vaccines: *opportunities and challenges*

R&D status

- Rh5 (*P. falciparum*) – first BSV candidate to show reduction in PMR in humans
  - Completed studies: Phase 2a studies in healthy adults in UK & Phase 1b studies in adults and infants in Tanzania[1]
  - Ongoing studies: Phase 2b in Burkina Faso with Matrix-M (ages 5-17 months)[2]; Phase 1b combined with R21 in Gambia (adults and infants)[3]; Ab responses in infants have exceeded GIA thresholds
- *P. vivax* Duffy binding protein (DBP) candidate – reduction in PMR after CHMI

1 https://clinicaltrials.gov/study/NCT03435874
2 https://clinicaltrials.gov/study/NCT05790889
3 https://clinicaltrials.gov/study/NCT05357560

PMR: parasite multiplication rate
GIA: growth inhibition assay
BSV: blood stage vaccine

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Blood stage vaccines: *opportunities and challenges*

Public health impact

- WHO strategic goal 2 – reduction of morbidity and mortality
- WHO strategic goal 1 – prevent blood stage infection (if very high efficacy to reduce parasites and/or combined with PEV)

Gaps/challenges

- Difficult to generate high antibodies levels required to neutralize high volume of parasites in blood stage (compared to low parasite volume in pre-erythrocytic stage)
- Antigenic diversity and multiple blood cell invasion pathways
  - Challenging to identify ideal antigen target
- Operational challenges (delivery, dose schedule) - same as PEV if targeted for infants/young children

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Transmission blocking vaccines: *opportunities and challenges*

R&D status

- Pfs25-EPA and Pfs230-EPA (developed by NIAID) – has completed Phase 2 trial in adults in Mali
- Pfs25-IMX313 (University of Oxford) - ongoing Phase 1b in adults and children in Tanzania

Public health impact

- WHO strategic goal 3 - elimination and very low transmission settings

Gaps/challenges

- No direct benefit to the vaccinee if not combined with pre-erythrocytic or blood stage vaccine
- Evaluation of efficacy against community level transmission challenging
  - Cluster randomized trials, large sample sizes required to demonstrate efficacy in low transmission settings
  - Lack of clear regulatory pathways for surrogate endpoints (feeding assays)

Transmission blocking vaccines: *opportunities and challenges*

Gaps/challenges (continued)

- Target age range likely to be larger (including adolescents and adults)
- Delivery strategies beyond childhood immunization platform needed

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Immune correlates of protection

- **No validated correlate of protection for malaria**
- Progress on **systems immunology** and potential correlates, but **validation with clinical outcomes required**
- **Measuring multi-marker responses** may be needed **- antibody function important** (not just antibody level/titres alone)
    - Avidity
    - Subclasses – IgG1 and IgG3 may play role in cytotoxic response
    - Cellular responses – cytokines (Th1 vs. Th2), CD4+ T cell responses
    - Complement fixation
    - Fc gamma receptors (engage NK cells)
- **WHO Dept of Immunization, Vaccines and Biologicals (IVB) and Global Malaria Programme (GMP) planning meeting of experts in 2024 to advise on state of the science, and steps needed to advance towards validated measures of correlates**

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mRNA vaccines

- **BNT165n1 (BioNTech)** - first malaria mRNA vaccine candidate to enter human testing
  - Targets *P. falciparum* CSP antigen (same as RTS,S and R21)
  - Phase 1 (safety, tolerability, immunogenicity) began December 2022[1]
    - 60 adults (18-55 years), US volunteers (malaria naïve)
    - 3 dose schedule, dose escalation study
    - Target primary endpoint completion March 2024, target study completion Sept 2024
- mRNA platform also being explored for other antigens (pre-clinical)
  - Pfs25, PfRh5, PfGARP, CelTOS
- Potential platform for vaccines targeting multiple parasite stages

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1 https://clinicaltrials.gov/study/NCT05581641

Monoclonal antibodies – potential use cases

- **Replacement or complement to seasonal malaria chemoprevention**
- **Replacement or complement to childhood vaccination**
  - 6-8 months duration of protection in seasonal settings
  - 8-12 months duration of protection in perennial settings*
  - Prior to RTS,S / R21 eligibility at 5 months
- **Post-discharge malaria chemoprevention (PDMC)**
  - Following admission to hospital with severe anaemia
  - Studies with anti-malarials (AL, SP, DP) have shown 77% reduction all cause mortality, 58% reduction in all-cause hospital re-admission
- **In adults (pregnancy)** - case report suggests anti-malarial mAbs may be safe in pregnancy*

*requires additional product modifications to extend half-life or increase potency

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Monoclonal antibodies to prevent malaria in infants/children

- **<u>L9LS (US NIH)</u>** - improvement on CIS43LS mAb candidate, with 3-fold higher potency
  - **Mali - Phase 2 in children aged 6-10 years (area with SMC in children <5 years), 2022[1]**
    - 77.4% efficacy against clinical malaria at 6 months after 1 dose
    - Expected study completion March 2024
  - **Kenya - Phase 2 in children aged 5 months to 10 years (no SMC, perennial transmission)[2]**
    - Single dose mAb vs placebo, subgroup receives 2nd dose 6 months after 1st dose
    - Results expected in Q1 2024 - efficacy at 6 months and Q3 2024 – efficacy at 12 months of 1 vs. 2 doses
  - To date, no safety concerns, well-tolerated (up to 2 mL SC administration in children)
- **<u>MAM01 (Gates MRI)</u>**
  - First in human testing began 2023, in US malaria naïve adults
  - First results expected 2024

1 https://clinicaltrials.gov/study/NCT05304611
2 https://clinicaltrials.gov/study/NCT05400655
3 https://clinicaltrials.gov/study/NCT05891236

SMC: seasonal malaria chemoprevention

Topics for WHO Technical Consultation or TAG

Immune correlates of protection

- Is there consensus on the set of markers most predictive of protection against clinical malaria?
- What steps are needed to develop standardized measurement of markers across labs?
  - What role can WHO play to facilitate their development?
- What is required for validation of markers/assays for use in regulatory approval?

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Topics for WHO Technical Consultation or Advisory Group

Clinical development pathways for pre-erythrocytic + blood stage vaccines

- What will be the different clinical development requirements for combined vs. co-administered vaccines?
- What needs to be demonstrated for each component to progress to late-stage clinical testing?

Clinical development pathways for pre-erythrocytic + transmission blocking vaccines

- What steps are needed to validate surrogate endpoints/assays for use in regulatory approval?
- From regulatory perspective, what outcomes can be demonstrated in phase 4 (post licensure) vs. phase 3 (for licensure)

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Thank you.

Credit: WHO/F.Combrink

December 12–14, 2023

Multi-target malaria vaccines

Presentation to WHO Product Development for Vaccines Advisory Committee (PDVAC)

Ashley J. Birkett, PhD
Global Head, Malaria Vaccines and Biologics
Center for Vaccine Innovation & Access (CVIA)

PATH

WHO Preferred Product Characteristics (PPC) for malaria vaccines

Source: Malaria vaccines: preferred product characteristics and clinical development considerations https://apps.who.int/iris/rest/bitstreams/1466146/retrieve

- **Strategic goal 1:** Malaria vaccines that prevent human blood-stage infection at the individual level
- **Strategic goal 2:** Malaria vaccines that reduce morbidity and mortality in individuals at risk in malaria-endemic areas
- **Strategic goal 3:** Malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human infection in the community

Multistage approaches have potential application for of all 3 strategic goals; however, the goals are associated with different use-cases and CDPs

1. Sequential opportunity (Goal 2)
2. Transformational opportunities (Goals 1 & 3)

Overview of presentation

- Review of key challenges and opportunities in developing vaccines associated with strategic goals 1, 2, and 3
- Strategic goal 2: Morbidity and mortality reduction
    - Biological basis for leading multi-antigen approaches
    - Important advancements in controlled human malaria infection models (sporozoite and blood-stage)
    - Leading multi-antigen approaches undergoing clinical testing
    - Leading whole parasite approaches

Strategic goals 1 and 3: Some key challenges

Strategic goal 1: Infection	Strategic goal 3: Transmission
For community effects, including parasite elimination, high levels of coverage and efficacy are likely to be needed.	
Many vaccinees likely to be infected at time of vaccination (drug clearance?).	
Leading approaches likely to require at least 3 immunizing doses and durable immunity not yet demonstrated.	

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TBV regulatory strategy: US FDA Type C Meeting (2014)

<u>**CBER Response:**</u> *We agree that **SSM-VIMT could meet the qualifying criteria for licensure under the Accelerated Approval (AA) regulations.** However, the information provided in your submission is not sufficient for us to determine whether the potential surrogate endpoints you have proposed are reasonably likely to predict clinical benefit. Please submit data to your IND to justify use of a specific surrogate endpoint or combination of endpoints that are reasonably predictive of prevention of P. falciparum infection at a community level. It may be necessary to discuss your proposed endpoint (or combination of endpoints) at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting prior to the conduct of pivotal trial(s).*

- CBER proposed the idea of a **small sponsor-agency technical working group to discuss the surrogate endpoint**, although the final recommendation would still need to go to the VRBPAC. Note: The Agency used this approach for the meningitis B conjugate vaccine licensure.
- CBER did not comment on the suggested potential to collaborate with CDER relative to the common challenge facing anti-gametocidal drug development.

TBV regulatory strategy: US FDA Type C Meeting (2014)

CBER Response: *We anticipate that* ***studies in pediatric subjects may be initiated following demonstration of an acceptable safety profile in adults****. Depending on the results of early phase trial(s) in adults, we may recommend an age de-escalation approach to mitigate risk in the youngest age groups.*

ELSEVIER

Vaccine
Volume 32, Issue 43, 29 September 2014, Pages 5531-5539

Perspective

Development of a transmission-blocking malaria vaccine: Progress, challenges, and the path forward

Julia K. Nunes [a 1], Colleen Woods [a b], Terrell Carter [a 2], Theresa Raphael [a], Merribeth J. Morin [a], Diadier Diallo [c], Didier Leboulleux [d], Sanjay Jain [a 3], Christian Loucq [a 4], David C. Kaslow [a e], Ashley J. Birkett [a]

ELSEVIER

Vaccine
Volume 33, Issue 13, 24 March 2015, Pages 1518-1526

Review

Design of a Phase III cluster randomized trial to assess the efficacy and safety of a malaria transmission blocking vaccine

Isabelle Delrieu [a], Didier Leboulleux [b], Karen Ivinson [c], Bradford D. Gessner [a]
For the Malaria Transmission Blocking Vaccine Technical Consultation Group

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Strategic goal 2: Opportunities and challenges

- **Leading multi-antigen approaches**
  - First-generation vaccine (RTS,S or R21) + blood-stage component
  - Accelerated development using transformational mRNA delivery platform
- **Opportunities**
  - Potential for additivity and/or synergy across pre-erythrocytic and blood stages
  - Modest incremental increase in cost of goods (COGs) for first-generation vaccines
  - Directly leverage first-generation vaccine development and introduction
- **Challenges**
  - Potential for immune interference
  - Potential for immune evasion (Especially at blood stages - massive replication)
  - Potential for asymptomatic carriage at blood stages

Biological activities targeted for strategic goal 2 vaccines

Clinical disease

Infectious mosquito bite

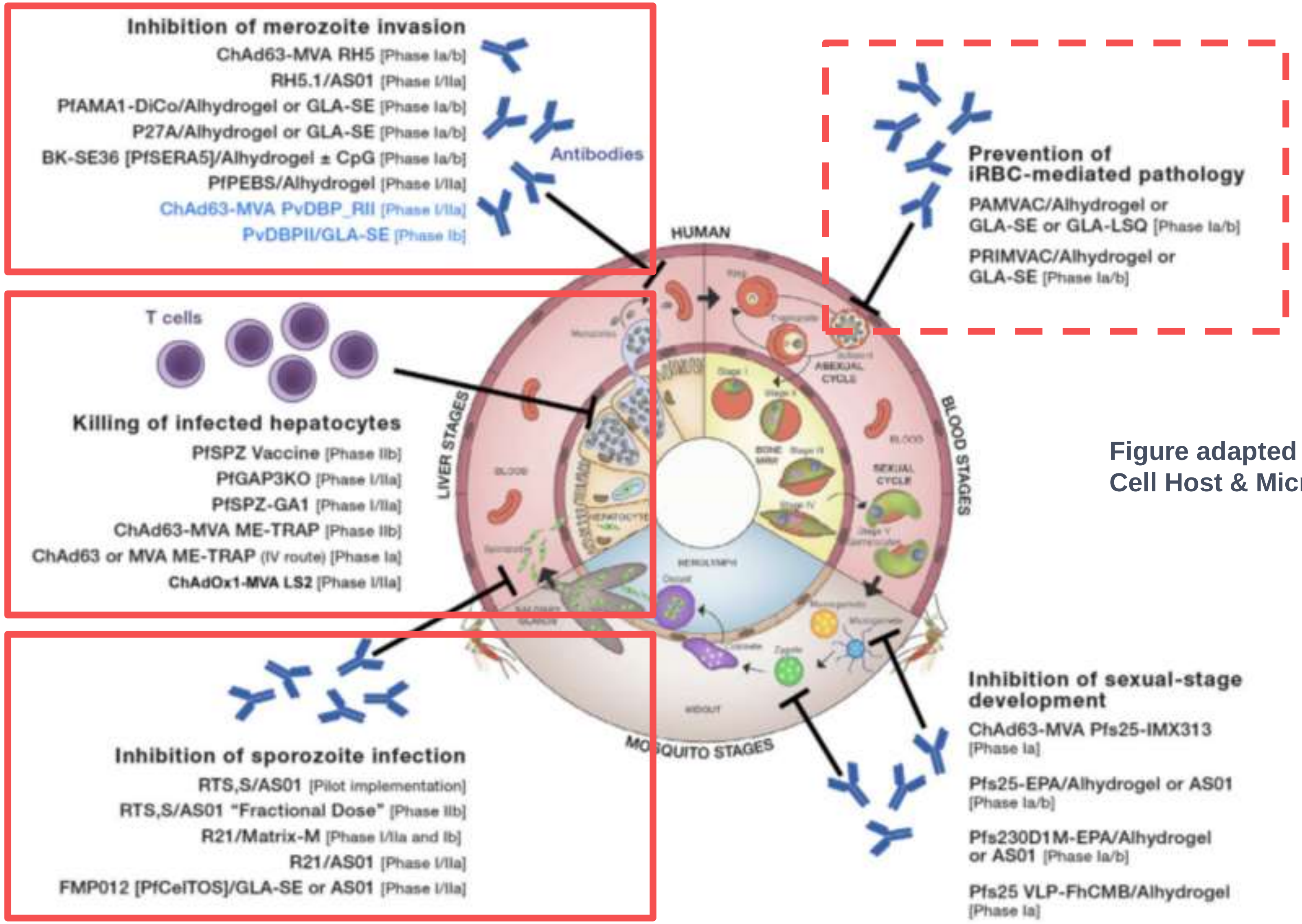

Figure adapted from: Draper et al, Cell Host & Microbe 24, July 11, 2018

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Recent advances in application of sporozoite controlled human malaria infection (CHMI) model

- *P. falciparum* sporozoite CHMI has proven a powerful tool for evaluating pre-erythrocytic vaccines and monoclonal antibodies.
- CHMI data have been generally predictive of outcomes in the target population.
- Two important limitations have been:
  - Concerns with biological relevance of IV-delivered purified cryopreserved sporozoites in testing efficacy of antibody-based vaccines in Africa.
  - The need to progress blood-stage vaccines to African children to inform initial proof-of-concept for blood-stage vaccine candidates.

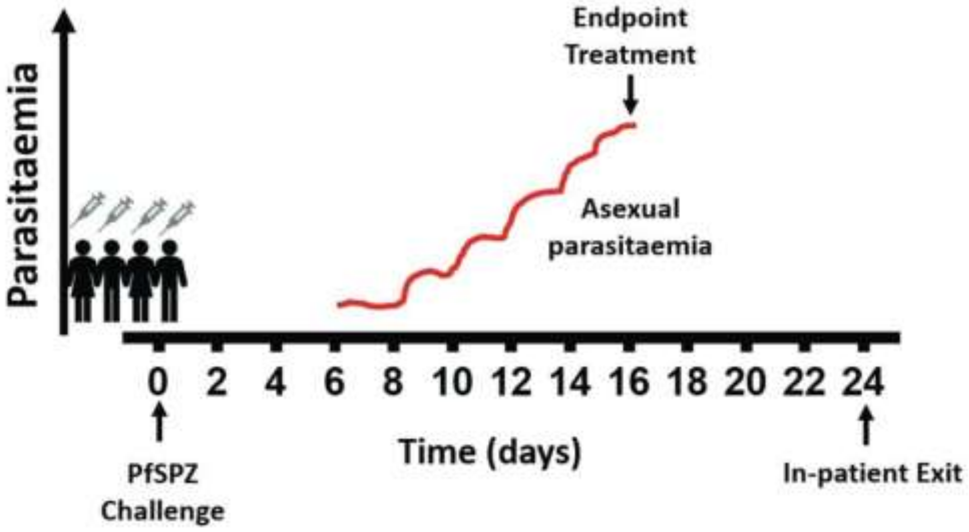
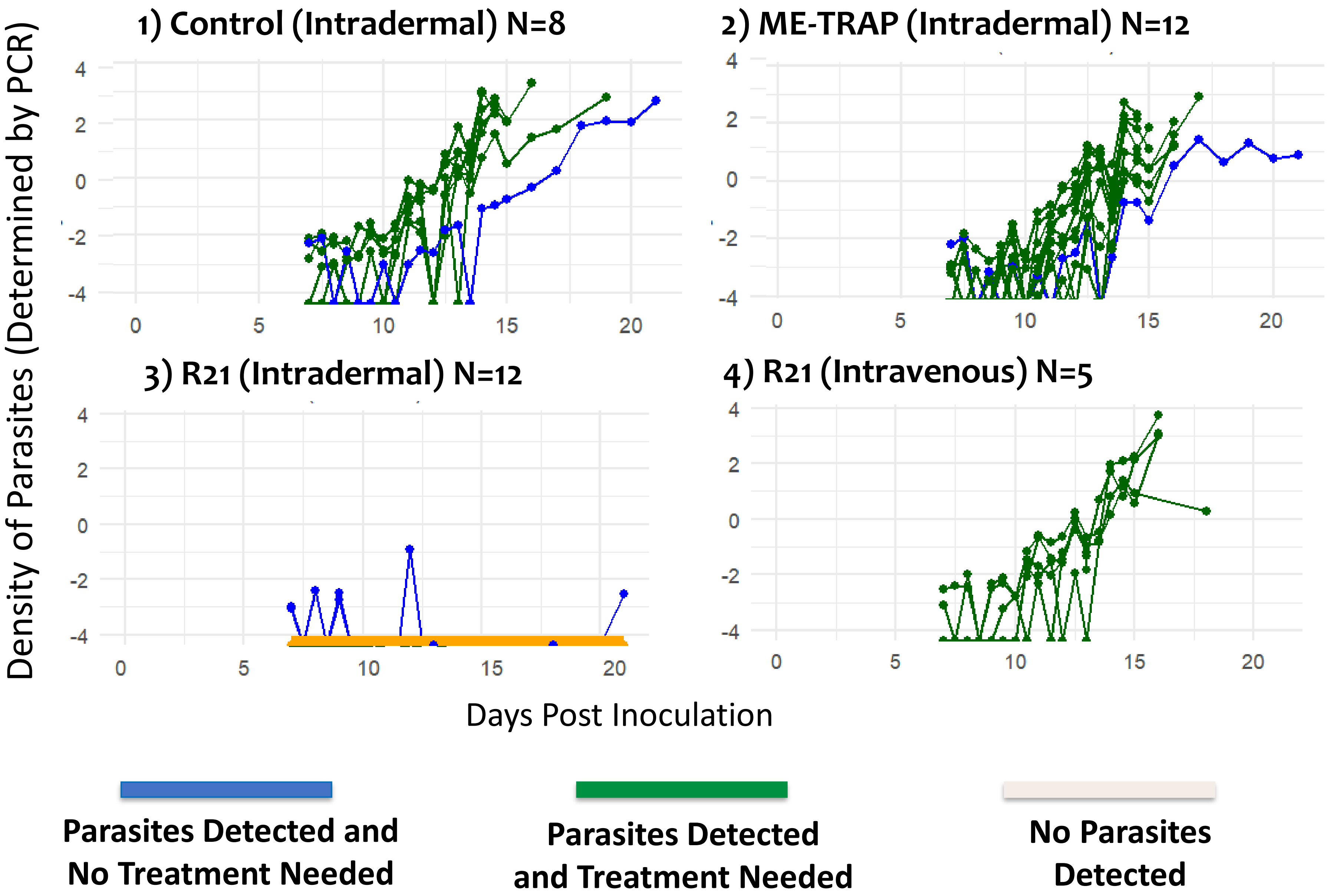


Figure: Kapulu at al., Wellcome Open Res. 2018; 3: 155.

Effective application of IV sporozoite CHMI in African volunteers



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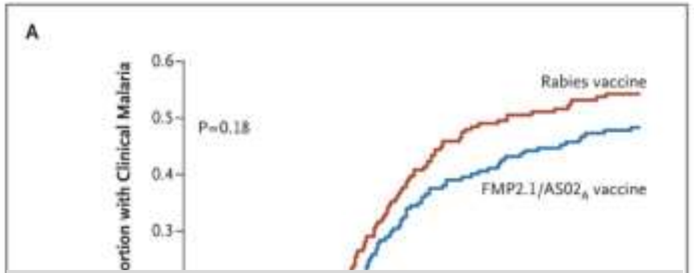
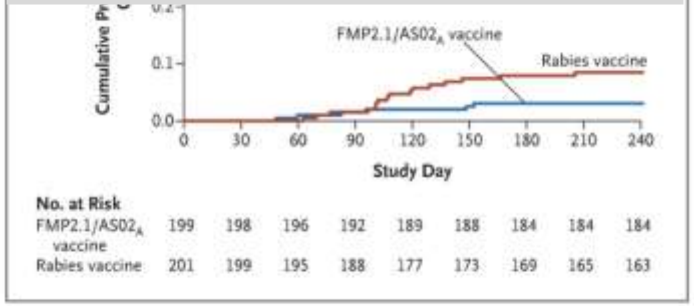
Proof of biological concept using blood-stage CHMI

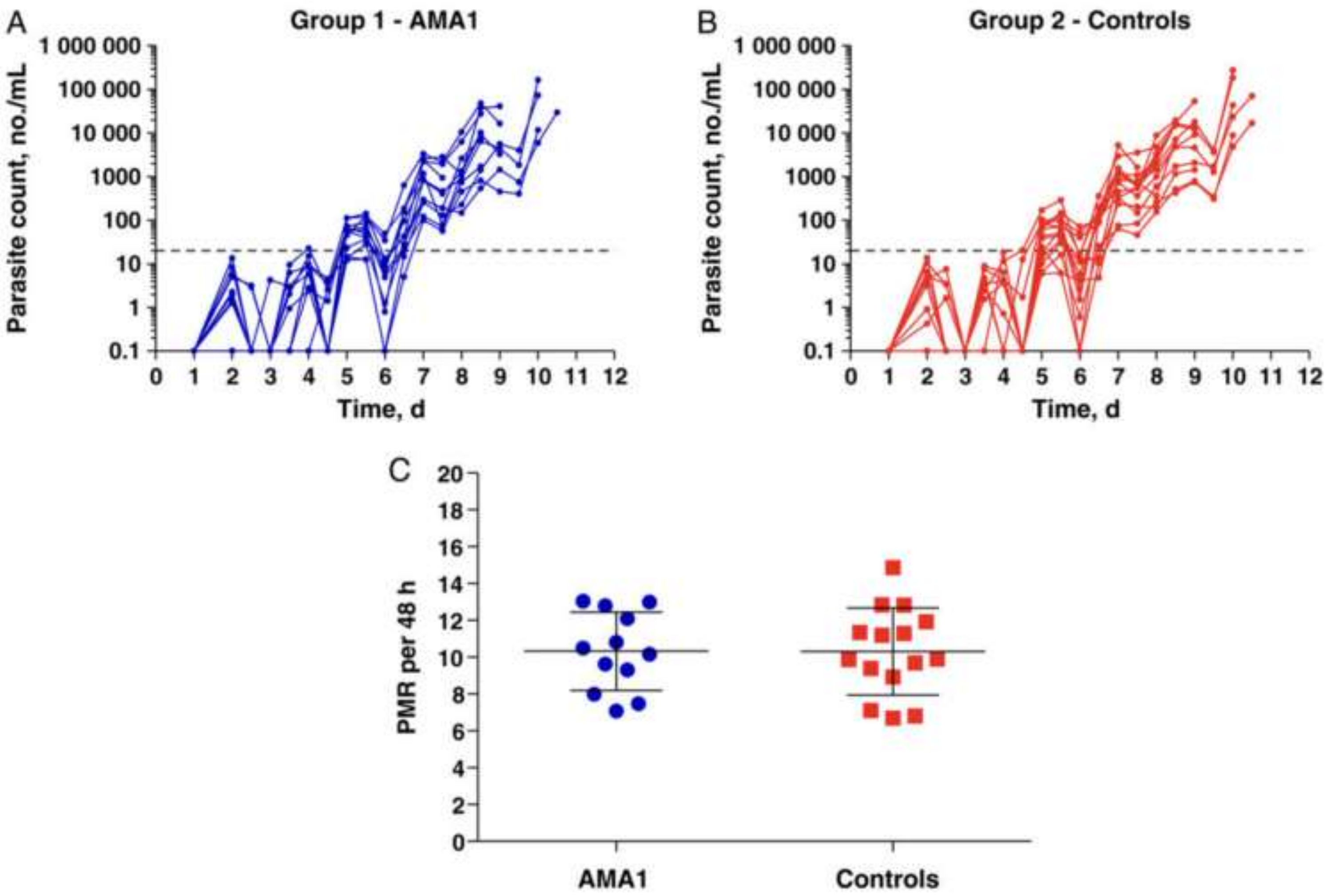


We conclude that vaccination with this AMA1-based malaria vaccine increased inhibition of parasite growth, but this increase was not associated with allele-specific efficacy in the first malaria season.

Laurens et al., PLoS ONE 12(3): e0173294.

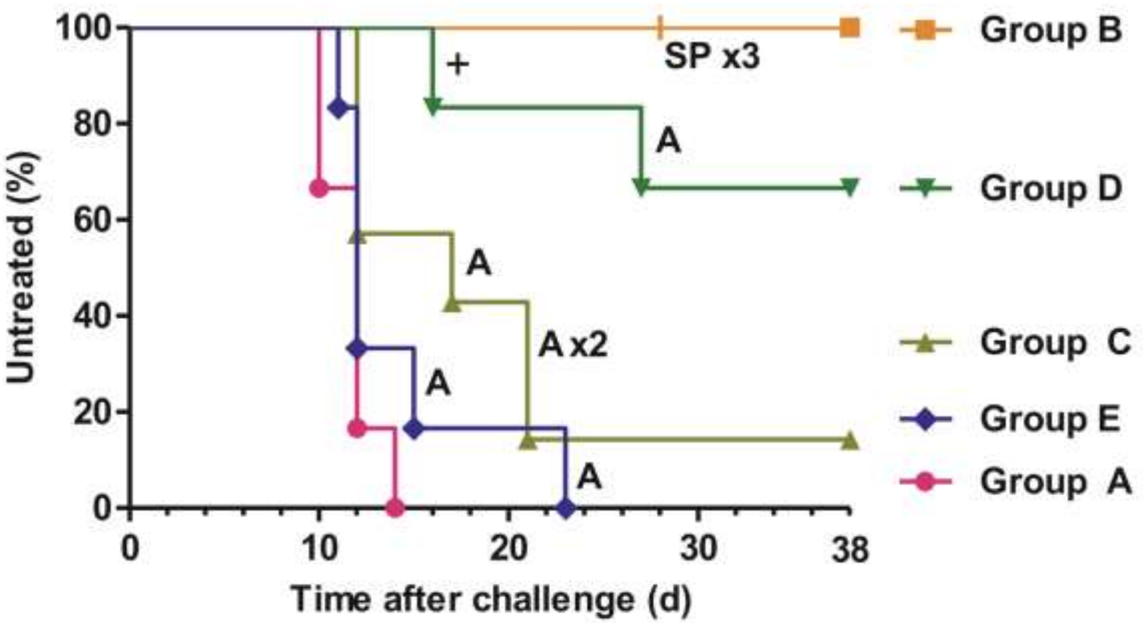


Thera et al., N Engl J Med 2011; 365:1004-1013

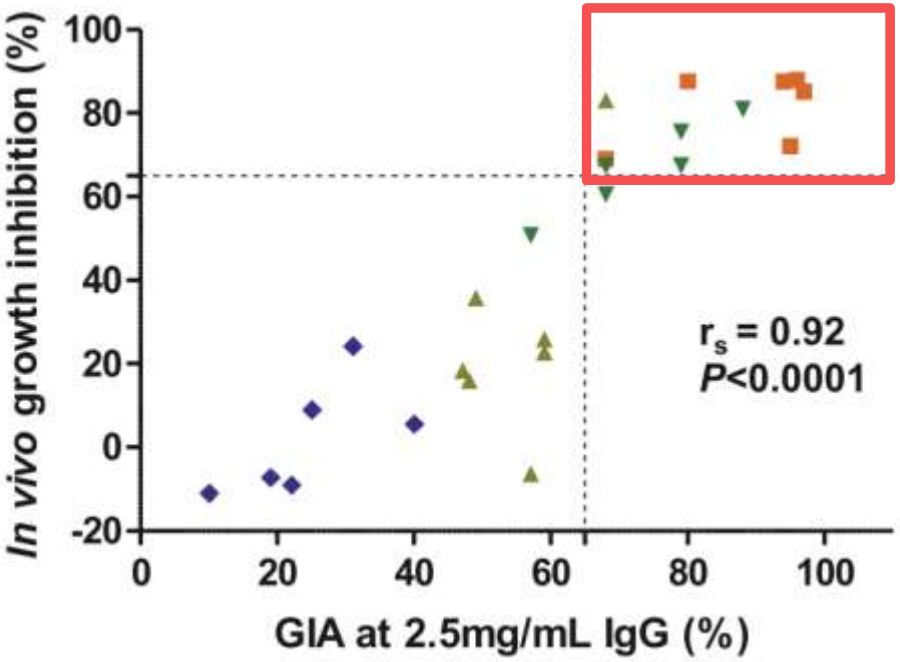


Payne et al., The Journal of Infectious Diseases 2016;213:1743–51

Rh5-mediated protection in Aotus monkeys is associated with in vitro parasite neutralizing activity as determined using GIA



Animals not requiring treatment



Group	Day 0	Day 26	Day 54	*n* =
A	ChAd63-RLuc	–	PBS – Abisco-100	6
B	PfRH5 – CFA	PfRH5 – IFA	PfRH5 – IFA	6
C	ChAd63-PfRH5	–	PfRH5 – Abisco-100	7
D	ChAd63-PfRH5	–	MVA-PfRH5	6
E	ChAd63-PfAMA1	–	PfAMA1 – Abisco-100	6

Douglas et al., Cell Host & Microbe 17, 130–139, January 14, 2015

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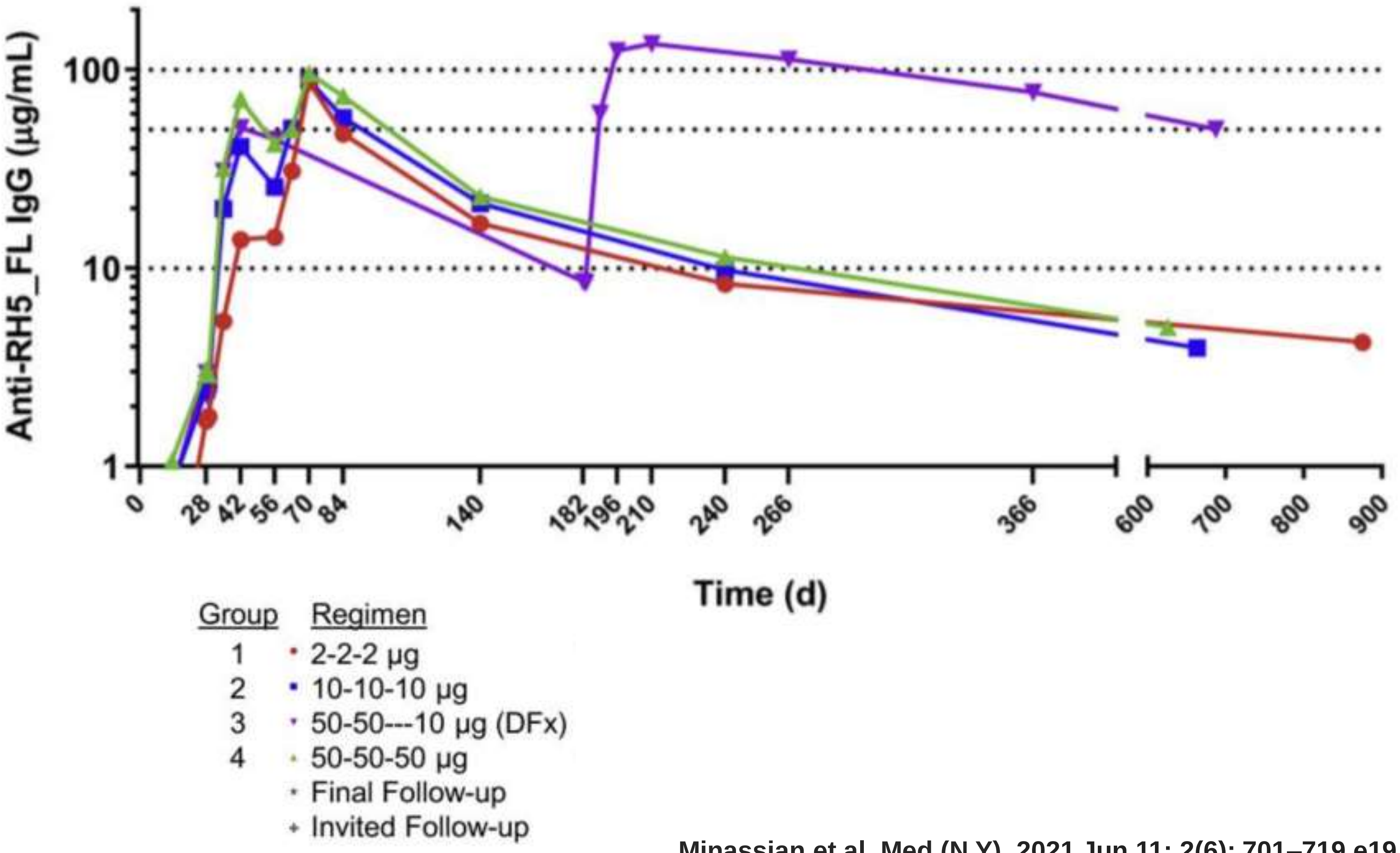
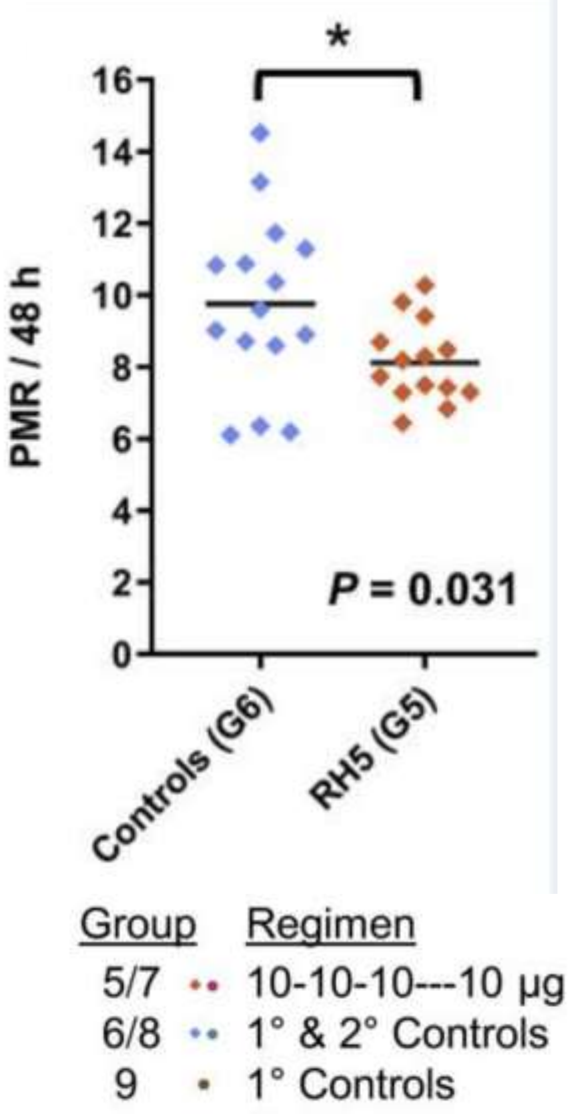
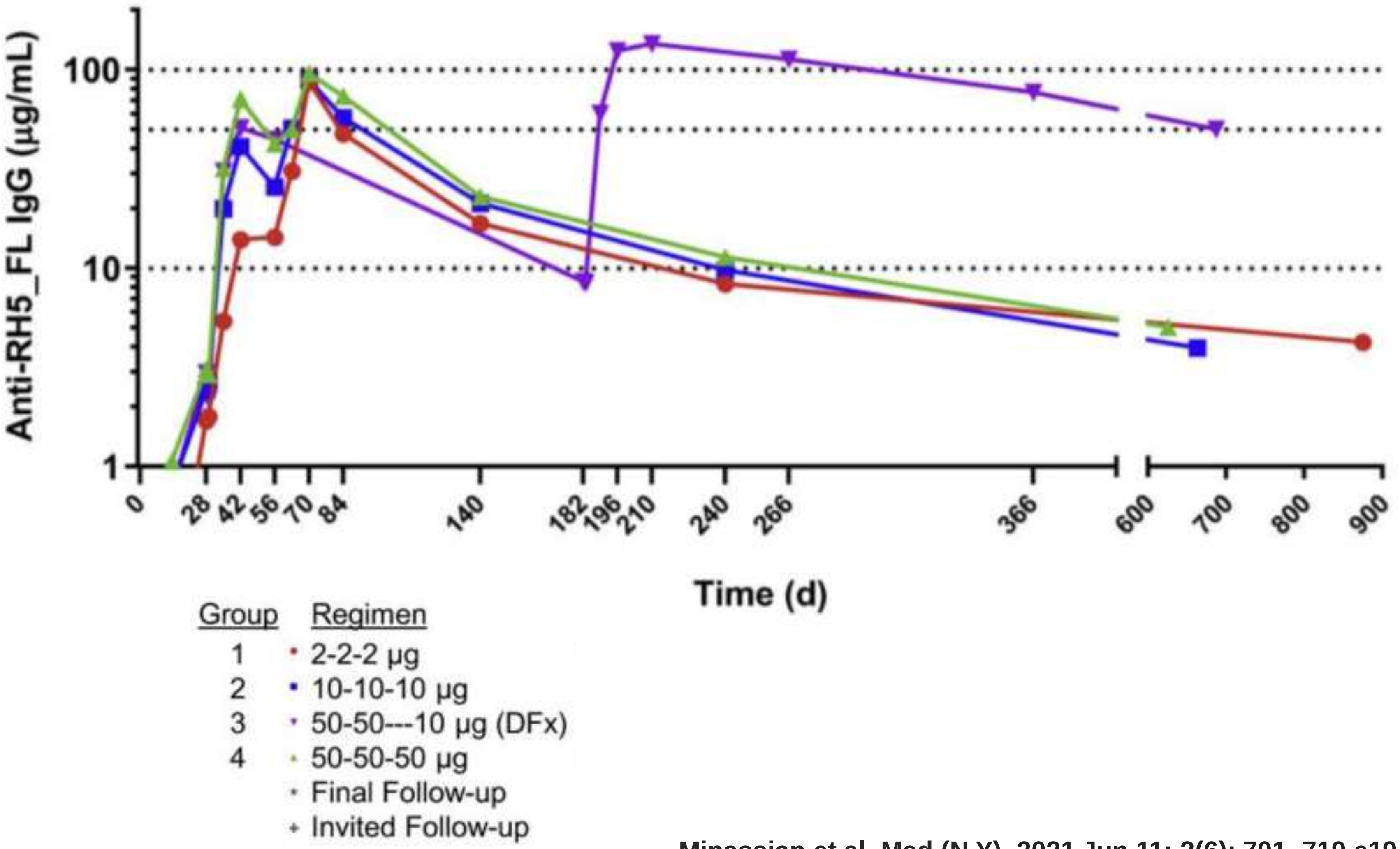
RH5/AS01B: First demonstration of biological activity in humans

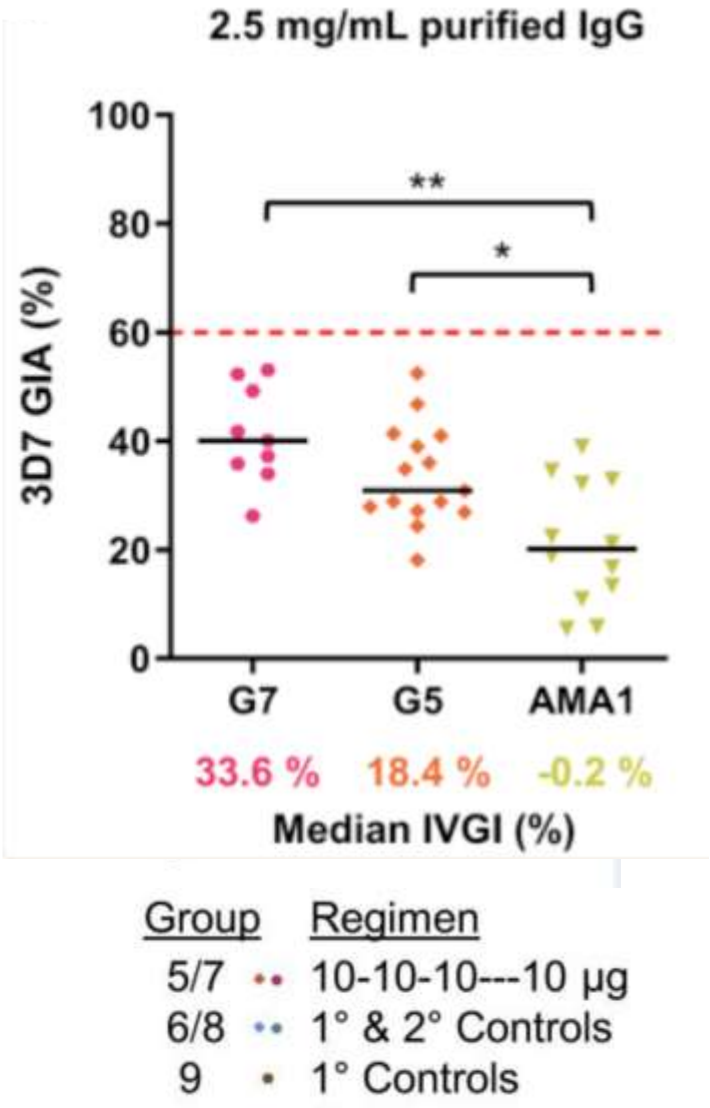




Minassian et al.,Med (N Y). 2021 Jun 11; 2(6): 701–719.e19.

RH5/AS01B: First demonstration of biological activity in humans





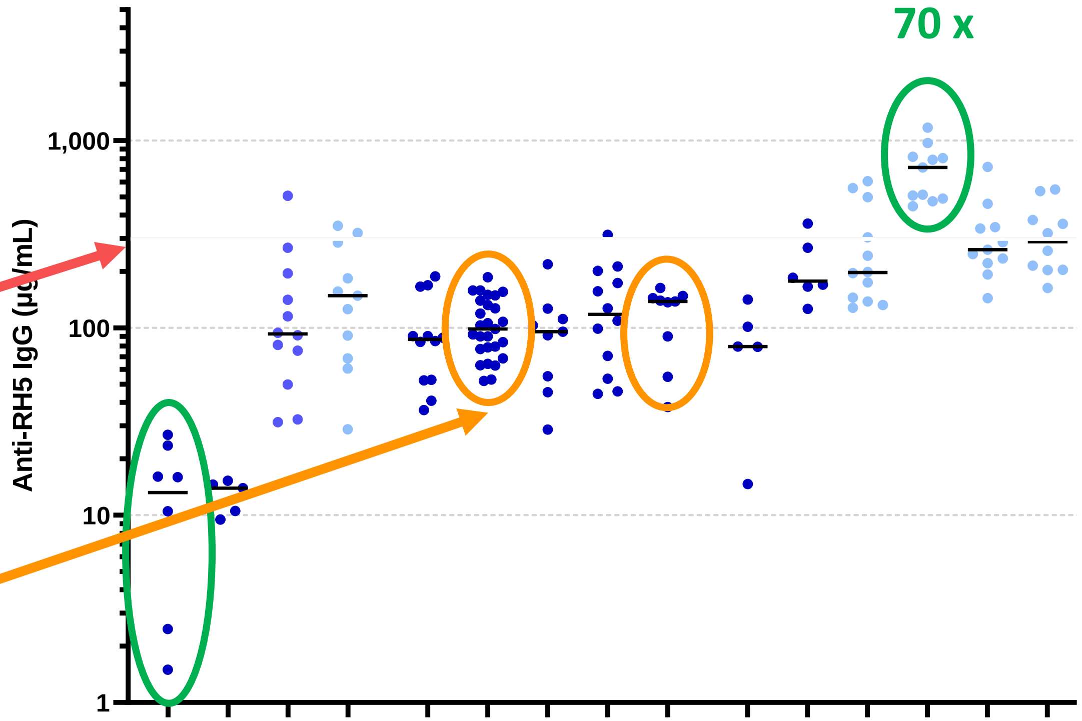
Minassian et al.,Med (N Y). 2021 Jun 11; 2(6): 701–719.e19.

Anti-RH5 serum IgG in clinical trials

Antibody quantity is significantly affected by:

1. Vaccine delivery platform
2. Population
3. Protein dose and regimen

Target threshold defined in *Aotus* monkey – *P. falciparum* challenge study



VAC063
Rh5.1/AS01$_B$
Reduced *Pf* growth by 20–33% in UK adult *Pf* CHMI

Minassian *et al.* (2021) Med.

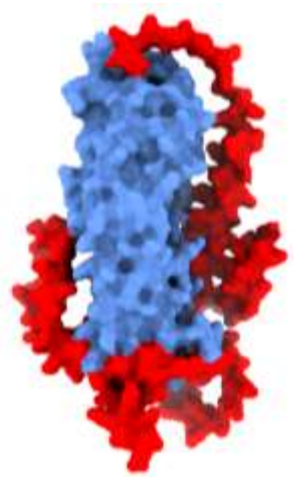
VAC057
Viral-Vectored Rh5
UK Adults

Payne *et al.* (2017) JCI Insight

- VAC080: Rh5.1/Matrix-M
- 5–17 mo old Tanzanian infants
- "Delayed" boost regimen

(NCT04318002)

RH5 (60 kDa)



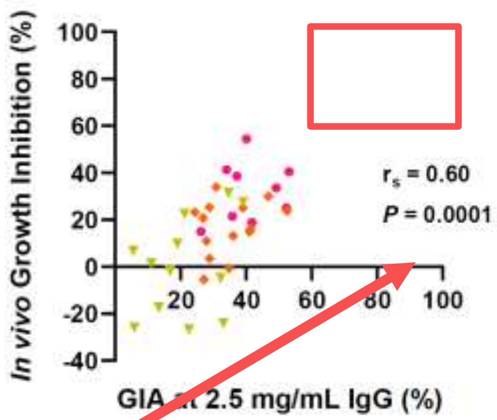
α-helical diamond

disordered N-terminus and internal loop

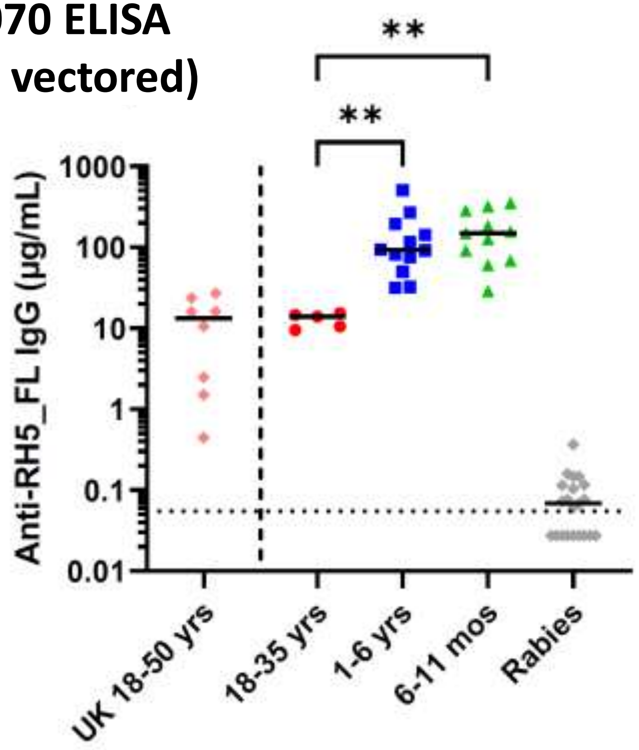
Anti-RH5 serum IgG in clinical trials

Antibody Quantity is Significantly Affected by:

2. Population: Young children > Adults
3. Protein dose and regimen: Delayed boost; lower dose

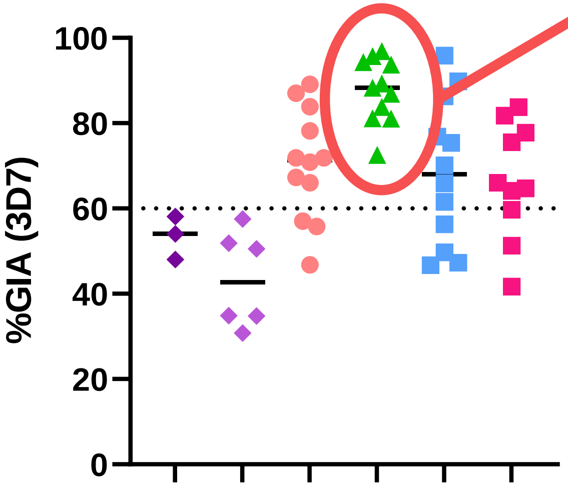


VAC070 ELISA (viral vectored)



Silk et al., (2023) Med.

VAC080 GIA

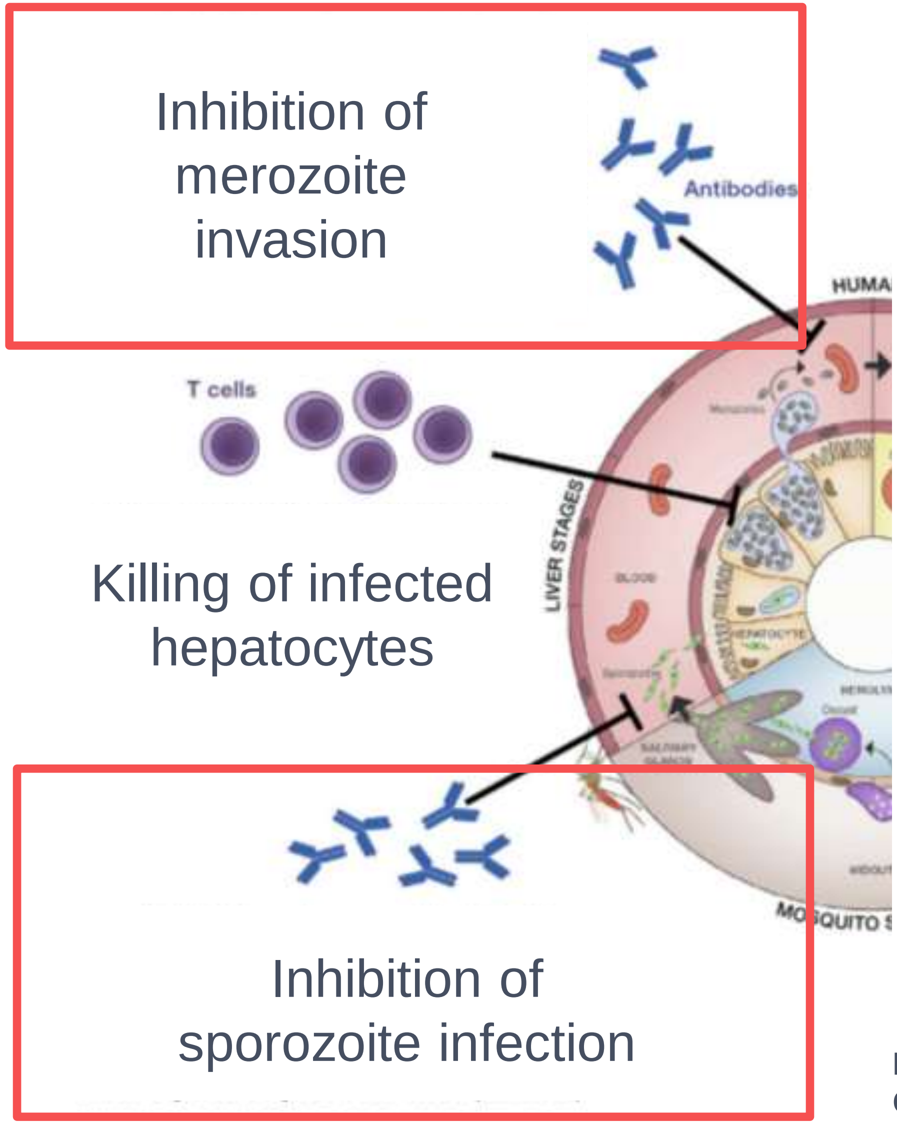


- Rh5.1/Matrix-M
- 5–17 mo old Tanzanian infants
- 0-1-6 month regimen
- 10 µg dose Rh5.1

(NCT04318002)

PATH

Protein-based multi-antigen vaccine (R21 + RH5)

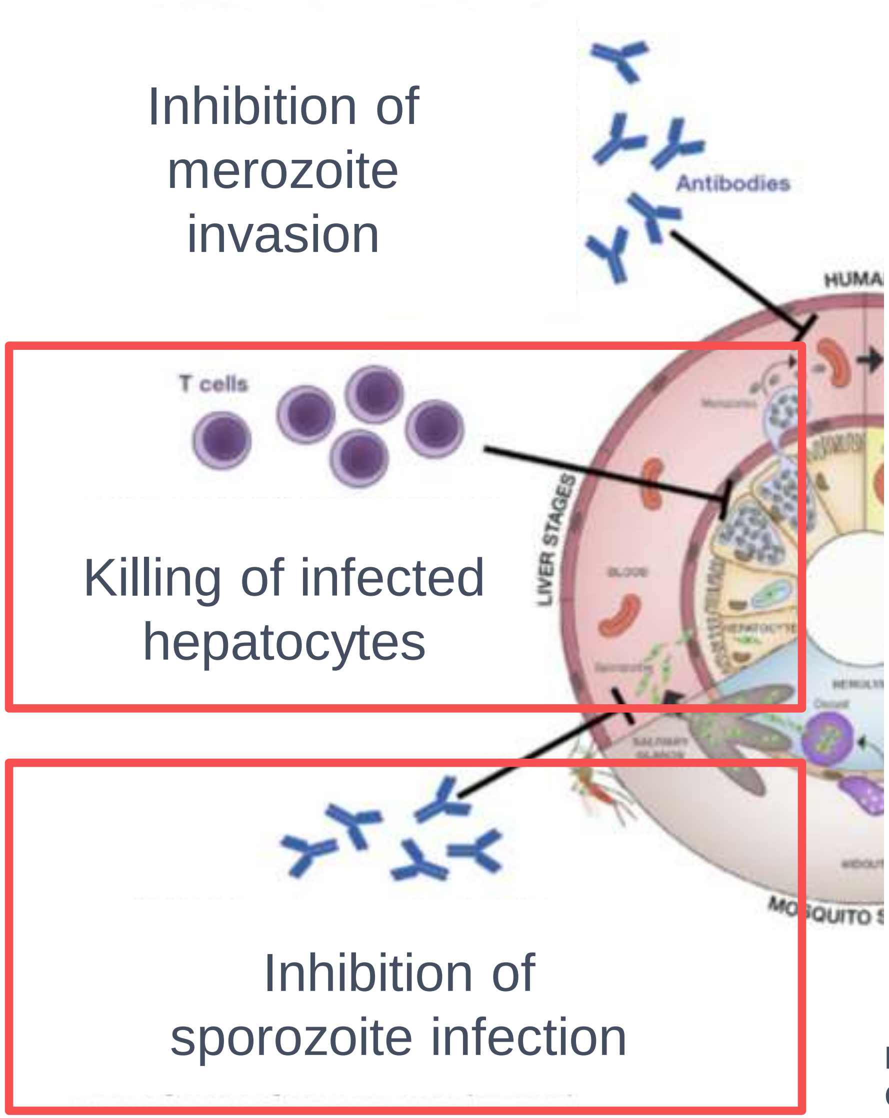


A Study to Assess the Experimental Malaria Vaccines RH5.2-VLP and R21 (Recruiting)

- **ClinicalTrials.gov ID:** NCT05357560
- **Sponsor:** University of Oxford
    - Phase Ib multi-stage *Plasmodium falciparum* malaria vaccine study to assess the safety and immunogenicity of the blood-stage vaccine candidate RH5.2 virus-like particle (VLP) in Matrix-MTM and the pre-erythrocytic stage vaccine candidate R21 in Matrix-M, both alone and in combination, in adults and infants in the Gambia Source: Clinicaltrials.gov (accessed, Dec 4, 2023)

Figure adapted from: Draper et al,
Cell Host & Microbe 24, July 11, 2018

mRNA based multi-antigen vaccine candidate



A Clinical Trial to Evaluate the Safety, Efficacy and Immune Responses After Vaccination With an Investigational RNA-based Vaccine Against Malaria (Recruiting)

- **ClinicalTrials.gov ID:** NCT06069544
- **Sponsor:** BioNTech SE
  - Randomized, dose-escalation Phase I/IIa trial to evaluate safety, tolerability, immunogenicity and efficacy of an investigational RNA-based vaccine (BNT165e) for prevention of *P. falciparum* malaria in healthy malaria-naive adults (US).
    (Note: BNT165e is a combination of three distinct RNAs, BNT165c and BNT165d (composed of BNT165d1 and BNT165d2), encoding *P. falciparum* antigens)

Source: Clinicaltrials.gov (accessed Dec 4, 2023)

Figure adapted from: Draper et al, Cell Host & Microbe 24, July 11, 2018

PATH

Report of an Expert Consultation on the Clinical Development Plan for a Multistage Malaria Vaccine Targeting the Circumsporozoite (CS) and Blood Stage (BS) Antigens

May 3–4, 2023

PATH

Strategic goal 2

Malaria vaccines that reduce morbidity and mortality in individuals at risk in malaria-endemic countries

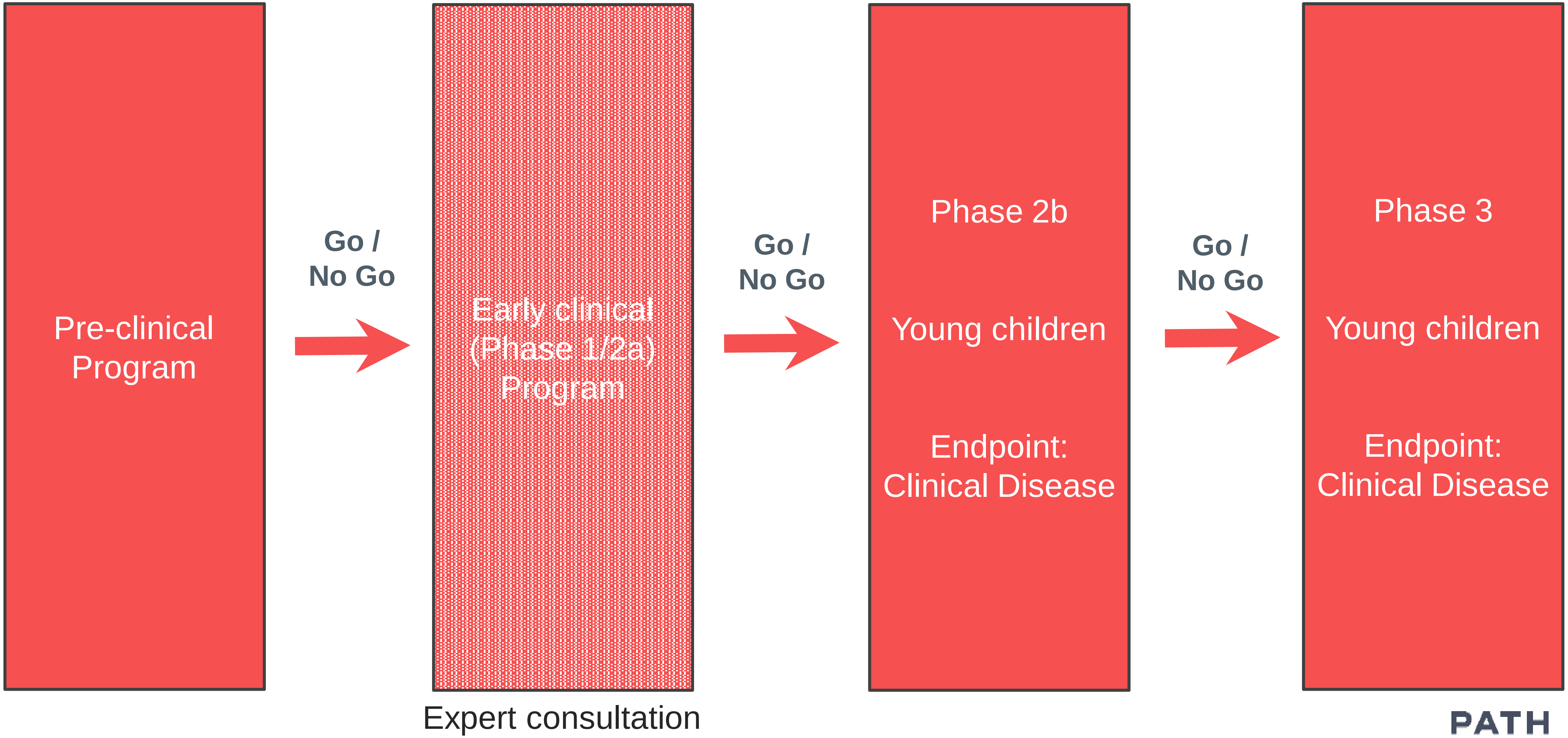
Pre-clinical Program ← Early clinical (Phase 1/2a) Program ← Phase 2b ← Phase 3

Pre-clinical Program	Early clinical (Phase 1/2a) Program	Phase 2b	Phase 3
		Young children	Young children
		Endpoint: Clinical Disease	Endpoint: Clinical Disease

PATH

Strategic goal 2

Malaria vaccines that reduce morbidity and mortality in individuals at risk in malaria-endemic countries



PATH

Questions for PDVAC

- Does the committee have input, and/or additional recommendations, on the findings detailed in the ‘Report of an Expert Consultation on the Clinical Development Plan for a Multistage Malaria Vaccine Targeting the Circumsporozoite (CS) and Blood Stage (BS) Antigens’?
    - See ‘Key recommendations to inform a clinical development plan for a CS+BS combination *P. falciparum* vaccine’ (p.11-14).

PATH

Thank you!

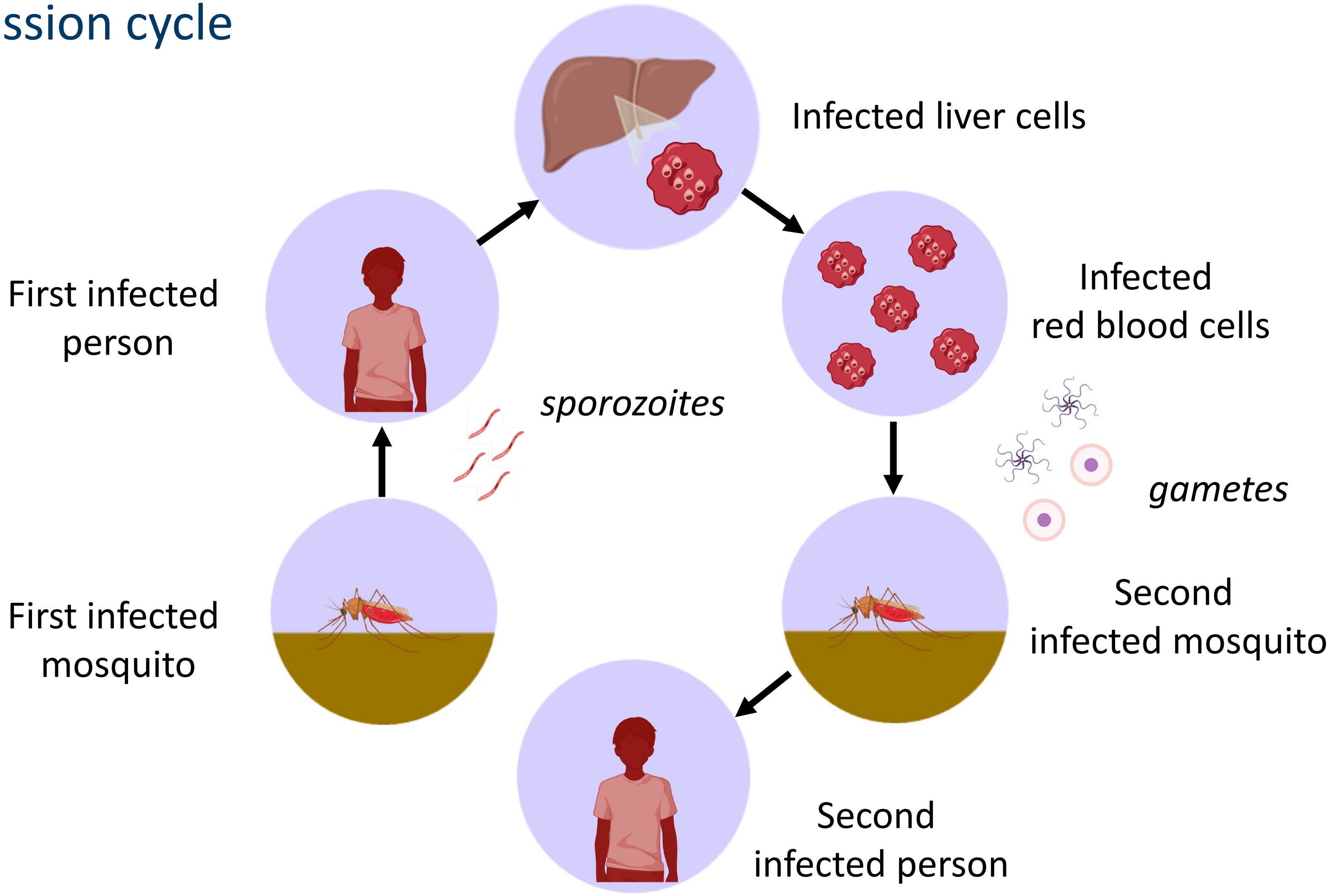
A multi-stage vaccine for malaria control and elimination:
Combining anti-infection vaccine R21
with transmission-blocking vaccine Pfs230D1

WHO Product Development for Vaccines Advisory Committee (PDVAC)
December 13, 2023

Patrick E. Duffy, M.D.
Chief and Senior Investigator
LMIV/NIAID/NIH

A Vaccine for *P. falciparum* Control and Elimination

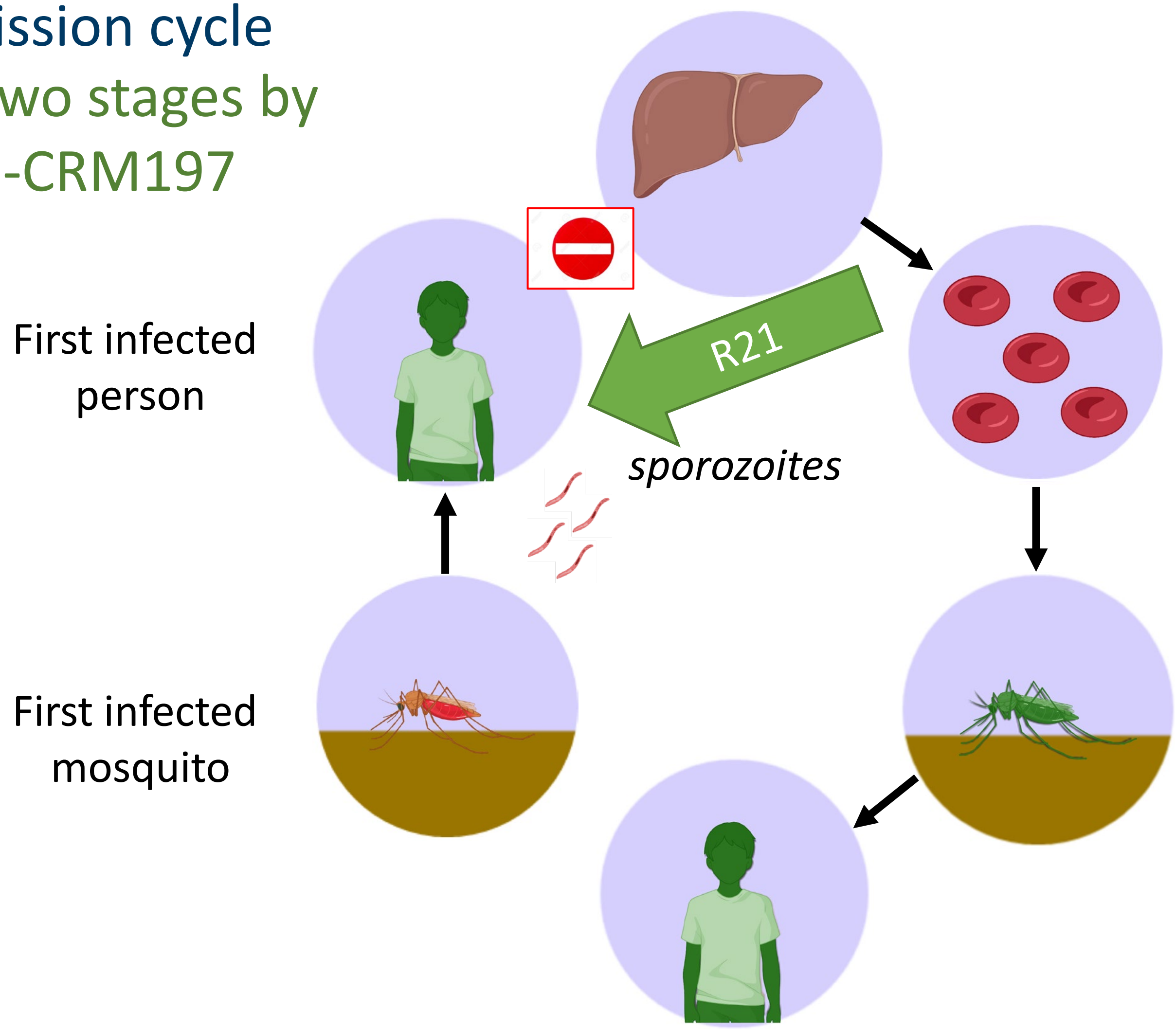
Malaria transmission cycle



National Institute of Allergy and Infectious Diseases
SERUM INSTITUTE OF INDIA
Cyrus Poonawalla Group

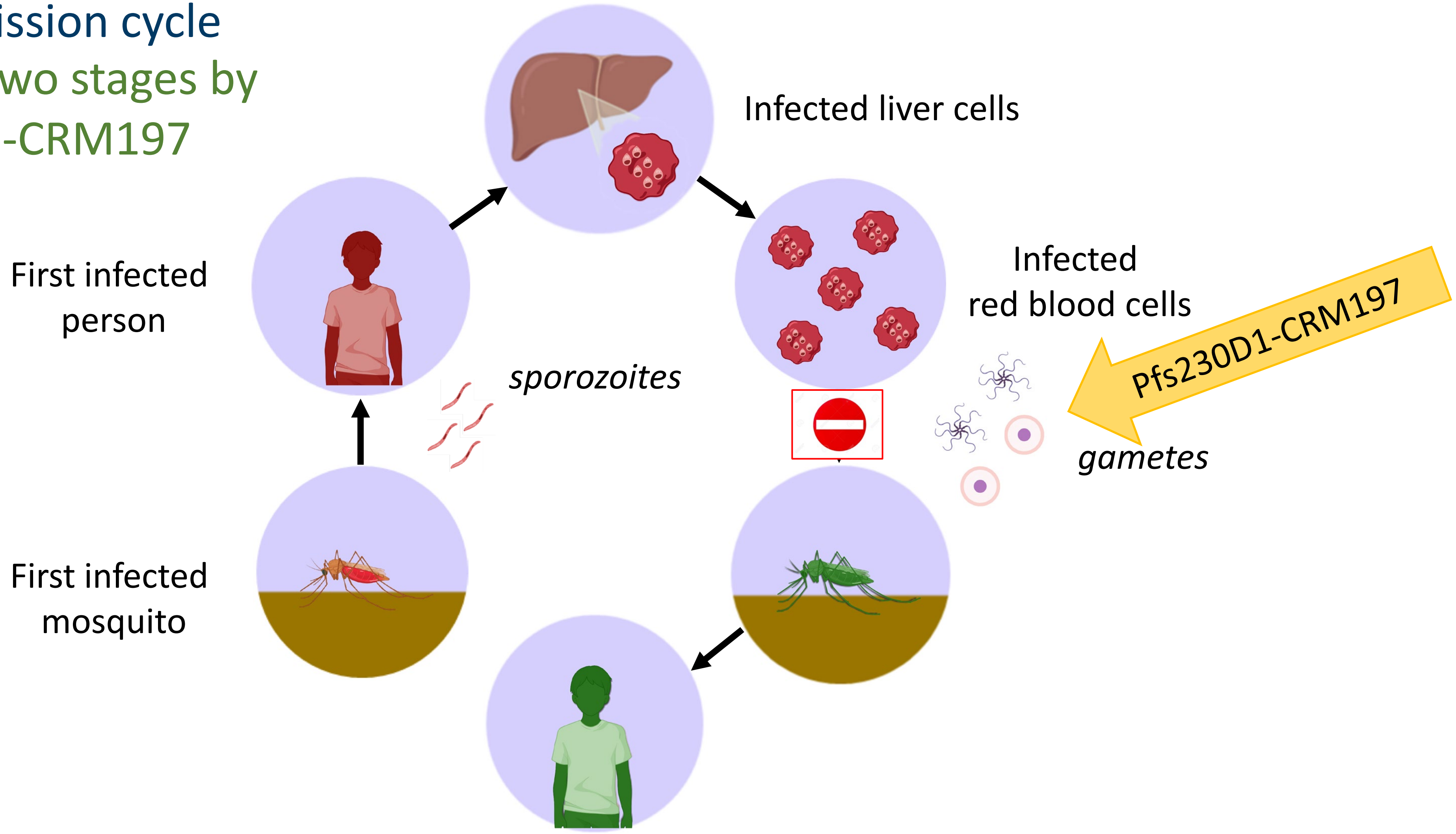
A Vaccine for *P. falciparum* Control and Elimination

Malaria transmission cycle interrupted at two stages by R21 + Pfs230D1-CRM197



A Vaccine for *P. falciparum* Control and Elimination

Malaria transmission cycle
interrupted at two stages by
R21 + Pfs230D1-CRM197



A Vaccine for *P. falciparum* Control and Elimination

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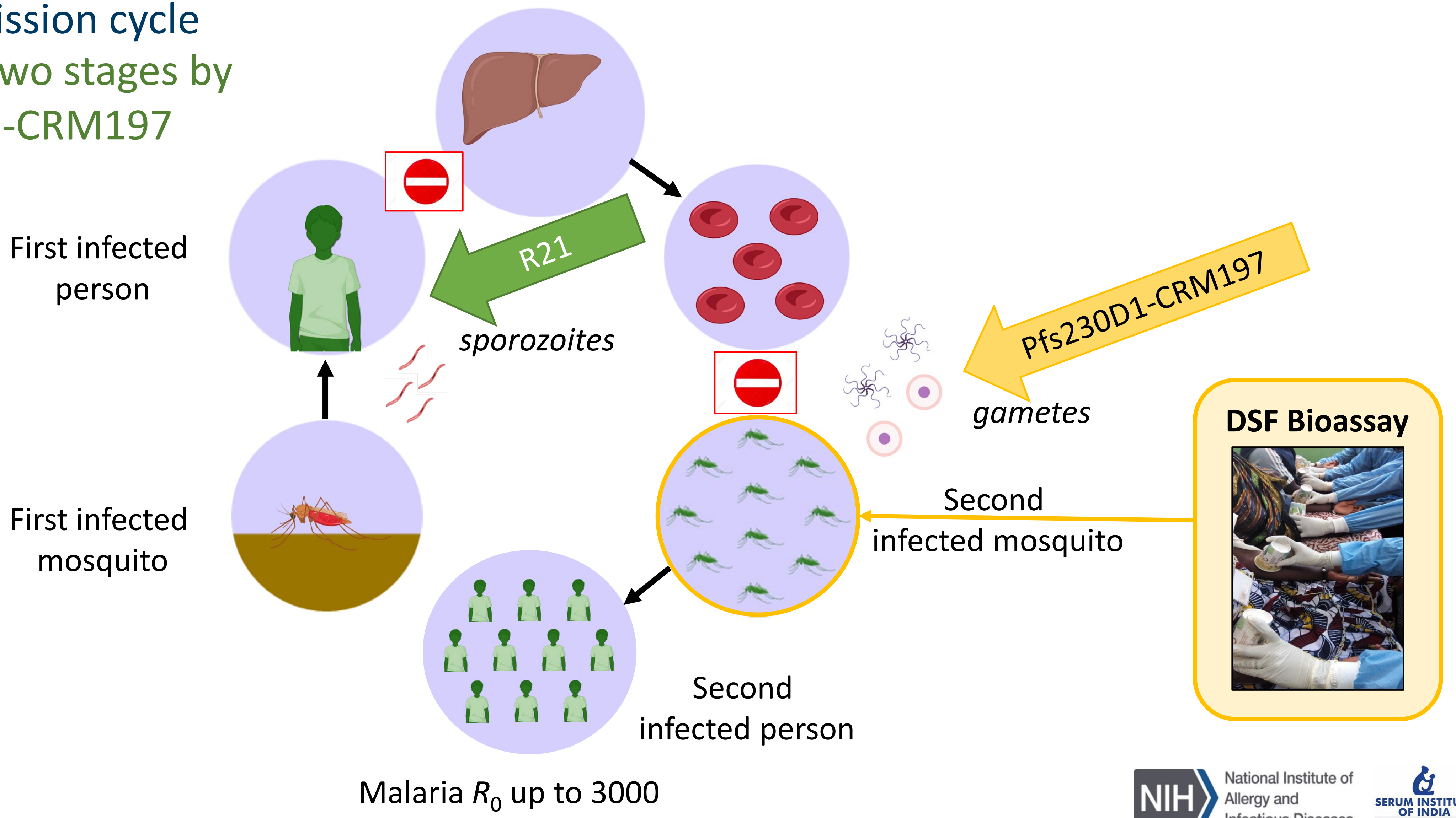

National Institute of Allergy and Infectious Diseases
SERUM INSTITUTE OF INDIA
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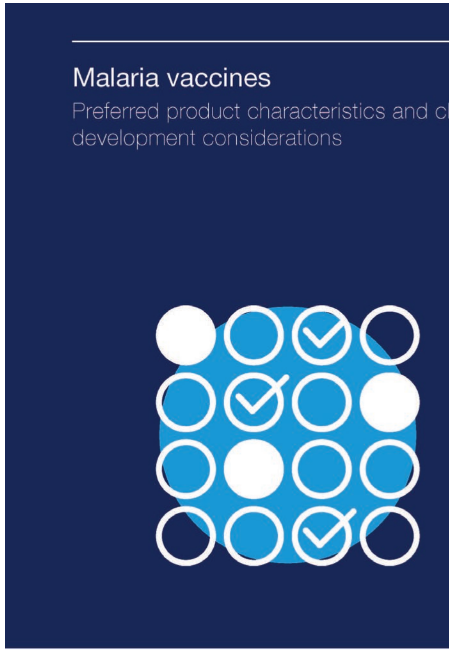

World Health Organization

Pre-erythrocytic vaccines (PEVs)

SSM-VIMTs

Blood-stage vaccines (BSVs)

END-POINTS

Malaria infection → **Uncomplicated malaria** → **Severe malaria** → **Malaria-related hospitalizations, mortality**

Human-to-mosquito transmission

Phase 1–2a
infection prevention, disease reduction

- End-points: infection incidence +/– prevalence, parasite density
- N < 100

- Exposure: CHMI
- Methods: microscopy, molecular assays

Phase 2b
infection prevention

- Primary end-point: infection incidence +/- clinical malaria
- Secondary end-points: clinical malaria, severe malaria
- N = 100s – 1000s

- Natural exposure
- Methods: microscopy, RDTs, molecular assays
- Strategy: ACD +/- PCD

Phase 2b
disease reduction

- Primary end-point: clinical malaria (first/only episode)
- Secondary end-points: infection, severe malaria
- N = 100s – 1000s

- Natural exposure
- Methods: microscopy, RDTs, molecular assays
- Strategy: ACD +/- PCD

Phase 3
infection prevention

- Primary end-points: infection incidence[a], clinical malaria (all episodes)
- Secondary end-points: severe malaria, hospitalizations, mortality
- N = 100s to 10 000s

- Natural exposure
- Methods: microscopy, RDTs, molecular assays
- Strategy: ACD +/- PCD, all infections / clinical episodes

Phase 3
disease reduction

- Primary end-point: clinical malaria (all episodes)
- Secondary end-points: infection +/- severe malaria, hospitalizations, mortality
- N = 1000s to 10 000s

- Natural exposure
- Methods: microscopy, RDTs, molecular assays
- Strategy: PCD, all clinical episodes

Phase 4
infection prevention, disease reduction

- End-points: incidence of clinical malaria, infection
- Severe disease end-points: severe malaria, malaria-related hospitalizations and mortality, all-cause mortality
- Total population size > 10 000s

- Natural exposure
- Methods: microscopy, RDTs, molecular assays
- Strategy: PCD

Phase 4
post-licensure community transmission studies[b]

- End-point: incidence of infection +/- clinical malaria
- Severe disease end-points: severe malaria, malaria-related hospitalizations and mortality, all-cause mortality
- Total population size > 10 000s

- Natural exposure
- Methods: microscopy, RDTs, molecular assays
- Strategy: PCD

Phase 1a
transmission reduction

- End-points: mosquito infection, parasite density (oocyst count)
- N < 100

- Methods: SMFA (cultured gametocytes), DMFA, DSFA (whole blood from natural infection or CHMI), ELISA, microscopy

Phase 1b-2
transmission reduction

- Mosquito feeding studies, bridging feeding data to field
- End-points: mosquito infection, parasite density (oocyst count)

- Methods: SMFA (cultured gametocyt
DSFA (whole blood from natural infe
CHMI), ELISA, microscopy

Accelerated approval
transmission reduction

- Requires validated surrogate end-point of transmission reduction in humans, approved by regulatory authority
- Conditional on establishing effectiveness in post-approval studies

*Safety is evaluated at all stages.

SSM-VIMTs → Vaccines to reduce malaria transmission

Blood-stage vaccines (BSVs)

Phase 1
transmission reduction

- End-points: mosquito infection, parasite density (oocyst count)
- N < 100

- Methods: SMFA (cultured gametocytes), DMFA, DSFA (whole blood from natural infection or CHMI), ELISA, microscopy

Phase 2
transmission reduction

- Mosquito feeding studies, bridging feeding data to field
- End-points: mosquito infection, parasite density (oocyst count)

- Methods: SMFA (cultured gametocytes), DMFA, DSFA (whole blood from natural infection or CHMI), ELISA, microscopy

Phase 3 Accelerated approval
transmission reduction

- Requires validated surrogate end-point of transmission reduction in humans, approved by regulatory authority
- Conditional on establishing effectiveness in post-approval studies

DSF Bioassay

- Natural exposure
- Methods: microscopy, RDTs, molecular assays
- Strategy: ACD +/- PCD

- N = 1000s to 10 000s
- Natural exposure
- Methods: microscopy, RDTs, molecular assays
- Strategy: PCD, all clinical episodes

Phase 1a
transmission reduction

- End-points: mosquito infection, parasite density (oocyst count)
- N < 100
- Methods: SMFA (cultured gametocytes), DMFA, DSFA (whole blood from natural infection or CHMI), ELISA, microscopy

Phase 1b-2
transmission reduction

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- End-points: mosquito infection, parasite density (oocyst count)

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World Health Organization

*Safety is evaluated at all stages.

SSM-VIMTs → Vaccines to reduce malaria transmission

Phase 1 transmission reduction	Phase 2 transmission reduction	Phase 3 Accelerated approval transmission reduction
N=240	N=1000	N=4000
ELISA titers	DSF Bioassay; ELISA titers; Microscopy	Surrogate end-point of transmission reduction in humans, approval conditional on establishing effectiveness in Phase 4 studies

Endpoints for trials of Pfs230D1-CRM197 + R21 in Matrix-M1

DSF Bioassay

- DSF recapitulates natural transmission
- DSF correlates with membrane feeding assay
- High between-cup correlation

*Safety is evaluated at all stages.

d approval

ction

ansmission reduction in

nsmission reduction

conditional on

in Phase 4 studies

DSF Bioassay

Reasonably likely surrogate end-point of transmission reduction:
Infected mosquitoes measured by DSF

*Safety is evaluated at all stages.

World Health Organization

Direct Skin Feeding (DSF) Bioassay

DSF assay to measure parasite transmission to mosquitoes

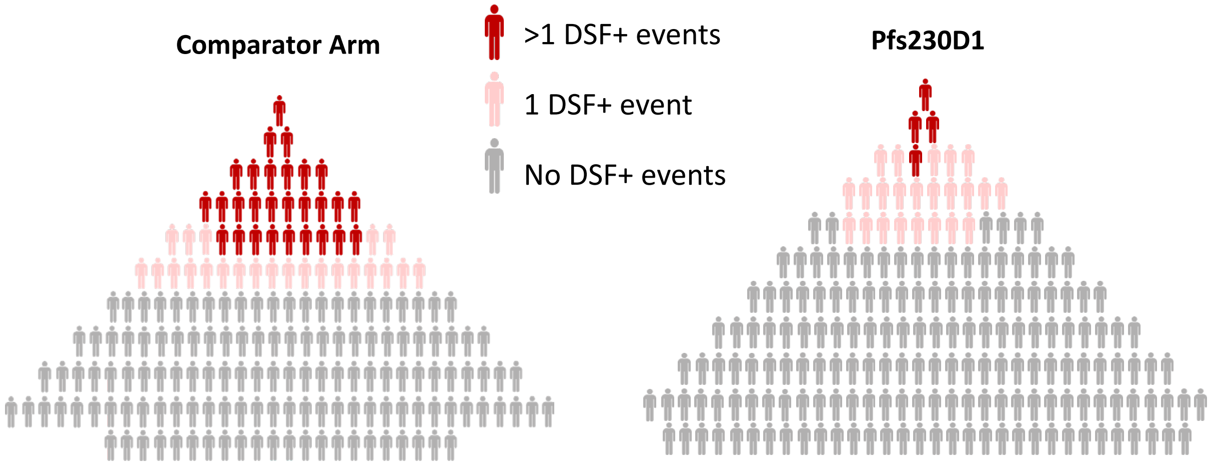
Mosquitos feed on participants **in vivo** in field studies

Stained mosquito gut 1 week later to count parasites

Pfs230D1 is efficacious against DSF surrogate endpoints:

Phase 2 trial in school-aged children

Proportion of Transmitters



Direct Skin Feeding (DSF) Bioassay

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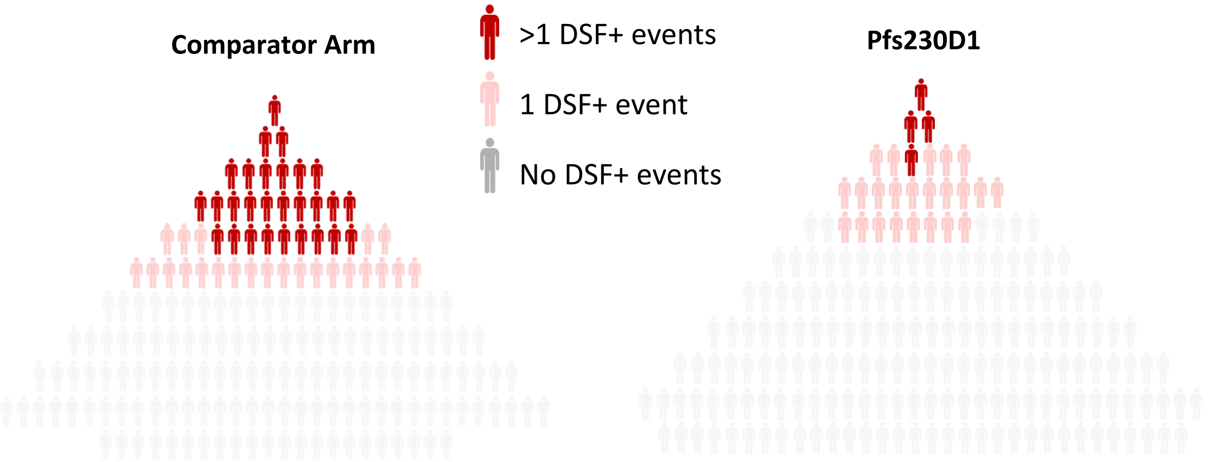
Pfs230D1 is efficacious against DSF surrogate endpoints:

- Reduces proportion of transmitters (i.e., fewer DSF+ subjects)

	Comparator	Pfs230D1	Transmission Reduction
DSF+ subjects	51/185 (27.6%)	27/195 (13.8%)	**50.0%**

Phase 2 trial in school-aged children

Proportion of Transmitters



Direct Skin Feeding (DSF) Bioassay

DSF assay to measure parasite transmission to mosquitoes

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Pfs230D1 is efficacious against DSF surrogate endpoints:

- Reduces proportion of transmitters (i.e., fewer DSF+ subjects)
- Reduces proportion of DSF+ (fewer repeatedly DSF+ subjects)

	Comparator	Pfs230D1	Transmission Reduction
DSF+ subjects	51/185 (27.6%)	27/195 (13.8%)	**50.0%**
DSF+ assays	121/2906 (4.2%)	33/3038 (1.1%)	**73.8%**

Phase 2 trial in school-aged children

Proportion of Transmitters

Direct Skin Feeding (DSF) Bioassay

DSF assay to measure parasite transmission to mosquitoes

Mosquitos feed on participants **in vivo** in field studies

Stained mosquito gut 1 week later to count parasites

Pfs230D1 is efficacious against DSF surrogate endpoints:

- Reduces proportion of transmitters (i.e., fewer DSF+ subjects)
- Reduces proportion of DSF+ (fewer repeatedly DSF+ subjects)
- Reduces proportion of infected mosquitoes

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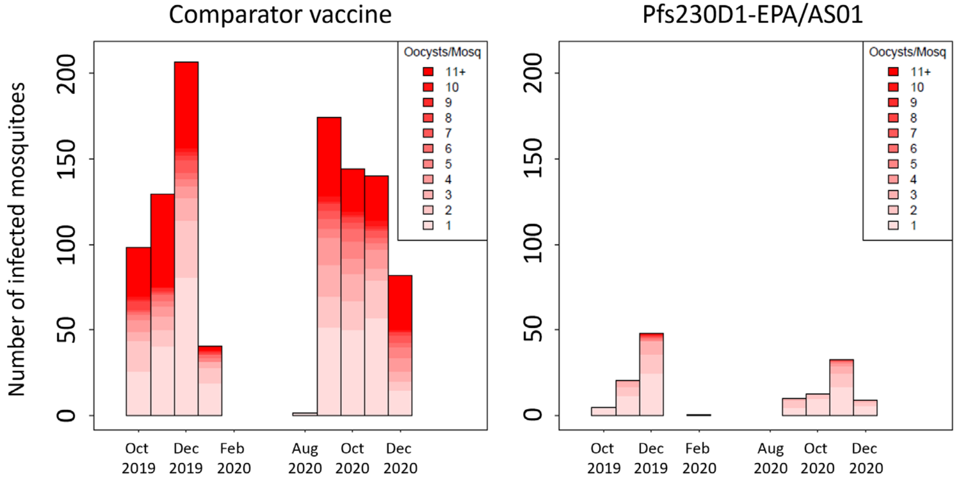
DSF+ subjects	51/185 (27.6%)	27/195 (13.8%)	**50.0%**
DSF+ assays	121/2906 (4.2%)	33/3038 (1.1%)	**73.8%**
Infected mosquitoes	1016/114888 (0.88%)	140/120981 (0.12%)	**86.4%**

Phase 2 trial in school-aged children

Infected Mosquito Count and Oocyst Parasite Burden

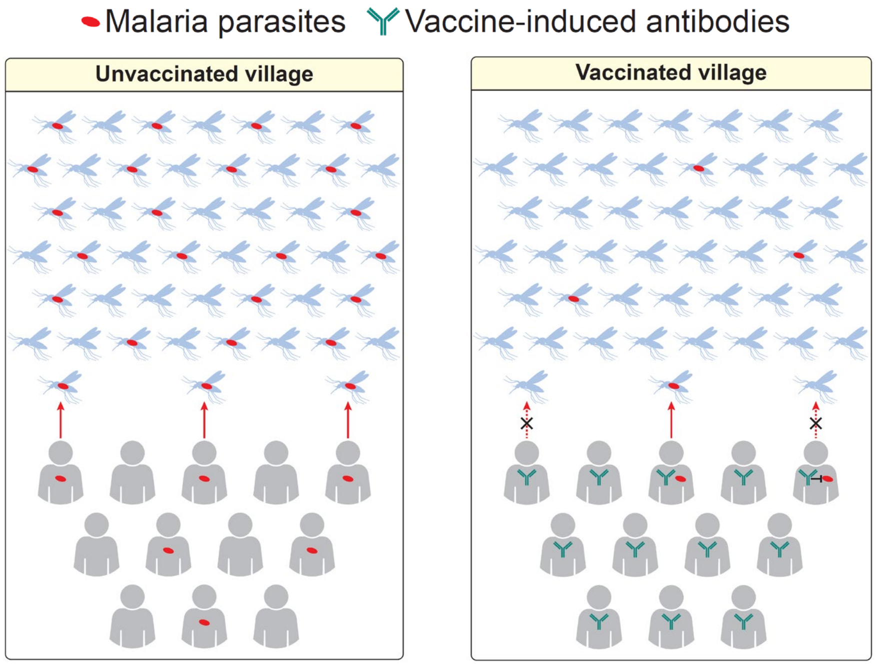


Direct Skin Feeding (DSF) Bioassay

DSF assay to measure parasite transmission to mosquitoes

Mosquitos feed on participants **in vivo** in field studies

Stained mosquito gut 1 week later to count parasites



Pfs230D1 is efficacious against DSF surrogate endpoints:

- Reduces proportion of transmitters (i.e., fewer DSF+ subjects)
- Reduces proportion of DSF+ (fewer repeatedly DSF+ subjects)
- <u>Reduces proportion of infected mosquitoes</u>

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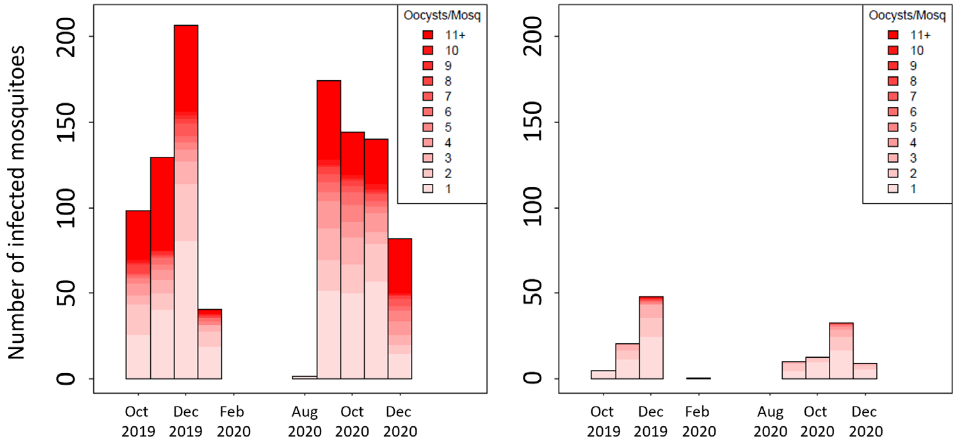
Phase 2 trial in school-aged children

Infected Mosquito Count and Oocyst Parasite Burden



Indication for use and target population

R21 in Matrix-M1

Indication	Target population
Prevent clinical malaria	Young children (5-36 months)

Phase 3 R21/Matrix-M1 efficacy results – Year 1

Modified per protocol analysis mean follow-up time – 298 days

Study arm	No. of participants	Rate (events/person years)	Unadjusted VE (95% CI)	p-value	Adjusted* VE (95% CI)	p-value
R21	3103	0.16 (383/2325)	**74%** (71-78)	<0.001	**75%** (71-78)	<0.001
Control	1541	0.60 (544/911)				

Approved in Ghana and Nigeria; Recommended by WHO (2023)

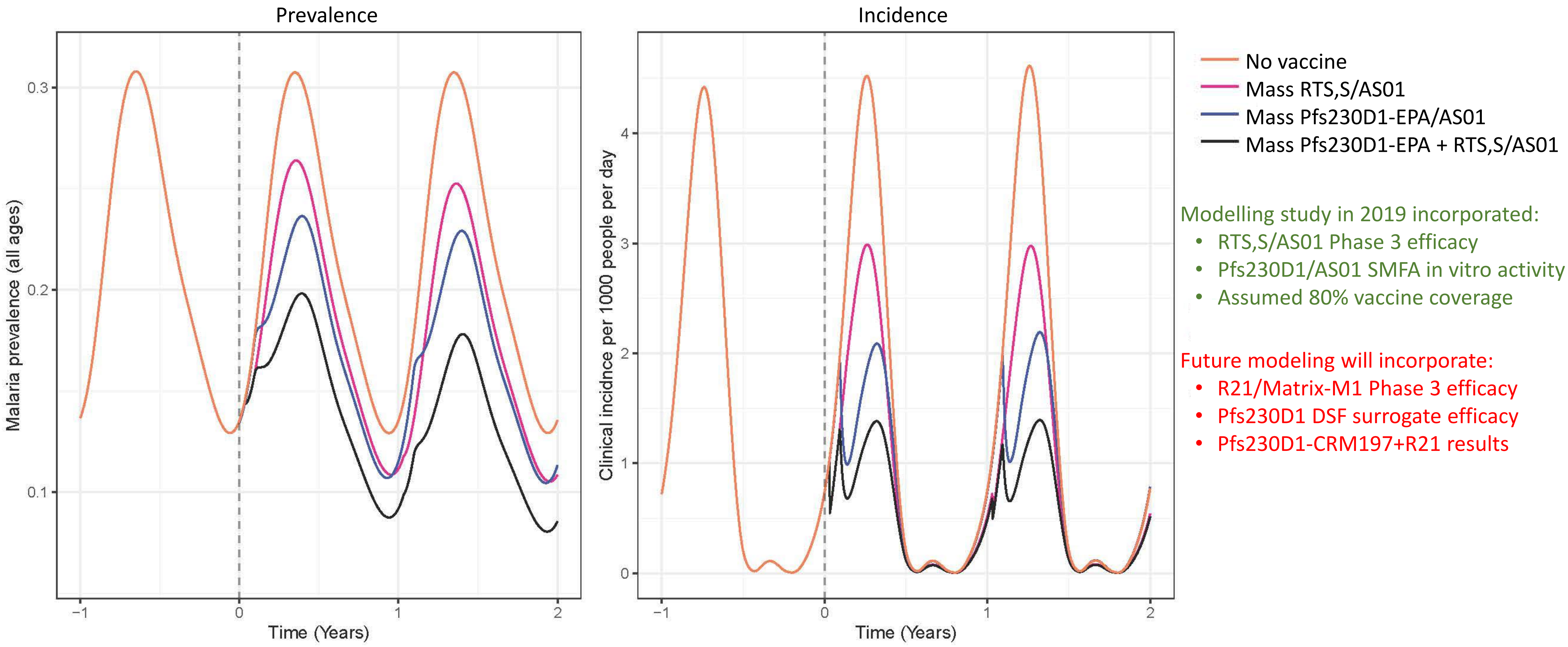
Indication for use and target population

Pfs230D1-CRM197 + R21 in Matrix-M1

Indication	Target population
Reduce malaria transmission and clinical malaria	Entire community (5 months to 99 years)

Phase 2 Pfs230D1-EPA/AS01 surrogate efficacy results
based on Direct Skin Feeding (DSF) bioassay – Years 1 and 2
Proportion of infected mosquitoes reduced by 86.4%

Modelling Pfs230D1 vaccine benefits against clinical malaria prevalence and incidence



Modelling study in 2019 incorporated:

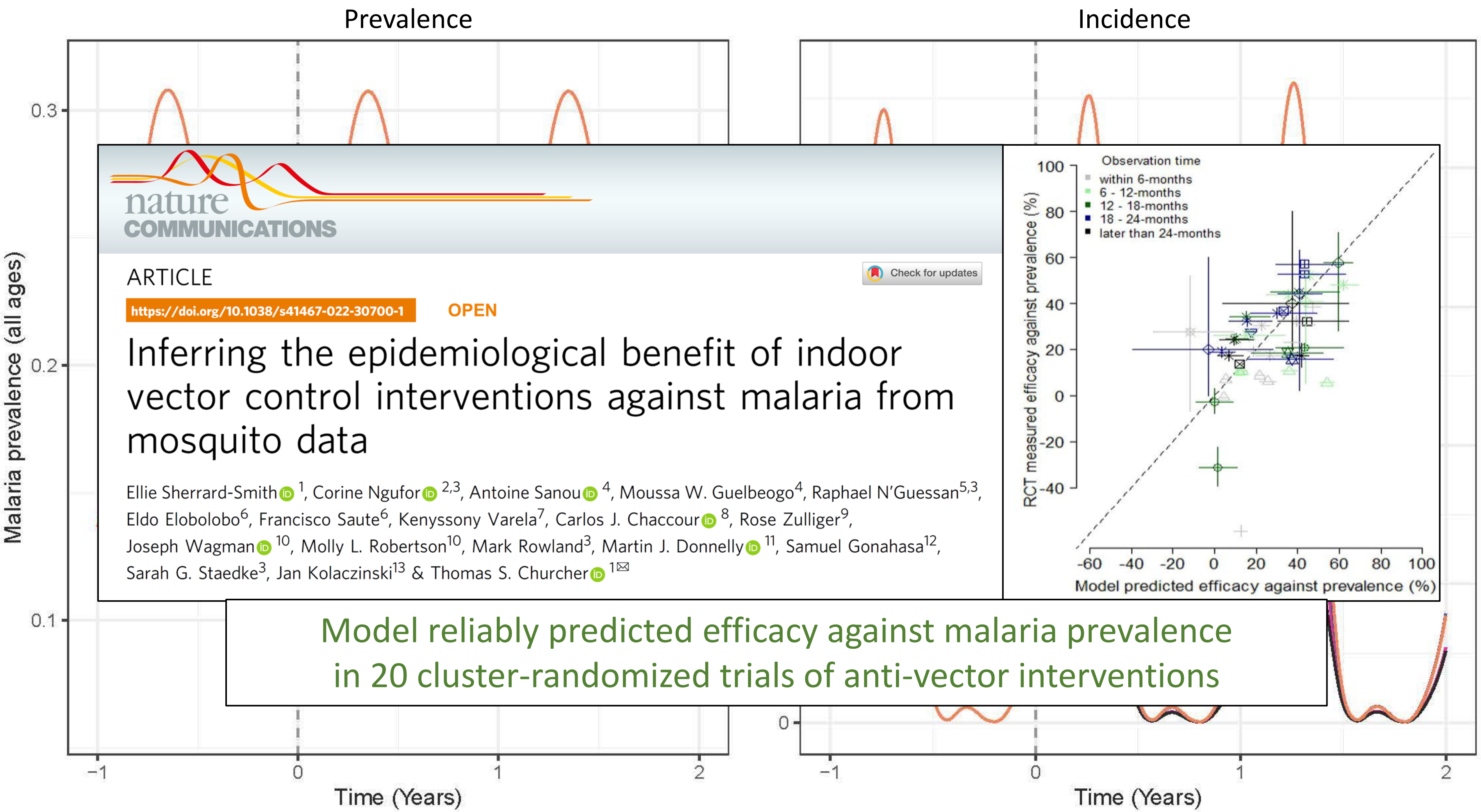
- RTS,S/AS01 Phase 3 efficacy
- Pfs230D1/AS01 SMFA in vitro activity
- Assumed 80% vaccine coverage

Future modeling will incorporate:

- R21/Matrix-M1 Phase 3 efficacy
- Pfs230D1 DSF surrogate efficacy
- Pfs230D1-CRM197+R21 results

Challenger and Churcher, unpublished, 2019

Modelling Pfs230D1 vaccine benefits against clinical malaria prevalence and incidence



nature COMMUNICATIONS

ARTICLE

Check for updates

https://doi.org/10.1038/s41467-022-30700-1 OPEN

Inferring the epidemiological benefit of indoor vector control interventions against malaria from mosquito data

Ellie Sherrard-Smith[1], Corine Ngufor[2,3], Antoine Sanou[4], Moussa W. Guelbeogo[4], Raphael N'Guessan[5,3], Eldo Elobolobo[6], Francisco Saute[6], Kenyssony Varela[7], Carlos J. Chaccour[8], Rose Zulliger[9], Joseph Wagman[10], Molly L. Robertson[10], Mark Rowland[3], Martin J. Donnelly[11], Samuel Gonahasa[12], Sarah G. Staedke[3], Jan Kolaczinski[13] & Thomas S. Churcher[1✉]

Model reliably predicted efficacy against malaria prevalence in 20 cluster-randomized trials of anti-vector interventions

Modelling study in 2019 incorporated:

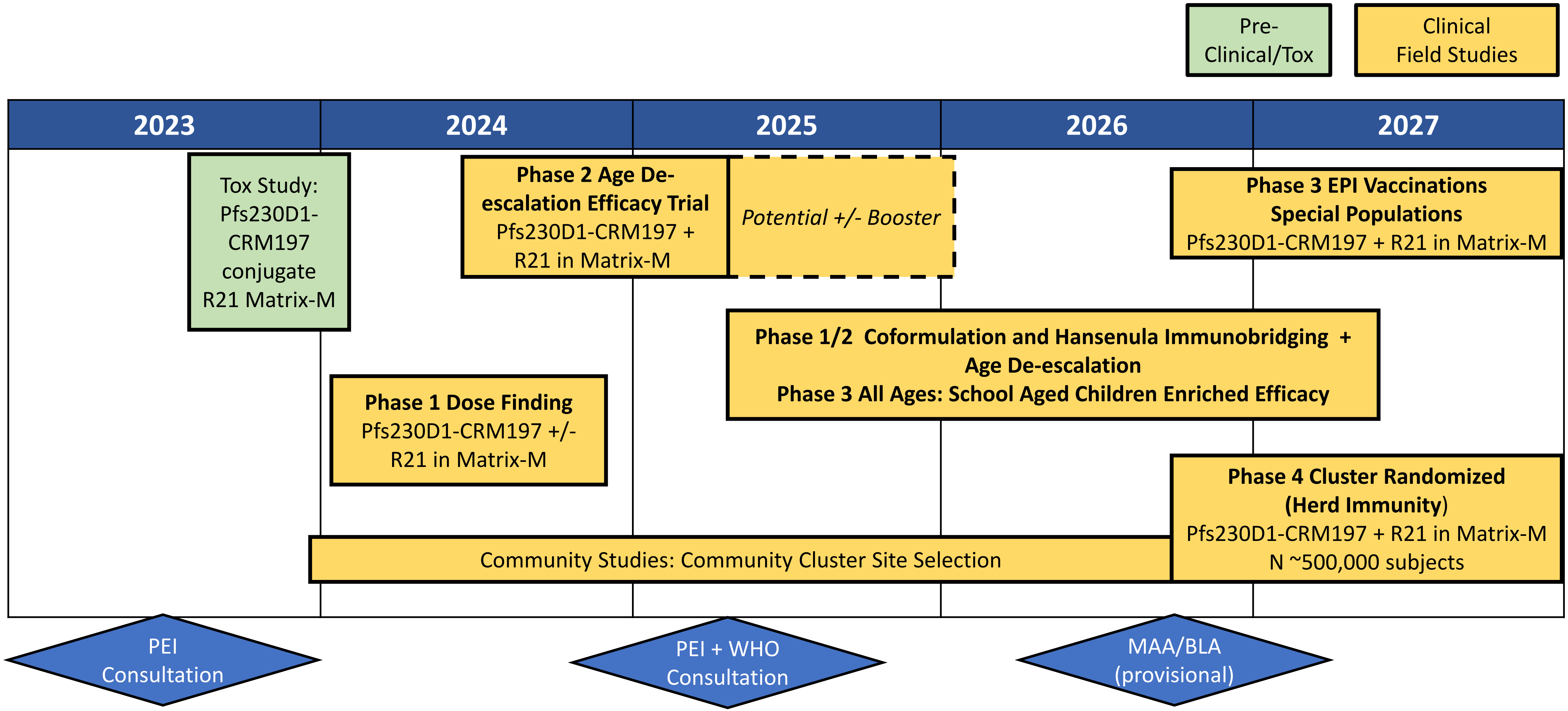
- RTS,S/AS01 Phase 3 efficacy
- Pfs230D1/AS01 SMFA in vitro activity
- Assumed 80% vaccine coverage

Future modeling will incorporate:

- R21/Matrix-M1 Phase 3 efficacy
- Pfs230D1 DSF efficacy
- Pfs230D1-CRM197+R21 efficacy

Challenger and Churcher, unpublished, 2019

Clinical Development Plan for Pfs230D1-CRM197 + R21 in Matrix-M1



Pfs230D1 + R21 supports WHO Global Technical Strategy

WHO GUIDELINES
for malaria
14 March 2023

Global technical strategy for malaria 2016-2030

Pillar 1	**Pillar 2**	**Pillar 3**
Ensure access to malaria prevention, diagnosis and treatment as part of universal health coverage	Accelerate efforts towards elimination and attainment of malaria-free status	Transform malaria surveillance into a key intervention

Supporting element 1. Harnessing innovation and expanding research

Supporting element 2. Strengthening the enabling environment for sustainable and equitable results

Summary

Vaccines that interrupt parasite life cycle can reduce malaria transmission

- Anti-infection vaccine (AIV): R21, RTS,S target sporozoites, may prevent human infection
- Transmission-blocking vaccine (TBV): Pfs230D1 targets gametes, blocks mosquito infection

Modeling studies indicate impact of TBV and AIV on malaria control & elimination

- Multi-stage combination vaccine increases impact and clinical benefit
- Model using surrogate mosquito endpoint predicted anti-vector agent efficacy in 20 CRTs

Direct Skin Feeding (DSF) Bioassay

- Recapitulates *in natura* malaria parasite transmission to mosquitoes
- Correlates to membrane feeding assay results; High between-cup correlation
- Assesses activity of TBV (Pfs230D1) to kill parasites in the mosquito
- Captures downstream effect of AIV (R21) to prevent parasitemia and thus transmission
- Evaluates vaccine impact on last step in causal pathway before next human infection
- Measures a reasonably likely surrogate endpoint of TBV efficacy: infected mosquitoes

Questions to PDVAC

- Are additional data / studies needed to validate a direct skin feeding (DSF) bioassay , analytically and biologically, as a surrogate measure of the efficacy of a vaccine to reduce transmission in humans that would be accepted by regulatory agencies for approval? How well does the current data on the DSF assay meet the needs for regulatory validation or acceptance?

- What are feasible clinical development and regulatory pathways for the approval of a transmission blocking vaccine or multistage vaccine to reduce malaria transmission?