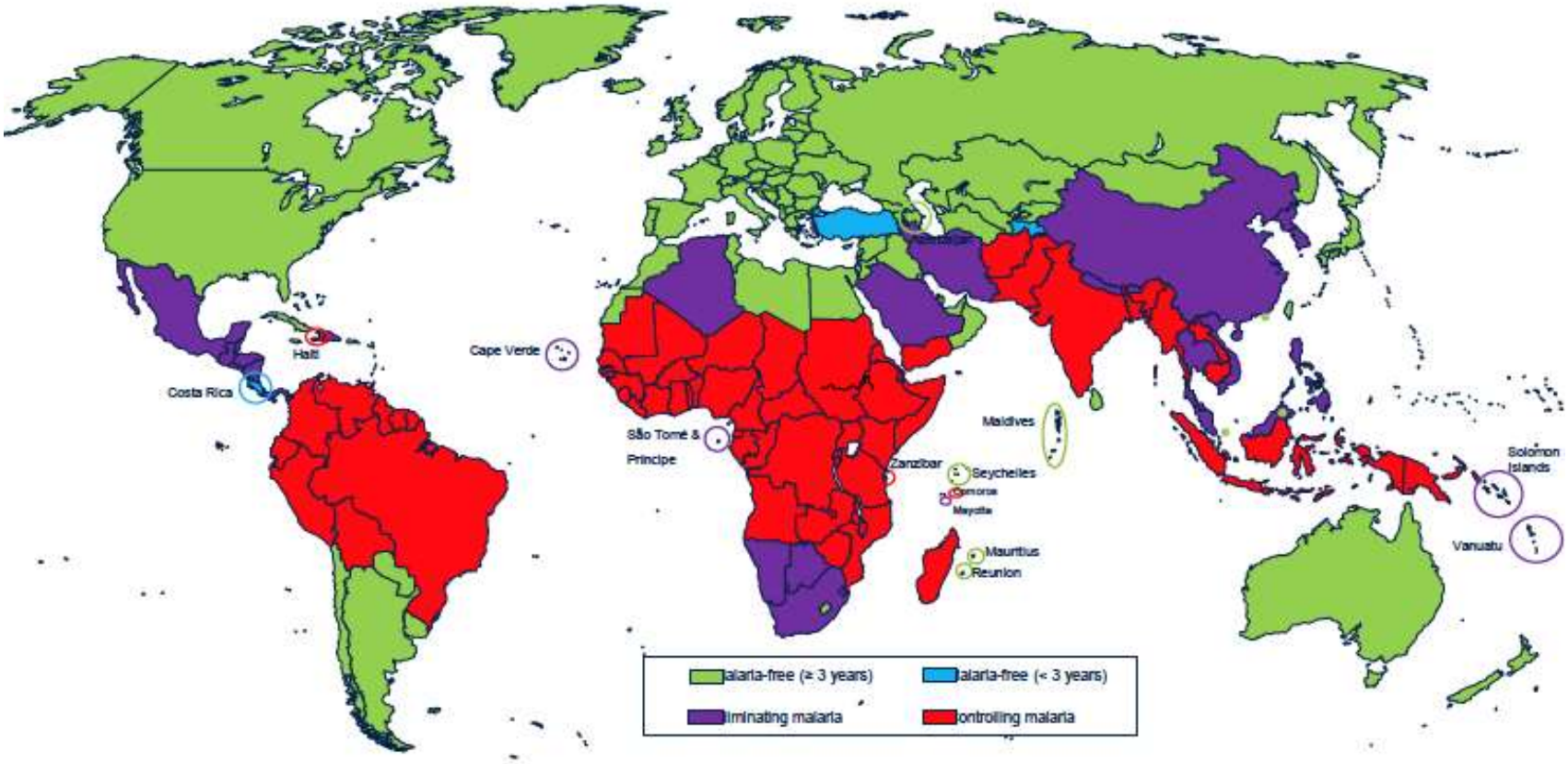
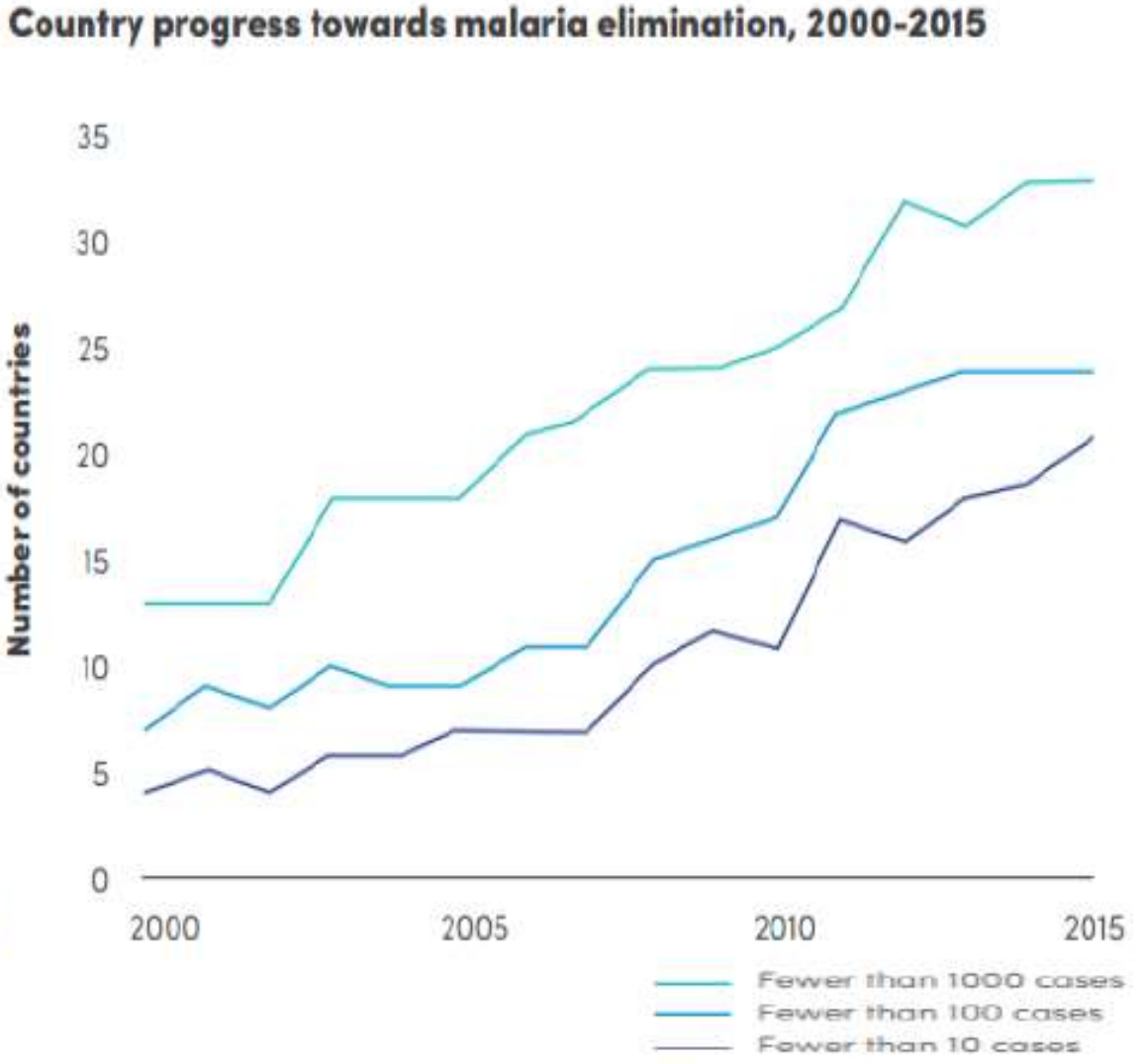
Global Pipeline for Malaria Vaccines: Progress and Challenges to accelerate vaccine development

Fred Binka MB ChB PhD FGCP
School of Public Health
University of Health and Allied Sciences, Ho. Ghana

Malaria in 2016



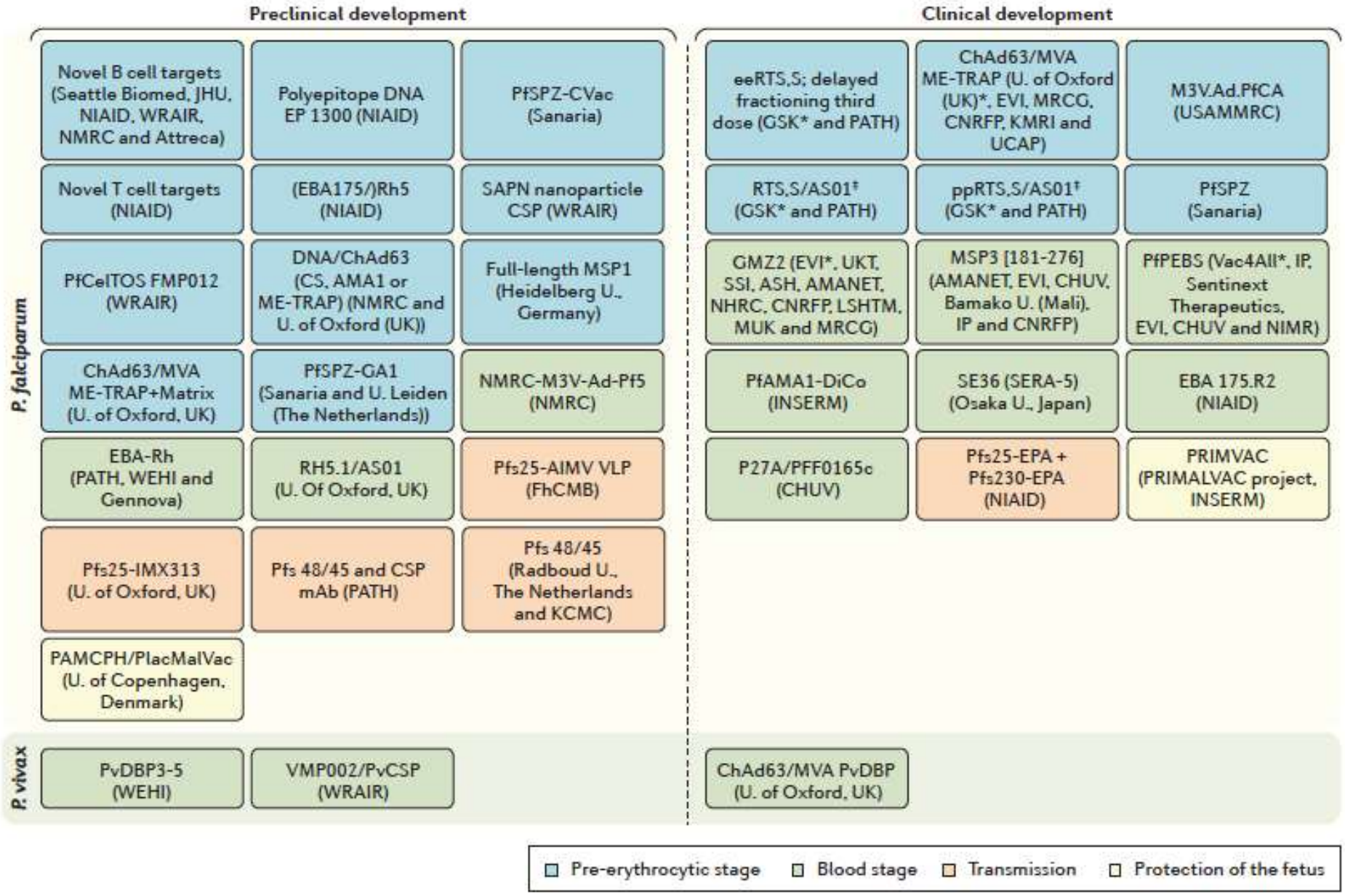
- More than half the 106 endemic countries reduced their burden by >75% between 2000 and 2015
- In 2014:
  - 16 countries reported zero locally transmitted cases
  - 3 additional countries reported fewer than 10 indigenous cases
  - 33 countries had fewer than 1,000 malaria cases



WHO, *Eliminating Malaria*, April 2016.

Major challenges in Malaria Control and Elimination effort

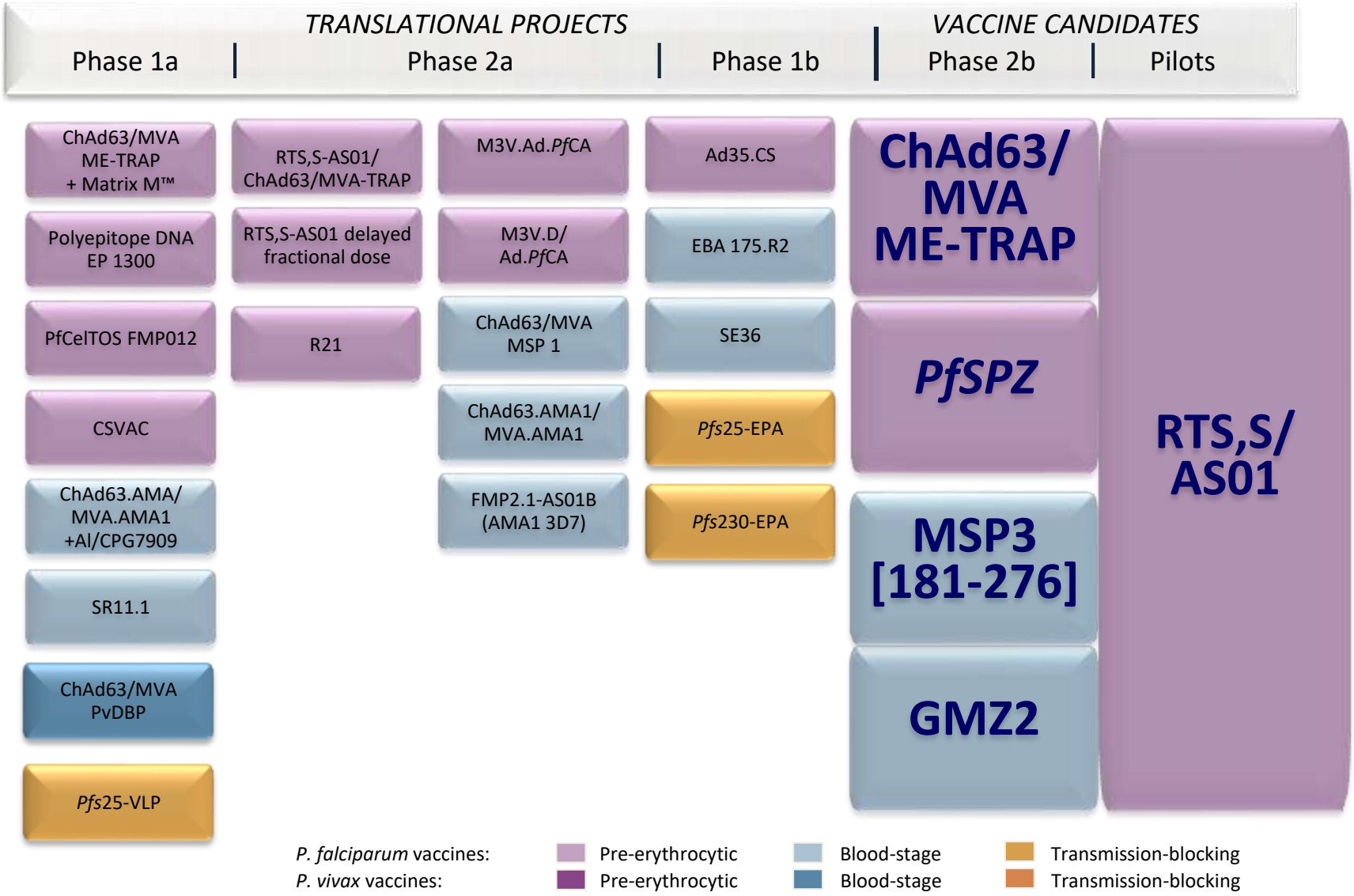
- Pf Parasite resistance to ALL antimalarial Drugs.. Development pipeline still weak
  - ACTs, mono-therapies for IPTp, IPTi
- Vector Resistance to Insecticides, development new insecticides complex.
- RDT, Diagnostics that have given as a leverage, access, cheaper, skills serts to be aggressive in treatment and prevention are under threat.
- Hence the need for Malaria Vaccines is critical



World Health Health Organizatio Rainbow tables.

WHO http://www.who.int/immunization/research/development/Rainbow_tables/en/(2017)

Global malaria vaccine pipeline



Data source: http://www.who.int/vaccine_research/links/Rainbow/en/index.html

THE JENNER INSTITUTE
DEVELOPING INNOVATIVE VACCINES

THE Pirbright INSTITUTE

UNIVERSITY OF OXFORD

R21: an improved anti-sporozoite malaria vaccine

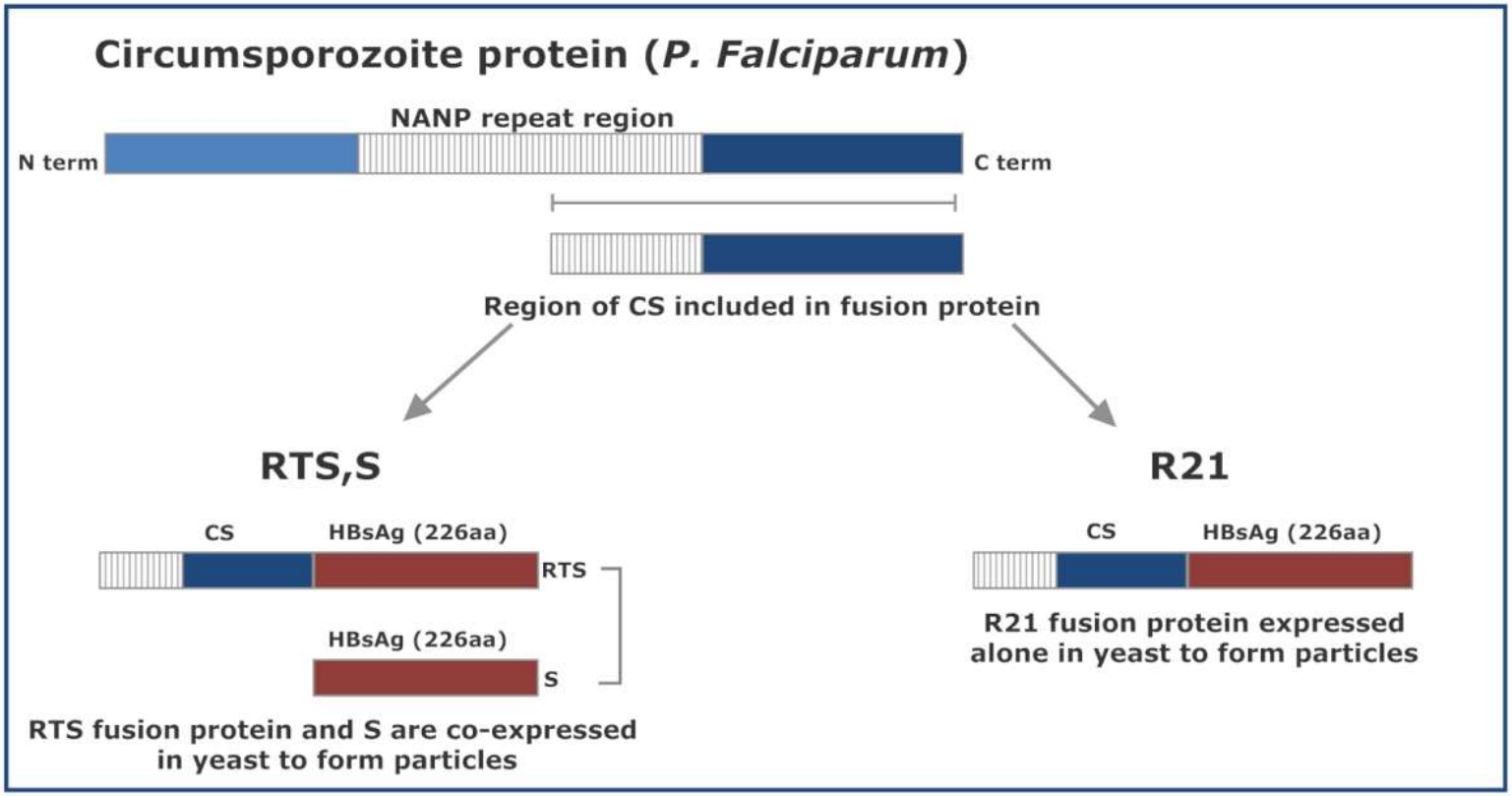
Adrian Hill

Jenner Institute, Oxford University

RTS,S vs R21

R21 is produced in *Pichia pastoris* yeast from a single fusion protein

- without co-expressing HBsAg



20% of molecules encode CS

100% of molecules encode CS

R21/Matrix-M: Clinical Development

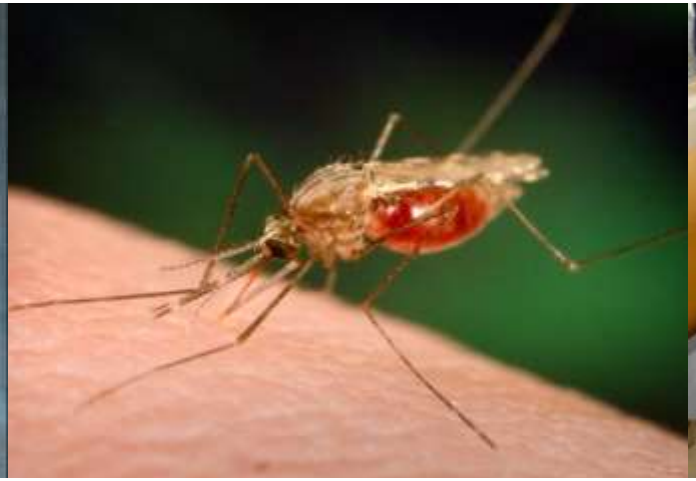
- **Four clinical trials completed in >100 subjects**
  - Three in Oxford, UK; one in Banfora, Burkina Faso
- **Safety**
  - well tolerated;
  - Significantly fewer local and systemic adverse events than with standard RTS,S/AS01 regimen
- **Immunogenicity**
  - Similar NANP antibody (and T cell) responses to RTS,S/AS01 and to RTS,S/matrix-M
  - But achievable with just 10mcg R21/matrix-M = dose sparing
  - 10μg R21 in 50 μg Matrix-M down-selected
- **Efficacy in CHMI** (Vac065, UK trial)
  - 82% sterile efficacy (9/11) at 4 weeks post third dose
  - 60% re-challenge sterile efficacy (3/5) at 8.5 months post third dose
  - Two dose regime also showed some efficacy (57% sterile, 4/7)
  - Overall, efficacy appears at least as high as with the 0,4,8 week RTS,S regimen

R21 Clinical Development Plan

- African adults, children and infants from Q3 2018
  - Phase Ib in Kilifi (EDCTP-funded)
    - First use of matrix-M in children and then infants
  - Lead-in group of Niger infants from early 2019
- Phase IIb efficacy trial at Kilifi from Q2 2019
  - N = ~600, 5-17 month olds
    - Booster 4th dose group at 1 year post 3rd dose
- Phase III under design with Epicentre (MSF)
  - Maradi, Niger from 2019
  - ~3,000 infants: @5-7 months; @3,4,9 months
- Indian phase I-III in adults and children
  - Likely 2019-2021, targeting Indian (DCGI) licensure

THE JENNER INSTITUTE
DEVELOPING INNOVATIVE VACCINES

UNIVERSITY OF OXFORD

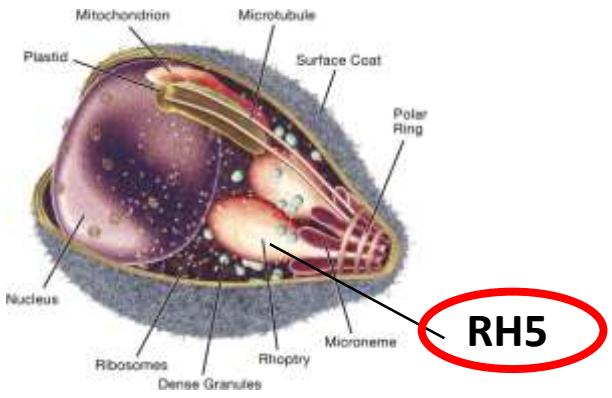

PfRH5-based Vaccines for Blood-Stage P. falciparum

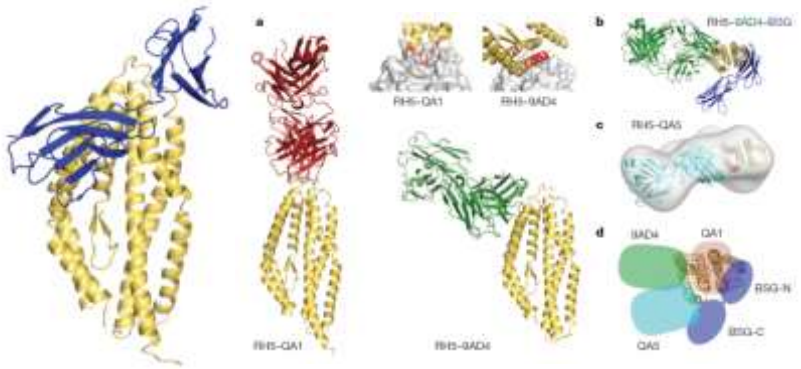
Simon Draper

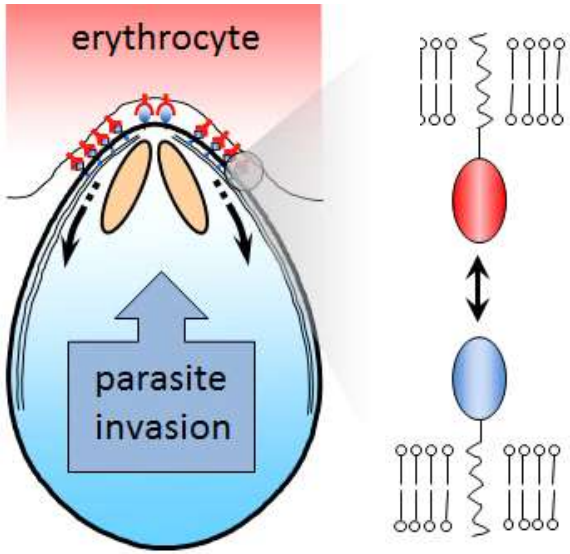
University of Oxford

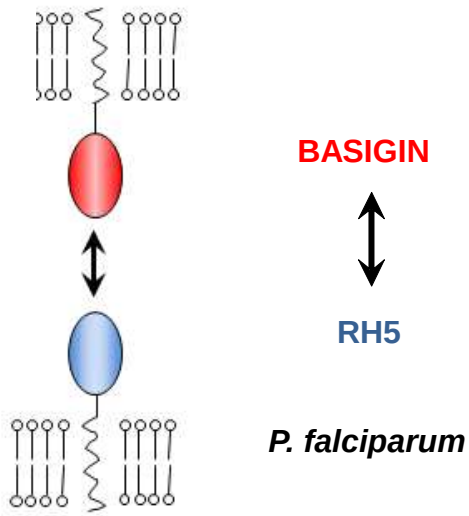
14th March 2018

Blood-Stage Vaccines based on *P. falciparum* RH5









- The first highly conserved target within the *P. falciparum* blood-stage merozoite to be susceptible to vaccine-induced broadly neutralising polyclonal antibody (Douglas *et al.* 2011, Nat Commun)
- Forms an essential interaction with basigin (CD147) on the erythrocyte surface (Crosnier *et al.* 2011, Nature) and an essential complex with PfRipr, PfCyRPA and PfP113 (Volz *et al.* 2016, Cell Host Microbe)
- Structure reported of RH5 bound to basigin and neutralising mAbs (Wright *et al.* 2014, Nature)
- *In vivo* efficacy and correlates of protection in *Aotus* monkeys (Douglas *et al.* 2015, Cell Host Microbe)

PfRH5 Vaccines: Clinical Development Status

- **VAC057 Phase Ia trial**: Healthy UK adults immunised with ChAd63-MVA RH5.
  - Payne RO *et al.* (2017) *JCI Insight* 2:96381

- **VAC070 Phase Ib trial**: Age de-escalation safety and immunogenicity trial of ChAd63-MVA RH5 in adults, children and infants in Tanzania.
  - Clinicaltrials.gov NCT03435874
  - Principal Investigator (Ifakara Health Institute, Bagamoyo): Dr Ally Olotu
  - Chief Investigator (Oxford): Dr Angela Minassian

- **VAC063 Phase I/IIa trial**: Healthy UK adults immunised with RH5.1 full-length protein vaccine in AS01B adjuvant (GSK) followed by blood-stage CHMI and re-challenge.
  - Clinicaltrials.gov NCT02927145
  - Chief Investigator (Oxford): Dr Angela Minassian

- RH5.2 virus-like particle (VLP) vaccine in preparation for cGMP manufacture funded by the Wellcome Trust

SANARIA
MALARIA ERADICATION THROUGH VACCINATION

PfSPZ Consortium

Development, Licensure and Deployment of a Highly Effective Malaria Vaccine

Stephen L. Hoffman, Kim Lee Sim, Thomas L. Richie

Sanaria Inc. Rockville, MD

PfSPZ Vaccine

- PfSPZ Vaccine is composed aseptic, purified, cryopreserved *Plasmodium falciparum* (Pf) sporozoites (SPZ) that are weakened (attenuated) by exposure to radiation.
- Controlled human malaria infection (CHMI) administered by mosquito bite (U.S.) and by using Sanaria's injectable infectious PfSPZ (PfSPZ Challenge in Germany, Tanzania, Mali, and EG.
- Significant VE against CHMI has been demonstrated for at least 14 months and against naturally transmitted Pf malaria for at least 6 months in Mali, Africa (2 trials in adults)

Sanaria PfSPZ-based Vaccines – Approach

- Core technology: Aseptic, purified, cryopreserved *P. falciparum* (Pf) sporozoites (SPZ), manufactured in GMP facility, Rockville, MD
- Three vaccine approaches with identical manufacturing:
  - *PfSPZ Vaccine*: Radiation-attenuated, non-replicating
    - 15 clinical trials in USA, Germany, Netherlands, Tanzania, Kenya, Mali, Burkina Faso, Equatorial Guinea
    - 1,130 adult/pediatric subjects (5 months to 65 years), >3650 injections
  - *PfSPZ Challenge*: Fully infectious, replicating, attenuated *in vivo* by chemoprophylaxis (*PfSPZ-CVac* approach)
    - 8 clinical trials in USA, Germany, Netherlands, Mali, Equatorial Guinea
    - 209 adult subjects, 555 injections
    - Chloroquine is gold standard partner drug
  - *PfSPZ-GA1*: Genetically-attenuated, non-replicating
    - 1 clinical trial in Netherlands, 45 subjects, 97 injections

PfSPZ Vaccines in Development

- PfSPZ Vaccine (radiation attenuated PfSPZ) (phase 2b by the rainbow table designation)
- PfSPZ-CVac (chemo-attenuated PfSPZ) (phase 2b by the rainbow table)
- PfSPZ-GA1 (genetically attenuated PfSPZ) (phase 2a by the rainbow table)

PfSPZ Vaccine Efficacy (VE)

Controlled Human Malaria Infection (CHMI)

- **Short term homologous protection**:
  - > **90%** protection against vaccine strain (NF54) in five different clinical trials in the U.S., Germany, Tanzania, and Mali at 3 weeks after last dose (4 trials with 100%).
    - 3 dose regimen in 3 cases, 5 dose regimen in 2 cases

  Seder, Science, 2013
  Epstein, JCI Insight 2018
  Jongo, NCT02613520
  Sissoko, Healy, NCT02627456
  Mordmüller, NCT02704533
- **Short term heterologous protection**:
  - **80% and 75%** protection against heterologous strain (7G8) at 3 weeks with 5 dose and 4 dose regimens.

  Epstein, JCI Insight 2018
- **Long term homologous protection**:
  - **55% to 65%** at 5, 6, and 14 months.
    - 3, 4, and 5 dose regimens (14 months is 4 dose regimen).

  Lyke, Epstein, NCT02601716
  Epstein, JCI Insight 2018
- **Long and medium term heterologous protection against infection**:
  - **54%** protection (5/6) against non-vaccine strain in the U.S. at 8 months after last dose (caveat: intervening homologous CHMI at 19 wks).

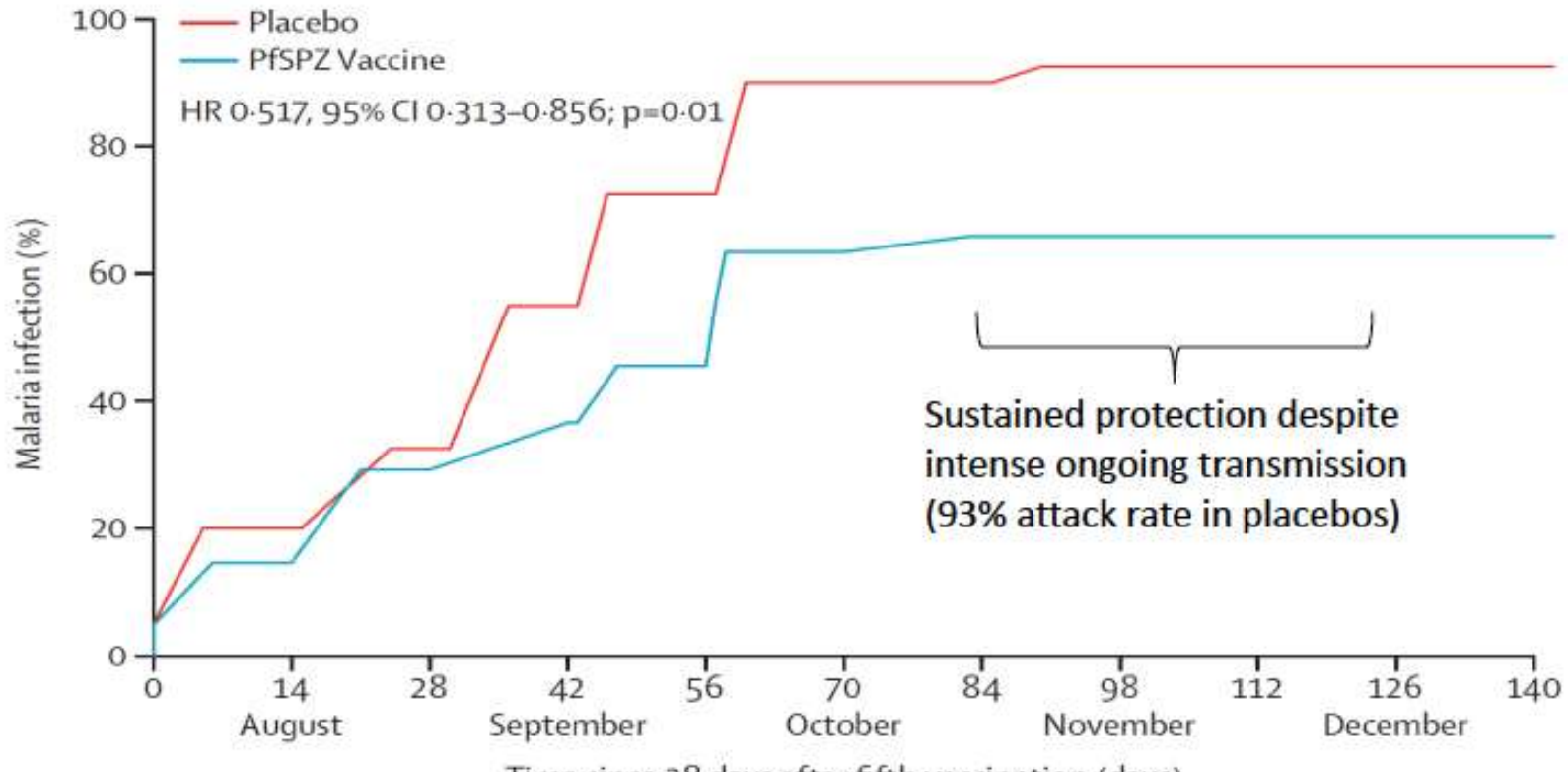
  Ishizuka, Nature Med 2016
  Lyke, PNAS 2017

Natural Exposure to Pf Malaria in the Field

- **Long term (6 months)**:
  - **52%** (time to event analysis) and **29%** (proportional analysis) protection against parasitemia in setting of intense natural infection in Malian adults. Initially with 5 dose regimen, now repeated with 3 dose regimen (**51%** and **24%**)

  Sissoko, Healy, Lancet Inf Dis 2017
  Sissoko, Healy, NCT02627456

Sustained protection in Mali (Sissoko et al, Lancet, 2017)



Number at risk

Placebo	40	36	31	25	15	8	4	3	3	3	3
PfSPZ Vaccine	41	37	31	29	25	16	14	14	14	14	14

Key Findings from PfSPZ Vaccine Clinical Trials

- PfSPZ Vaccine is well-tolerated and safe in Malian adults[1]
- PfSPZ Vaccine showed significant protection against *P. falciparum*[1]
  - Protection throughout an entire malaria season[1]
  - Protection with both 5-dose[1] and 3-dose regimens
- Future studies will assess PfSPZ Vaccine for benefits in pregnant women
  - Assess efficacy of accelerated (28 day) regimens in non-pregnant population
  - Assess efficacy of boosting at one year
  - st priate regimens in pregnant women

LABORATORY OF MALARIA Immunology & Vaccinology

MALARIA RESEARCH & TRAINING CENTER BAMAKO, MALI

SANARIA MALARIA ERADICATION THROUGH VACCINATION

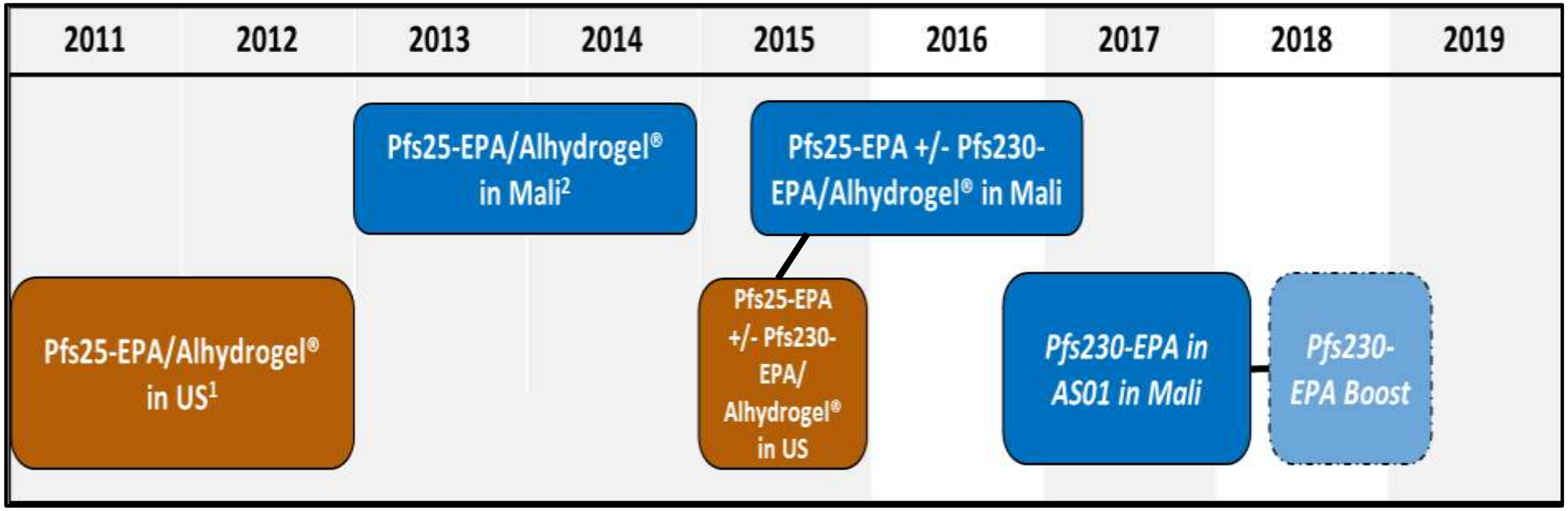
[1]Sissoko and Healy et al, Lancet

Plans

- Phase 3 trials in USA & EU (>1000 adult), 3 sites in Africa (>2000 adults, teenagers, children, infants)
- Submit licensing application for PfSPZ Vaccine to FDA/EMA and receive licensure (market authorization) for adults in 2020
- Follow with extension of the license to all age groups in 2021
- Demonstrate PfSPZ Vaccine can be used to halt transmission and eliminate malaria in geographically defined areas where transmission has been reduced by standard control measures

Transmission Blocking Vaccines (TBV)

Clinical Trials of Transmission Blocking Vaccines: LMIV/NIAID and MRTC/Mali trials 2011-2019



[1]Talaat et al, PLOS One, 2016

[2]Sagara and Healy et al, submitted to Lancet ID, 2018

Clinical Trial Numbers

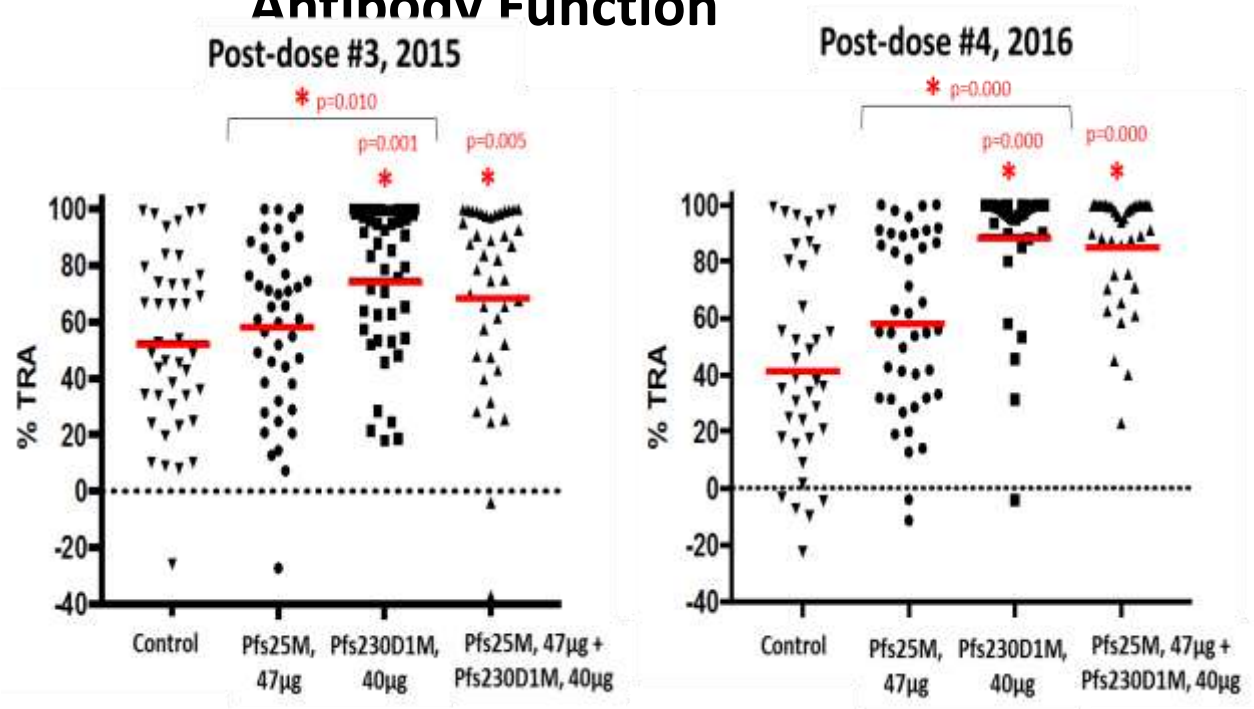
NCT01434381
NCT01867463
NCT02334462
NCT02942277

LABORATORY OF MALARIA Immunology & Vaccinology

MALARIA RESEARCH & TRAINING CENTER
BAMAKO, MALI

Pfs25M-EPA/ Alhydrogel® and Pfs230D1M-EPA/Alhydrogel® in Mali: Antibody Function

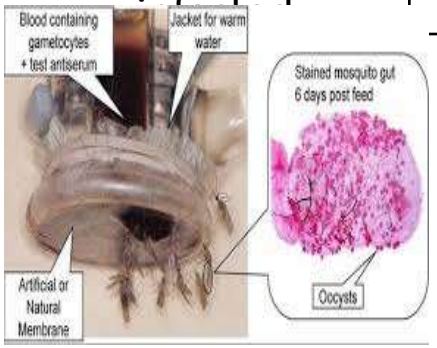
Transmission Reducing Activity (reduction in oocyst counts)



Transmission Blocking Activity (reduction in

Control	Pfs25M	Pfs230D1M	Pfs25M + Pfs230D1M
52% (43-62)	58% (49-67)	75% (67-83)	69% (57-79)

Control	Pfs25M	Pfs230D1M	Pfs25M + Pfs230D1M
39% (28-55)	58% (49-68)	89% (82-96)	85% (78-92)



LABORATORY OF MALARIA Immunology & Vaccinology

MALARIA RESEARCH & TRAINING CENTER BAMAKO, MALI

TBV

- a reduction in average oocyst burden (TRA) or in % infected mosquitoes (TBA) compared to malaria-naïve US sera in the assay, because malaria-exposed individuals have background TRA/TBA, as can be seen in the control group.
- Compared to the control group, Pfs230 vaccinees have significant activity after 3 or 4 doses; Pfs25 vaccinees have significant activity after 4 doses. Pfs230 activity after 4 doses is significantly greater than Pfs25 activity after 4 doses.
-

Key Findings from LMIV TBV Clinical Trials

- Pfs25-EPA[1] and Pfs230-EPA in Alhydrogel® are safe and immunogenic
- Pfs25 induces functional activity in US[1] and Mali[2] after 4 doses
  - Antibody titers in Mali are roughly half the level of titers in US[2]
- Pfs230-EPA/Alhydrogel® induces functional activity after 2 or 3 doses
- Liposomal adjuvants (e.g. AS01) enhance functional immunogenicity
- 3-dose Pfs230-EPA/AS01 clinical trial in Mali unblinds in Spring 2018

LABORATORY OF MALARIA Immunology & Vaccinology

MALARIA RESEARCH & TRAINING CENTER BAMAKO, MALI

[1]Talaat et al, PLOS One, 2016

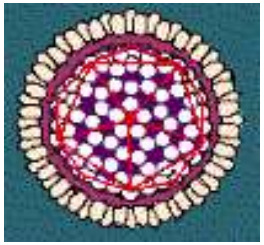
[2]Sagara and Healy et al, submitted to Lanc

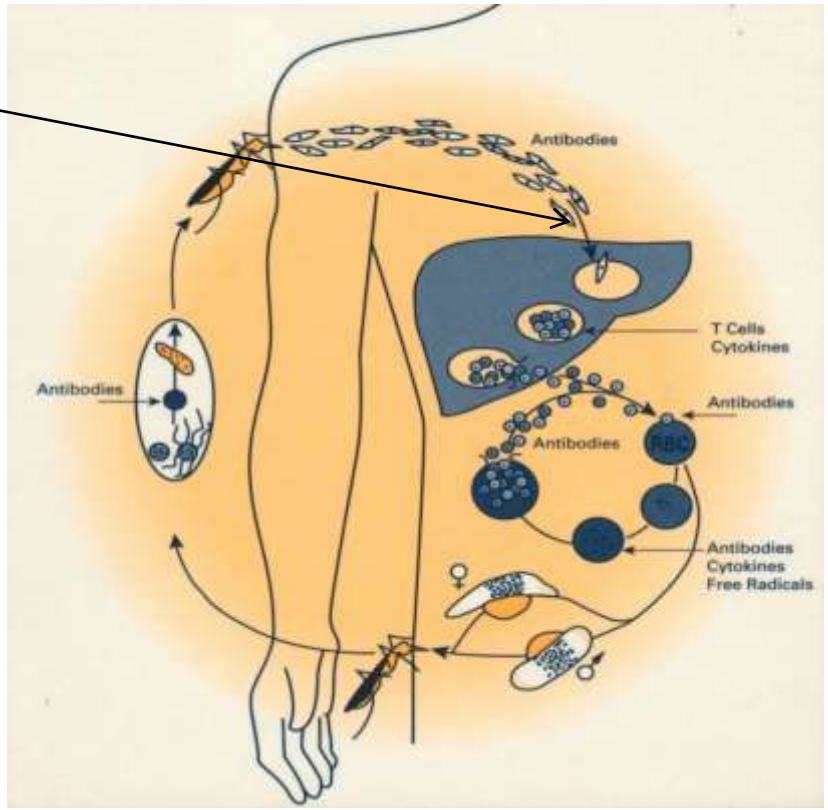
MOSQUIRIX®

- A recombinant protein-based malaria vaccine
- The world's first licensed malaria vaccine

RTS,S/AS01 Vaccine

- RTS,S/AS01 vaccine





  - Combines CS protein, hepatitis B surface antigen, and AS01 adjuvant to create a more robust immune response than nature
  - Targets the CS protein on the sporozoite of *P*

RTS,S/AS01 vaccine product characteristics

- Reconstituted 2-dose vaccine
- 2 vials attached together by a “clip”
  - Antigen RTS,S lyophilized in one vial
  - Adjuvant AS01 liquid in the other vial
- To be used within 6 hours of reconstitution

Phase 3 Trial Key Results: Vaccine efficacy during 4 years follow-up in children first vaccinated at age 5-17 months, 4 doses*

5-17 month age category	4 doses
Clinical malaria	**39% (34;43)**
Severe malaria	**32% (9;48)**
Incident severe malaria anaemia	**61% (27-81)**
Blood transfusion	**29% (4 - 47)**
Malaria hospitalization	37% (24;49)
All cause hospitalization	15% (4-25)
*All-cause mortality***	*-18% (-105;32)*

Safety signals

Associated:

- Increased risk of febrile convulsions within 7 days of vaccination
  - By 30 days post vaccination, frequency equalized between study arms

Unknown association observed in phase 3 trial:

- Meningitis
- Cerebral malaria
- In setting of low mortality, numerically more female deaths than male
- **No vaccine–related deaths**

Source: Summary of Key Points from Malaria Vaccine: WHO Position Paper January 2016

EMA Opinion (Article 58) and WHO Position

- **EMA** issued a **positive scientific opinion** in July 2015
- Implies that the quality of the vaccine and its risk/benefit profile is favourable from a regulatory perspective
- **WHO** recommends further evaluation of RTS,S in a series of pilot implementations, addressing several gaps in knowledge, before considering wider country level introduction
- Vaccines should be given in 4 dose schedule, starting around 5 months of age, with fourth dose provided 15-18 months after 3rd dose
- Data will inform policy on the use of RTS,S
- Expected timeline – by 2022
- Pilot Countries selected using standardized criteria
  - GHANA, KENYA, MALAWI

Rationale for pilot implementations recommended by WHO

- WHO recommends pilot implementations of RTS,S/AS01 to answer outstanding questions before wider scale-up is considered. The pilots should allow:
  - Assessment of operational feasibility of providing malaria vaccine in target age group at the recommended 4-dose schedule in the context of health service delivery.
  - Evaluation of the impact of the vaccine on all cause child mortality when implemented in the setting of concomitant recommended malaria interventions.
  - Surveillance of adverse events following vaccination, with an emphasis on meningitis and cerebral malaria.

Malaria Vaccine Rainbow table

- Pre-clinical and
- Early phase clinical development
- None in Phase III development

- Great success for Malaria
  - One licensed and but in pilot deployment, early wild scale deployment NOT before 2022/23

  Great strides but we need to pay attention to the RTSS story.

RTS,S Malaria Vaccine Implementation Programme

26th July 2017

Post Licensure of Mosquirix®

1. Pilot implementation to address the third pillar
2. Fraction dose studies to improve on immunogenicity
3. Use in a prevention mode with anti-malaria drugs

RTS,S Malaria Vaccine Pilot Evaluation

Overall design

- **Not a trial of vaccine efficacy. Efficacy of vaccine is known. This is evaluation of vaccine implementation in the context of routine delivery.**
- **Rigorous Evaluation, supported by research institutions, of**:
  - **Operational feasibility** of providing RTS,S at the recommended four-dose schedule when implemented through the routine EPI (coverage);
  - **Impact** of the vaccine on all cause child mortality (overall and by gender), malaria-specific mortality and severe malaria;
  - **Safety**: frequency of adverse events following immunisation (AEFI), with an emphasis on meningitis and cerebral malaria

RTS,S Implementation

- Vaccine introduction Sub-national through the routine immunization programme (EPI)
  - In close collaboration with National Malaria Control Programmes, ensuring continued use of other malaria prevention and treatment measures

- Introduction will be randomized, with some areas introducing RTS,S at the beginning of the programme, while other act as comparison areas

RTS,S schedule

WHO position: A 4-dose schedule is required, with the first dose given as soon as possible after 5 months of age, doses 2 and 3 given at monthly intervals, and the fourth dose given 15–18 months after the third dose

Example: Ghana vaccination schedule

Age / Vaccine	Birth	6 weeks	10 weeks	14 weeks	5 mo	6 mo	7 mo	9 mo	12 mo	18 mo	22mo	24 mo
BCG	X											
OPV	X											
DPT-HepB-Hib (penta)		X	X	X								
PCV		X	X	X								
Rota		X	X									
IPV				X								
MenA										X		
MR								X		X		
YF								X				
RTS,S Ghana						**X**	**X**	**X**				**X**
RTS,S Kenya						**X**	**X**	**X**				**X**
RTS,S Malawi					**X**	**X**	**X**				**X**	
VitA						X			X	X		X

Impact

- Assess the impact of the RTS,S vaccine on:
  - all cause child mortality
    - Community based surveillance relying on village reporters
  - malaria-specific mortality
    - In patient surveillance
  - severe malaria
    - In patient surveillance

- Implementation in the setting of concomitant recommended malaria interventions

The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

Fractional Third and Fourth Dose of RTS,S/AS01 Malaria Candidate Vaccine: A Phase 2a Controlled Human Malaria Parasite Infection and Immunogenicity Study

Jason A. Regules,[1,3,6] Susan B. Cicatelli,[4] Jason W. Bennett,[1,3,6] Kristopher M. Paolino,[4] Patrick S. Twomey,[2,3] James E. Moon,[1,3] April K. Kathcart,[1,3] Kevin D. Hauns,[1,3] Jack L Komisar,[1,3] Aziz N. Qabar,[1,3] Silas A. Davidson,[5] Sheetij Dutta,[1,3] Matthew E. Griffith,[6] Charles D. Magee,[6] Mariusz Wojnarski,[2,3] Jeffrey R. Livezey,[2,3] Adrian T. Kress,[2,3] Paige E. Waterman,[4] Erik Jongert,[9] Ulrike Wille-Reece,[7] Wayne Volkmuth,[8] Daniel Emerling,[8] William H. Robinson,[8] Marc Lievens,[9] Danielle Morelle,[9] Cynthia K. Lee,[7] Bebi Yassin-Rajkumar,[7] Richard Weltzin,[7] Joe Cohen,[9] Robert M. Paris,[3] Norman C. Waters,[1,3] Ashley J. Birkett,[9] David C. Kaslow,[9] W. Ripley Ballou,[9] Christian F. Ockenhouse,[7] and Johan Vekemans[9]

Result:

The fractional dose boosting increased antibody somatic hypermutation and avidity and sustained high protection upon rechallenge.

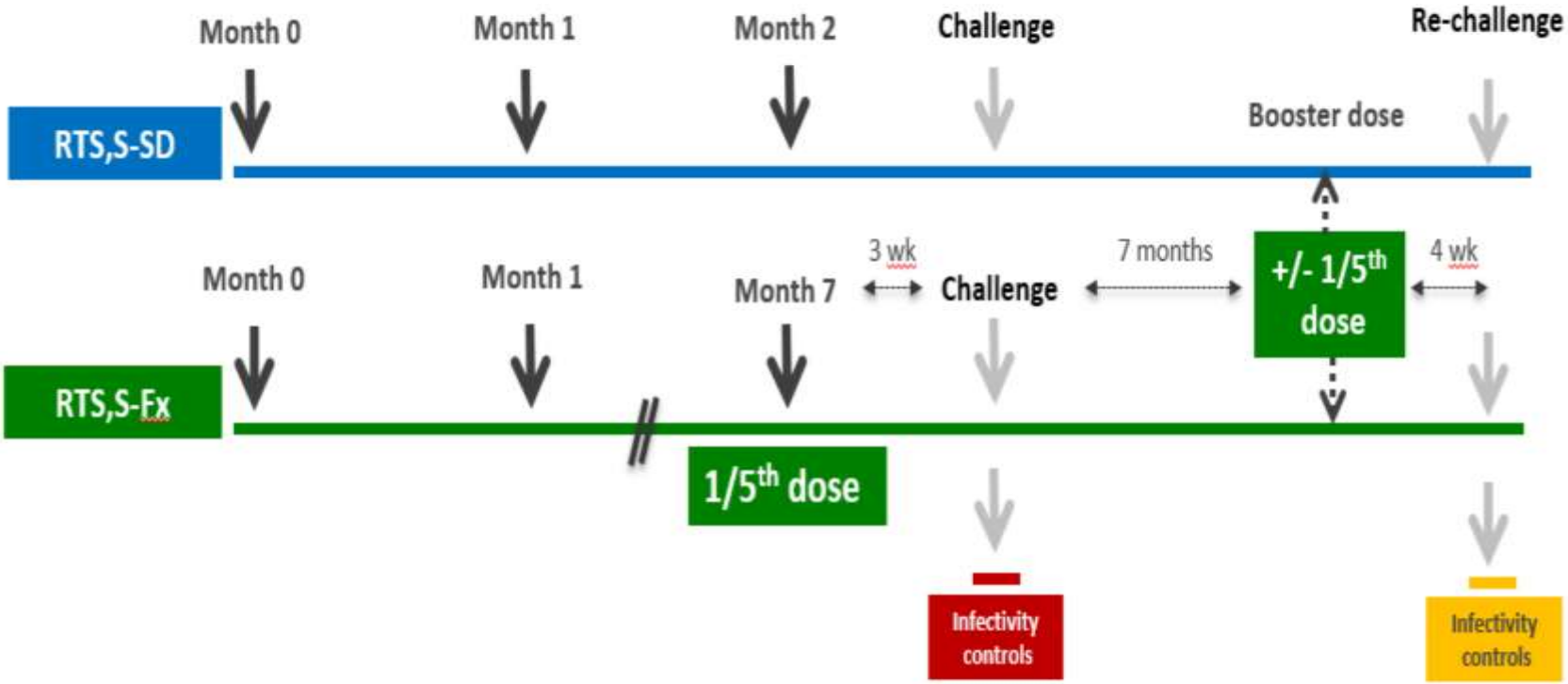
Conclusion

A delayed third fractional vaccine dose improved immunogenicity and protection against infection. Optimization of the RTS,S/AS01 immunization regimen may lead to improved approaches against malaria.

Study design: Repeat of original CHMI study published in NEJM in 1997

Study groups

1. RTS,S/AS01B-Standard Dose (RTS,S-SD) (n = 16)
2. RTS,S/AS01B-Delayed Fractional 3rd Dose (RTS,S-Fx) (n = 30)
3. Infectivity controls (n = 12)



Fx = delayed fractional dose; SD = standard dose and schedule

Regules et al., *J Infect Dis*. 2016 Sep 1;214(5):762-71

Ongoing clinical studies

- **MAL092 (CHMI – US adults) (Reporting 2018)**
  - Can pediatric (RTS,S/AS01E) formulation be used effectively in adults?
  - Are 2 priming doses necessary, or is 1 sufficient?
  - Is there a benefit to also fractionating dose 2?
- **MAL094 (Natural exposure – 5-17 mo infants (Reporting 2021/2023)**
  - Does fractional booster dose concept translate to endemic setting with respect to prevention of infection and clinical disease?
  - What is optimal interval between doses 2 and 3?
- **BAKMAL1605 (Phase 1 – Thai adults) (Reporting 2018)**
  - Is RTS,S/AS01 safe and immunogenic in Thai adults
  - Is vaccine immunogenicity impacted when co-administered with drug (to clear parasites)?

2 African centers (To be announced)

Medium-term goal: Community-based assessment, with parasite prevalence endpoint, to assess acceleration of parasite elimination

PROPOSED TRIAL OF SEASONAL VACCINATION WITH RTS,S

TRIAL FEATURES

Objective: To determine whether (a) seasonal vaccination with RTS,S would be non-inferior to SMC and/or (b) if the combination of the two interventions would be superior to either used alone.

Study sites: Hounde district, Burkina Faso and Bougouni district, Mali.

Study children: Aged 5-17 months at the time of primary immunisation.

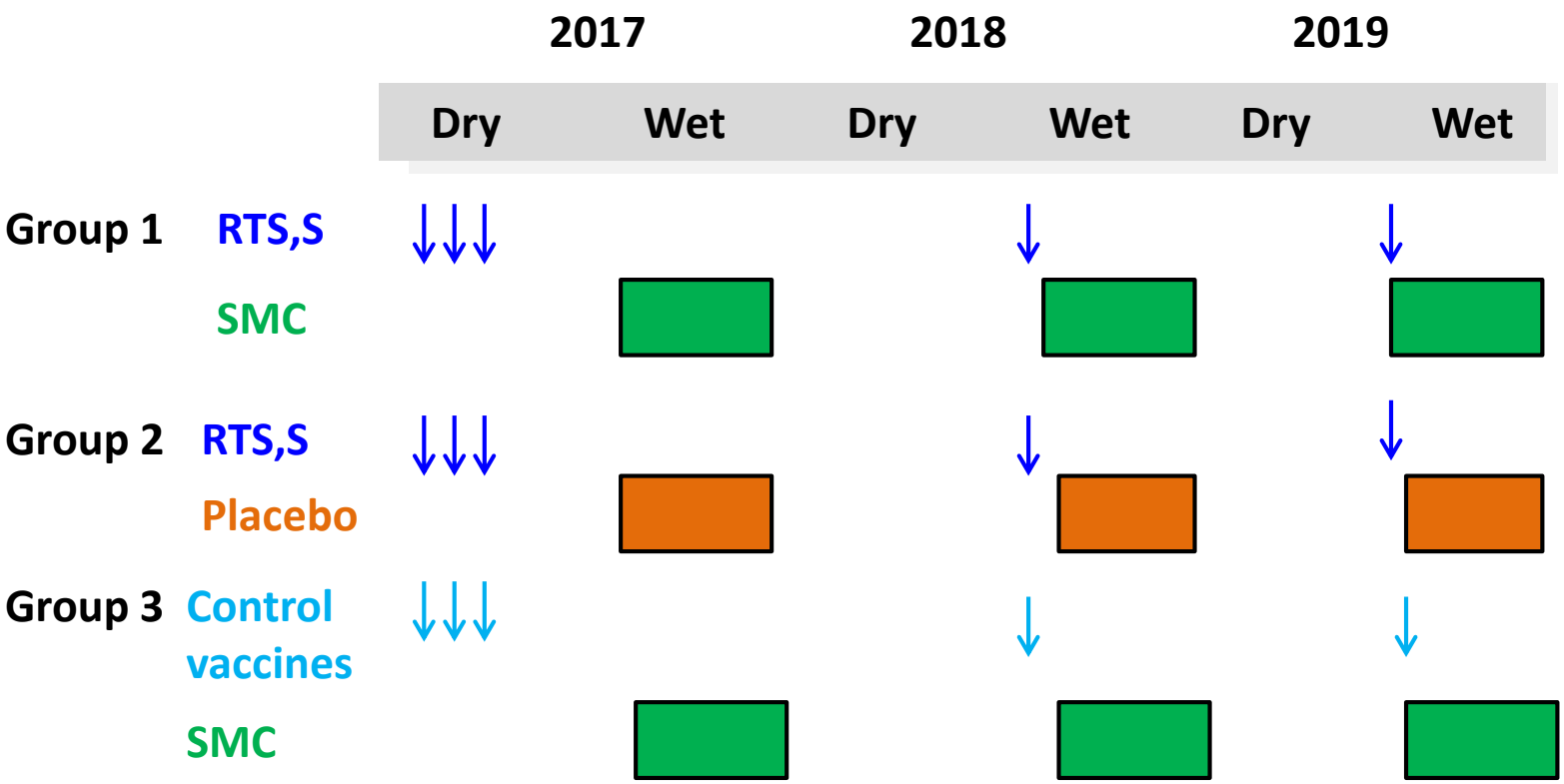
Numbers: 2,000 children in each of three groups.

Primary end-point: Clinical episodes of malaria detected by passive case detection.

Funding: MRC/DFID/Wellcome Trust Global Clinical Trials Programme

PROPOSED TRIAL OF SEASONAL VACCINATION WITH RTS,S

STUDY GROUPS



Seasonal Malaria Chemoprevention (SMC)+ RTS,S trial
Numbers of children vaccinated during each round of RTS,S/AS01 or rabies vaccine.

	Burkina Faso	***Mali***
Round 1		
Dates of vaccination	22nd April-13th May17	17th-29th April
Number vaccinated	2777	3143
Round 2		
Dates of vaccination	5th-14th June	3rd-14th June
Number vaccinated	2678	3034
Round 3		
Dates of vaccination	30 Jun – 14 July	28 Jun- 14 July
Number vaccinated	2603	2929

Summary

Cross-Cutting issues for accelerated vaccine development

- Controlled Human Malaria Infection (CHMI) models reduce risk and accelerates vaccine development
- Correlates of immunological protection still elusive but would make a great difference in the next generation of vaccines.
- The pilots will address mortality and safety endpoints

- Partially Efficacious vaccines
  - Requirement for Booster doses
- Vaccine Schedules within the EPI-- early engagement of the Immunization team/SAGE.
  - MPAC/SAGE engagement led to the pilot studies for RTSS
  - Post licensure demonstration projects
  - Who bears the cost of these additional studies?
- Bridging studies for new vaccines

Mind the gap: bridging licensure and large-scale use

We are entering an era where the path from licensure to widespread use requires more than SAFETY and EFFICACY data. Policy recommendations for new vaccines may only be realised through implementation research to determine how to most effectively ensure widespread use. Failure to tackle this implementation phase with the same commitment shown to the licensure phase will pose greatest risks for vaccines developed mainly for the world's poorest people. Thus implementation assessments must become the third component of the core vaccine evaluation tripod joining safety and efficacy. The essential value of this third phase has not been fully appreciated.

Lancet May 7 2016 Kate O'Brien, Fred Binka, Kevin Marsh, Jon Abramson