U.S. Army Malaria Prevention in Sub-Saharan Africa

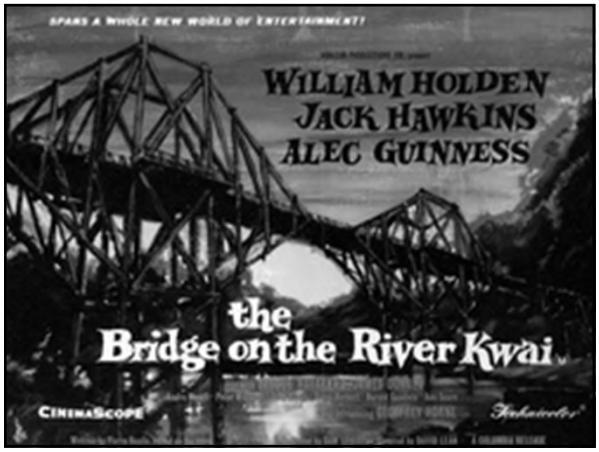
Anthony C. Littrell, MD, MPH

Learning Objectives:

After this lecture, you will be able to:

- Gain an understanding of the etiology of Blackwater fever
- Appreciate the association between rapid hemolysis and treatment for P. falciparum malaria
- Understand the increased risk of G6PD deficient patients and hemolytic anemia
- Recognize why developing an effective vaccine to prevent P. falciparum malaria is a goal of the U.S. Military
- Learn about effectiveness of RTS,S as an investigational new vaccine in children in Sub-Saharan Africa

2



Annals of Internal Med, 1968:

ORIGINAL RESEARCH | 1 JANUARY 1968

Coombs'-Positive Hemolytic Disease in Malaria

MARVIN M. ADNER, M.D.; LESLIE B. ALTSTATT, M.D.; MARCEL E. CONRAD, M.D., F.A.C.P.

FULL TEXT

MORE

Abstract

SUMMARY In a study of 131 soldiers evacuated from Vietnam with drug-resistant *Plasmodium falciparum* malaria, 4 patients were found with a positive direct antiglobulin test of the immunoglobulin (Ig) G type. In three patients the positive Coombs' tests seemed temporally related to the administration of quinine for relapsed malaria and were associated with hemolysis. Two of these patients had a quinine-related dermatitis, one developed blackwater fever within hours after the initiation of quinine therapy, and another had a panagglutinin in quinine-free red cell eluates. The fourth patient had compensated hemolysis and a positive direct Coombs' test which seemed unrelated to quinine therapy. The indirect Coombs' test was negative in all subjects, and no antiquinine antibodies were found in sera or red cell eluates from these patients.

Complications of malaria

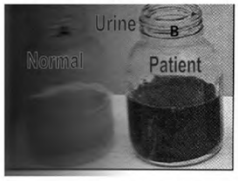
The complications are more common due to *P. falciparum* infection than due to other three species

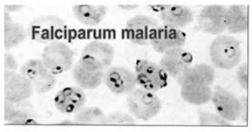
Complications of *P. falciparum* infection

Blackwater fever

- It is seen in patients who have experienced repeated falciparum malaria infections and inadequately treated with quinine
- Clinical manifestations include bilious vomiting and prostration with passage of dark red or blackish urine (black water)
- The pathogenesis is believed to be massive intravascular hemolysis caused by antierythrocyte autoantibodies, leading to haemoglobinaemia and haemoglobinuria

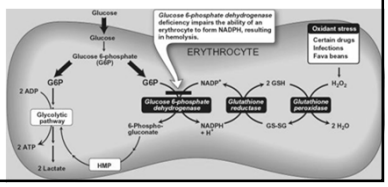
Cerebral malaria (black-water fever)



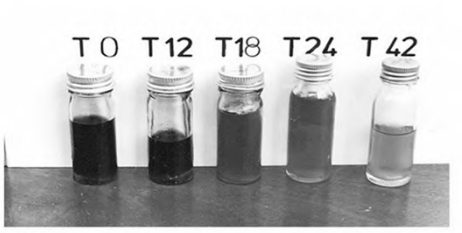


Glucose-6-Phosphate Deficiency:

- G6PD in a common enzyme deficiency associated with rapid hemolysis with certain Anti-malaria drugs
- MOA - Oxidative stress in RBC



Various States of Hemolysis:



Malaria Drug Classification:

1) 4-Aminoquinolines	**Chloroquine**
	Amodiaquine
2) Quinoline methanol	**Mefloquine**
3) Cinchona alkaloid	**Quinine**
	Quinidine
4) 8 - Aminoquinolines	**Primaquine**

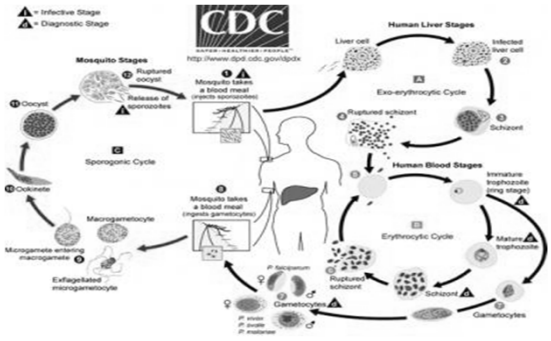
Malaria Drug Classification Cont.

Sesquiterpine lactones	**Artesunate**
	Artemether
	Arteether
Amino alcohols	**Halofantrine**
	Lumefantrine
Naphthyridine	**Pyronaridine**
Naphthoquinone	**Atovaquone**

U.S. Marines in Liberia 2003

- Marine Combat Task force deployed to provide security to Gov of Liberia during civil conflict.
- Approximately 225 marines were deployed to airport and within roughly 4 weeks nearly a 25% were evacuated with Falciparum malaria.
- The marines were receiving daily Malaria Chemoprophylaxis drugs

What Stage of Infection to Target?



Pre-erythrocytic Stage Vaccines

- How they work:
  - Generates Anti-body response against sporozoites and prevents them from invading the liver
  - Prevents intra-hepatic multiplication by killing parasite-infected hepatocytes
- Intended Use:
  - Ideal for travelers - protects against malaria infection

•Major Challenges to Success:

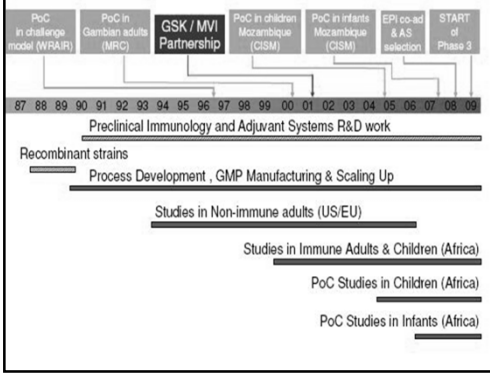
Scientific

- No vaccine in human use against a parasite
- Malaria parasite has ~6,000 genes, many more than a virus
- How to predict a vaccine candidate's success?

Commercial

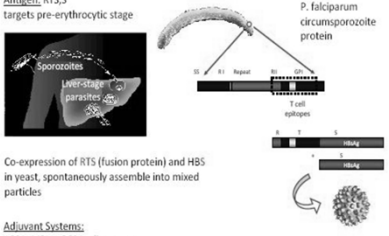
- Limited market in developed countries
- Malaria-endemic countries mostly poor
- Vaccine development is high-risk, high-cost

History and major Milestones of the RTS,S/AS Phase 2 program



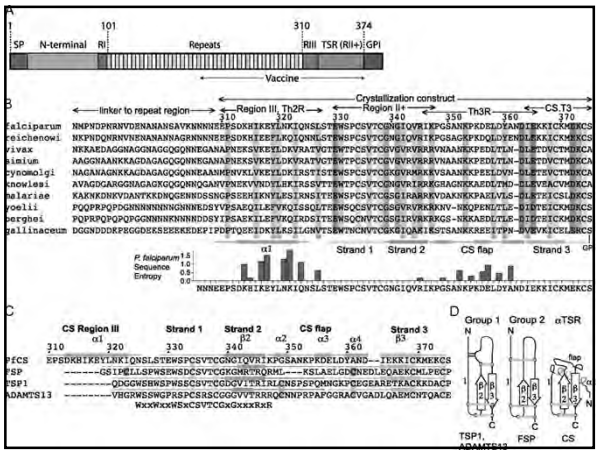
The RTS,S vaccine antigen and Adjuvant Systems

Antigen: RTS,S targets pre-erythrocytic stage



Co-expression of RTS (fusion protein) and HBS in yeast, spontaneously assemble into mixed particles

Adjuvant Systems:
AS01: MPL + QS21 + liposomes
AS02: MPL + QS21 + oil-in-water emulsion



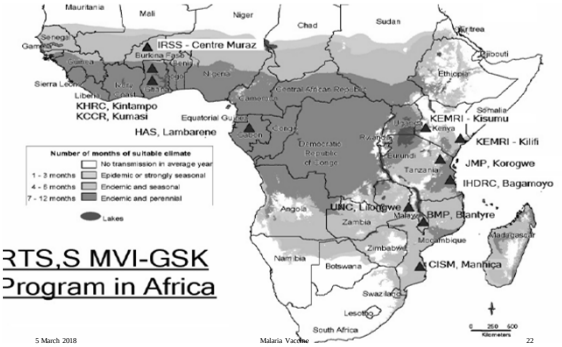
Primary Objectives of RTS,S Malaria Vaccine Trial:

- Test a vaccine capable of protecting infants & children residing in malaria endemic regions
- Reduce incidence of both clinical and severe disease from Plasmodium Falciparum
  - Ensure Vaccine is safe and well tolerated
  - Compatible with EPI vaccines
  - Complement existing malaria control measures

Progress: to Phase III

- Consistent efficacy in different transmission settings throughout Sub-Saharan Africa.
- Favorable safety and immunogenicity profiles
- Can be co-administered with routine EPI childhood immunizations.
- Induction of CS protein specific humoral immunity correlating with protection against repeated malaria infections.

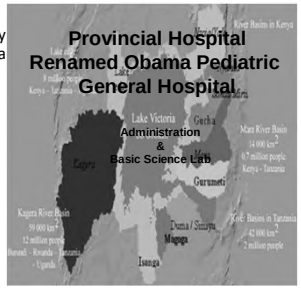
RTS,S Phase III Clinical Centers



RTS,S MVI-GSK Program in Africa

Why choose Nyanza Kenya for a Malaria Vaccine Trial?

- Lake Victoria region known for it's very high incidence of P. Falciparum malaria (Inci 25%per year)
- Affected population in the district 1.6 million



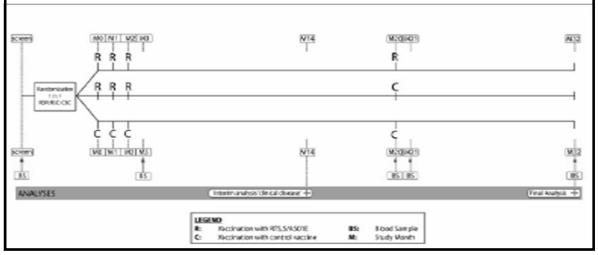
Study design Overview:

Randomized double blind controlled trial: 16,000 children

-6-12 weeks EPI co-administration

- Booster at 20 months

-Follow-up for a total of three years



Treatment groups and vaccination schedule

5-17 months	
Primary vaccination (0, 1, 2 mo schedule)	**Boost at M20**
RTS,S/AS01	RTS,S/AS01
RTS,S/AS01	MCC Vaccine
Rabies Vaccine	MCC Vaccine

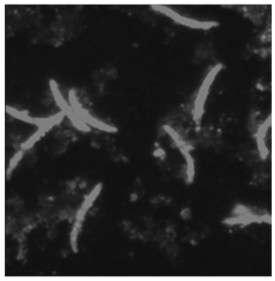
6-12 weeks	
Primary vaccination (0, 1, 2 mo schedule)	**Boost at M20**
RTS,S/AS01 + Tritanrix-HepB/Hib + OPV	RTS,S/AS01 + OPV
RTS,S/AS01 + Tritanrix-HepB/Hib + OPV	MCC Vaccine + OPV
MCC Vaccine + Tritanrix-HepB/Hib + OPV	MCC Vaccine + OPV

Immunogenicity

- The geometric mean titer (GMT) of anti–circumsporozoite antibody at enrollment was low in the two study groups and remained low in the control group.
- One month after the administration of the third dose of study vaccine, 99.9% of children in the RTS,S/AS01 group were positive for anti–circumsporozoite antibodies, with a geometric mean titer of 621 EU per milliliter (95% CI, 592 to 652).

Florescent Antibody Staining:

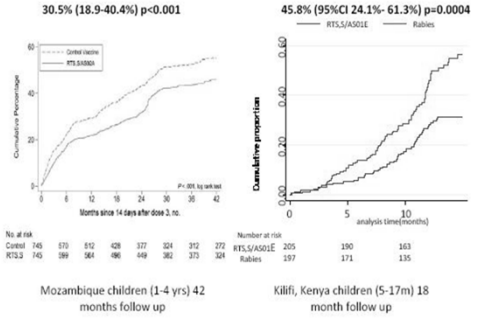
- FAS of specific circumsporozoite antibodies adhering to the outer surface of circumsporozoite



Milestones:

- First infant vaccinated on the 26th of May 2009 in Bagamoyo, Tanzania
- By December 2010 more than 11,000 infants and children had received at least 1 dose of RTS,S
- By Oct 2011 we had preliminary immunogenicity data on more than 6000 children

Efficacy of RTS,S to date



Mozambique children (1-4 yrs) 42 months follow up

Kilifi, Kenya children (5-17m) 18 month follow up

Goals to Progress to Licensure:

- Consistent efficacy in different transmission settings throughout Sub-Saharan Africa
- Favorable safety and efficacy data with limited reactogenicity
- Can be administered with minimal to no interpherence with EPI vaccines
- Induction of high levels of protective titers of anti-circumsporite antibodies profiles

Additional Studies in the Phase III Plan of Action:

- To study separately the safety and efficacy of RTS,S vaccine in infants who were positive for HIV
- Compare potency of vaccine 1 to 3 months following it's manufacture and production
- Study the effects on hepatitis B immunization as this is one of the EPI immunizations
- Efficacy in sickle cell disease patients

5 March 2018 Malaria Vaccine 31

Acknowledgements:

- **PATH/MVI**
- **GSK Biologicals**
- **Clinical Trials Partnership Alliance**
- **U.S. Army Medical Research MC**
- **MOH Kenya, Tanzania, Uganda**
- **The 11 Sites who volunteered to be part of the RTS,S/ASO1 clinical vaccine trials**

5 March 2018 H5N1 32

Centre for Global Health Research:

Collaboration Between Walter Reed & KMRI

5 March 2018 Malaria Vaccine 33

Questions!

5 March 2018 Malaria Vaccine 34