- Provision of signed or thumb printed and dated informed consent form
- Stated willingness to comply with all study procedures and availability for the duration of the study
- Male or female between 18 and 55 years of age, inclusive
- In good general health as evidenced by medical history and clinical examination before entering the study
- Ability to take oral medication and be willing to adhere to the medication regimen
- For females, she must be of non-childbearing potential or use appropriate measures to prevent pregnancy for 30 days prior to vaccination through 2 months after completion of the vaccine series. Non-childbearing potential means she is surgically sterilized or at least one year post-menopausal. Appropriate measures to prevent pregnancy include abstinence or adequate contraceptive precautions (i.e. intrauterine contraceptive device; oral contraceptives; diaphragm or condom in combination with contraceptive jelly, cream or foam; Norplant or Depo-Provera). Clinical trial site staff will assist with provision of acceptable birth control for study entry and will discuss with volunteer at screening visit.

Exclusion Criteria:

- Planned administration/administration of a vaccine not foreseen by the study protocol from within 30 days before the first dose of study vaccine until 30 days after the last dose of study vaccine.†

  † In the context of the COVID-19 pandemic, the administration of the COVID-19 vaccine will be allowed as an exception to this exclusion criteria as follows. The study team will work with the participant to attempt to have any COVID-19 vaccine administration occur 30 days or more before or after study vaccinations. When this is not possible, COVID-19 vaccination will be allowed 10 days or more before or after study vaccination. Intervals shorter than 10 days can be allowed on a case-by-case basis in discussion with the sponsor.

- Any prior receipt of any rabies vaccine or experimental malaria vaccine.
- Confirmed or suspected significant immunosuppressive or immunodeficient condition as determined by the investigator, including clinical stage 3 or 4 human immunodeficiency virus (HIV) infection.
- A family history of congenital or hereditary immunodeficiency.
- History of allergic reactions, significant immunoglobulin E (IgE)-mediated events or anaphylaxis to previous immunizations.
- History of any neurologic disorders.
- Acute disease (defined as the presence of a moderate or severe illness with or without fever), including acute malaria, at the time of enrolment. All vaccines can be administered to persons with a minor illness, such as diarrhea or mild upper respiratory infection without fever, i.e. Oral temperature < 37.5°C*. Individuals excluded with acute disease, including acute malaria, can become eligible again after complete recovery of the illness, including appropriate treatment as applicable, and can be rescreened at a later date. *Temperature readings may be taken by site staff either using either oral, axillary, or infrared thermal thermometers during clinic or field visits, while subjects enrolled in the reactogenicity cohort will be supplied with oral thermometers for the purposes of recording their own temperature measurements in the memory aid over 7 days after each vaccination.
- Acute or chronic, clinically significant pulmonary, cardiovascular (including cardiac arrythmias) , hepatic or renal functional abnormality, as determined by medical history, physical examination or laboratory screening tests.
- History of homozygous sickle cell disease (Hgb SS).
- Any clinically significant laboratory abnormalities as determined by the investigator on screening labs.
- History of splenectomy.
- Administration of immunoglobulins, blood transfusions or other blood products within the three months preceding the first dose of study vaccine or planned administration during the study period.
- Pregnant (i.e. a positive pregnancy test) or lactating female during immunization phase of the study (refer to section 2.3 for rationale). If a woman becomes pregnant after all vaccinations are complete, she will not be excluded from the remainder of the study.
- Female planning to become pregnant or planning to discontinue contraceptive precautions during the vaccination phase.
- History of chronic alcohol consumption and/or drug abuse.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose (for corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed).
- Major congenital defects or serious chronic illness.
- Simultaneous participation in any other clinical trial [apart from participation in the Health and Demographics Surveillance System (HDSS) network].
- Any other findings that the investigator feels would increase the risk of having an adverse outcome from participation in the trial.

Contacts and Locations

Locations

Kenya

Lucas O Tina

Kisumu, Kisumu County, Kenya, 40100

Investigators

Principal Investigator: Lucas O Tina, MD, MTM&H Kombewa Clinical Research Center

Study Documents (Full-Text)

Documents provided by PATH

Study Protocol [PDF] April 6, 2023

Statistical Analysis Plan [PDF] April 15, 2023

More Information

Publications:

RTS,S Clinical Trials Partnership; Agnandji ST, Lell B, Soulanoudjingar SS, Fernandes JF, Abossolo BP, Conzelmann C, Methogo BG, Doucka Y, Flamen A, Mordmuller B, Issifou S, Kremsner PG, Sacarlal J, Aide P, Lanaspa M, Aponte JJ, Nhamuave A, Quelhas D, Bassat Q, Mandjate S, Macete E, Alonso P, Abdulla S, Salim N, Juma O, Shomari M, Shubis K, Machera F, Hamad AS, Minja R, Mtoro A, Sykes A, Ahmed S, Urassa AM, Ali AM, Mwangoka G, Tanner M, Tinto H, D'Alessandro U, Sorgho H, Valea I, Tahita MC, Kabore W, Ouedraogo S, Sandrine Y, Guiguemde RT, Ouedraogo JB, Hamel MJ, Kariuki S, Odero C, Oneko M, Otieno K, Awino N, Omoto J, Williamson J, Muturi-Kioi V, Laserson KF, Slutsker L, Otieno W, Otieno L, Nekoye O, Gondi S, Otieno A, Ogutu B, Wasuna R, Owira V, Jones D, Onyango AA, Njuguna P, Chilengi R, Akoo P, Kerubo C, Gitaka J, Maingi C, Lang T, Olotu A, Tsofa B, Bejon P, Peshu N, Marsh K, Owusu-Agyei S, Asante KP, Osei-Kwakye K, Boahen O, Ayamba S, Kayan K, Owusu-Ofori R, Dosoo D, Asante I, Adjei G, Adjei G, Chandramohan D, Greenwood B, Lusingu J, Gesase S, Malabeja A, Abdul O, Kilavo H, Mahende C, Liheluka E, Lemnge M, Theander T, Drakeley C, Ansong D, Agbenyega T, Adjei S, Boateng HO, Rettig T, Bawa J, Sylverken J, Sambian D, Agyekum A, Owusu L, Martinson F, Hoffman I, Mvalo T, Kamthunzi P, Nkomo R, Msika A, Jumbe A, Chome N, Nyakuipa D, Chintedza J, Ballou WR, Bruls M, Cohen J, Guerra Y, Jongert E, Lapierre D, Leach A, Lievens M, Ofori-Anyinam O, Vekemans J, Carter T, Leboulleux D, Loucq C, Radford A, Savarese B, Schellenberg D, Sillman M, Vansadia P. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med. 2011 Nov 17;365(20):1863-75. doi: 10.1056/NEJMoa1102287. Epub 2011 Oct 18.

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Responsible Party: PATH

ClinicalTrials.gov Identifier: NCT04661579

Other Study ID Numbers: CVIA 078
PACTR202006896481432

Last Verified: January 2024

Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD: No

Human Subjects Protection Review Board Status: Approved

Studies a U.S. FDA-regulated Drug Product: No

Studies a U.S. FDA-regulated Device Product: No

Study Results

Participant Flow

Recruitment Details	Participants were recruited from the villages in the Kombewa Health and Demographics Surveillance System (HDSS) consisting of half of Kisumu West and all of Seme sub-counties of Kisumu County, Kenya. Prior to enrollment participants were tested for the presence or absence of asymptomatic infection with Plasmodium falciparum (P. falciparum, the parasite that causes malaria) measured using a highly sensitive polymerase chain reaction (PCR) assay.
Pre-assignment Details	Participants were stratified by baseline P. falciparum parasitemia status and then block randomized. The first 105 participants who were positive for parasitemia at baseline were randomized in a 1:1:1 ratio with 35 participants assigned to each of Groups 1, 3 and 4. The next 258 participants with baseline parasitemia were randomized in a 1:1 ratio to Groups 1 and 4. Participants who were negative for parasitemia at baseline were randomized in a 1:1 ratio to Groups 2 and 5.

Arm/Group Title	Group 1: Positive Parasitemia; Anti-malarial Treatment + RTS,S/AS01E Vaccine	Group 2: No Parasitemia; Anti-malarial Prophylaxis + RTS,S/AS01E Vaccine	Group 3: Positive Parasitemia; RTS,S/AS01E Vaccine	Group 4: Positive Parasitemia; Anti-malarial Treatment + Rabies Vaccine	Group Parasiten malarial Pro Rabies V
Arm/Group Description	Participants with detectable Plasmodium falciparum parasitemia at baseline received anti-malarial treatment with dihydroartemisinin-piperaquine (DHA/Pip) plus low dose primaquine (LD PQ) 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a course of artemether/lumefantrine (A/L) plus LD PQ was administered. Participants were randomized to receive 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants were randomized to receive 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with detectable P. falciparum parasitemia at baseline did not receive any anti-malarial medications to clear parasites. Participants were randomized to receive 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations. This group is included only for immunological assessment and not for vaccine efficacy.	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with dihydroartemisinin-piperaquine (DHA/Pip) plus low dose primaquine (LD PQ) 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a three-day course of artemether/lumefantrine (A/L) plus LD PQ was administered. Participants were randomized to receive 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.	Participants detectable P parasitemia received anti prophylaxis DHA/Pip plus weeks prior t vaccination a course of DH LD PQ 2 wee the second v One week be third vaccina course of A/L PQ was adm Participants randomized vaccinations Abhayrab ral vaccine on a month schec

immunizations.

Period Title: **Overall Study**

Started	164	128	36	164	128
Received Study Vaccination	160	124	35	159	127
Completed	136	108	32	148	115
Not Completed	28	20	4	16	13
Reason Not Completed					
Lost to Follow-up	19	10	2	7	
Physician Decision	2	0	0	1	
Withdrawal by Subject	1	4	0	2	
Death	1	0	0	0	
Other NOTE : "Other" is not sufficiently descriptive for "Other" Reason Not Completed. Please provide a more descriptive label.	1	2	1	1	
Randomized but Did Not Receive Study Product	4	4	1	5	
(Not Public)	Not Completed =28 Total from all reasons =28	Not Completed =20 Total from all reasons =20	Not Completed =4 Total from all reasons =4	Not Completed =16 Total from all reasons =16	Not Total from

Baseline Characteristics

NOTE : A Study Specific Baseline Measure for an Outcome Measure has not been entered.

Arm/Group Title	Group 1: Positive Parasitemia; Anti-malarial Treatment + RTS,S/AS01E Vaccine	Group 2: No Parasitemia; Anti-malarial Prophylaxis + RTS,S/AS01E Vaccine	Group 3: Positive Parasitemia; RTS,S/AS01E Vaccine	Group 4: Positive Parasitemia; Anti-malarial Treatment + Rabies Vaccine	Group 5: No Parasitemia, Anti-malarial Prophylaxis + Rabies Vaccine	Total
Arm/Group Description	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants were randomized to receive 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants were randomized to receive 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with detectable P. falciparum parasitemia at baseline did not receive any anti-malarial medications to clear parasites. Participants were randomized to receive 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations. This group is included only for immunological assessment and not for vaccine efficacy.	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a three-day course of A/L plus LD PQ was administered. Participants were randomized to receive 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.	Participants with no detectable P. falciparum parasitemia at baseline received anti-malarial prophylaxis with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and a 2nd course of DHA/Pip plus LD PQ 2 weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants were randomized to receive 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.	

Baseline Participants

▼ Baseline Analysis Population Description		The total vaccinated cohort (TVC) includes all randomized participants who received at least one vaccination.					
Age, Continuous Mean (Standard Deviation) Unit of measure: years	Number Analyzed	160 participants	124 participants	35 participants	159 participants	127 participants	605 participants
		31.94 (8.04)	34.02 (7.63)	34.57 (8.93)	31.76 (8.49)	34.04 (8.04)	32.91 (8.19)
Sex: Female, Male Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	160 participants	124 participants	35 participants	159 participants	127 participants	605 participants
	Female	72 45%	80 64.52%	21 60%	75 47.17%	75 59.06%	323 53.39%
	Male	88 55%	44 35.48%	14 40%	84 52.83%	52 40.94%	282 46.61%
Race (NIH/OMB) Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	160 participants	124 participants	35 participants	159 participants	127 participants	605 participants
	American Indian or Alaska Native	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
	Asian	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
	Native Hawaiian or Other Pacific Islander	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
	Black or African American	160 100%	124 100%	35 100%	159 100%	127 100%	605 100%
	White	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
	More than one race	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
	Unknown or Not Reported	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
Race/Ethnicity, Customized Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	160 participants	124 participants	35 participants	159 participants	127 participants	605 participants
	Luo	158 98.75%	122 98.39%	35 100%	159 100%	125 98.43%	599 99.01%
	Luhya	2 1.25%	2 1.61%	0 0%	0 0%	2 1.57%	6 0.99%
Region of Enrollment Measure Type: Number Unit of measure: participants	Number Analyzed	160 participants	124 participants	35 participants	159 participants	127 participants	605 participants
Kenya		160	124	35	159	127	605

Outcome Measures

1. Primary Outcome

Title:	Time to First PCR-detectable Malaria Infection During the Active Detection of Infection (ADI) Phase in Groups 1 and 4
▼ Description:	Participants were actively monitored for malarial infection starting 2 weeks after the third vaccination. Blood samples were assayed using a highly sensitive polymerase chain reaction (PCR) (Plasmodium falciparum/ Pan-Plasmodium 18S ribosomal ribonucleic acid (rRNA) laboratory developed test [LDT]) that can detect sub-clinical parasitemia at the US Army Medical Research Directorate-Africa (USAMRD-A) / Kenya Medical Research Institute (KEMRI) laboratories in Kisumu, Kenya. A positive PCR result from blood samples collected during the ADI was recorded as a positive event for the presence of P. falciparum blood stage infection. The time to first malaria infection is expressed in terms of rate of first malaria infection, that is, the number of malaria infection events reported over the time period elapsed until the event occurred (i.e. events per Persons Year at Risk

Time Frame:	The active detection of infection phase began 2 weeks after the third vaccination (approximately week 30) for up to 35 weeks. Participants provided blood samples every 21 days during the ADI phase for PCR assays.

▼ Outcome Measure Data ✔

▼ Analysis Population Description

The primary endpoint was pre-specified to be analyzed in Groups 1 and 4 only. The According to Protocol (ATP) cohort for efficacy includes all participants in the TVC with no major protocol deviations that could potentially interfere with the efficacy assessment of the study vaccine and who contributed to the time at risk starting 14 days after the third dose.

Arm/Group Title	Group 1: Positive Parasitemia; Anti-malarial Treatment + RTS,S/AS01E Vaccine	Group 4: Positive Parasitemia; Anti-malarial Treatment + Rabies Vaccine
▼ Arm/Group Description:	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a course of A/L plus LD PQ was administered. Participants received 3 vaccinations with malarial vaccine RTS,S/AS01E by intramuscular injection given on a 0, 1, and 7 month schedule with the final dose being 1/5 of the dose of the first two immunizations.	Participants with detectable P. falciparum parasitemia at baseline received anti-malarial treatment with DHA/Pip plus LD PQ 4 weeks prior to the first vaccination and another course of DHA/Pip plus LD PQ two weeks before the second vaccination. One week before the third vaccination, a three-day course of A/L plus LD PQ was administered. Participants received 3 vaccinations of Abhayrab rabies vaccine on a 0, 1, 7 month schedule.
Overall Number of Participants Analyzed	151	151
Measure Type: Number Unit of Measure: Events per person year at risk	1.01	1.49

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Group Selection	Group 1: Positive Parasitemia; Anti-malarial Treatment + RTS,S/AS01E Vaccine, Group 4: Positive Parasitemia; Anti-malarial Treatment + Rabies Vaccine
	Comments	Vaccine efficacy against the first PCR-positive P. falciparum infection among adults who were P. falciparum positive at baseline was assessed using Cox proportional hazards regression model with a covariate for group assignment to compare Groups 1 and 4. HIV status, Age (tertiles), and sleep under a bednet were included as covariates.
	Type of Statistical Test	Other
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.009
	Comments	[Not specified]
	Method	Other [Wald test]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other[Vaccine Efficacy]
	Estimated Value	35.9
	Confidence Interval	(2-Sided) 95% 10.3 to 54.2
	Estimation Comments	Vaccine efficacy (VE) is defined as the percent reduction in the hazard, i.e. one minus the hazard ratio (HR, RTS,S/AS01E Vaccine vs. Rabies vaccine).

2. Secondary Outcome

Title:	Time to First PCR-detectable Malaria Infection During the Active Detection of Infection Phase in Groups 2 and 5
▼ Description:	Participants were actively monitored for malarial infection starting 2 weeks after the third vaccination. Blood samples were assayed using a highly sensitive PCR (Plasmodium falciparum/ Pan-Plasmodium 18S rRNA LDT) that can detect sub-clinical parasitemia. A positive PCR result from blood samples collected during the ADI phase was recorded as a positive event for the presence of P. falciparum blood stage infection. The time to first malaria infection is expressed in terms of rate of first malaria infection, that is, the number of malaria infection events reported over the time period elapsed until the event occurred (i.e. events per Persons Year at Risk [PYAR]) for each group.