Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: http://www.tandfonline.com/loi/khvi20

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To cite this article: Shima Mahmoudi & Hossein Keshavarz (2017): Efficacy of phase 3 trial of RTS, S/AS01 malaria vaccine: The need for an alternative development plan, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2017.1295906

To link to this article: http://dx.doi.org/10.1080/21645515.2017.1295906

Accepted author version posted online: 08 Mar 2017.
Published online: 08 Mar 2017.

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2017, VOL. 0, NO. 0, 1–4
http://dx.doi.org/10.1080/21645515.2017.1295906

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COMMENTARY

Efficacy of phase 3 trial of RTS, S/AS01 malaria vaccine: The need for an alternative development plan

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ABSTRACT

Although vaccines would be the ideal tool for control, prevention, elimination, and eradication of many infectious diseases, developing of parasites vaccines such as malaria vaccine is very complex. The most advanced malaria vaccine candidate RTS,S, a pre-erythrocytic vaccine, has been recommended for licensure by EMEA. The results of this phase III trial suggest that this candidate malaria vaccine has relatively little efficacy, and the vaccine apparently will not meet the goal of malaria eradication by itself. Since there are many vaccine candidates in the pipeline[1] that are being evaluated in vaccine trials, further study on using of alternative parasite targets and vaccination strategies are highly recommended.

ARTICLE HISTORY
Received 24 January 2017
Revised 4 February 2017
Accepted 13 February 2017

KEYWORDS
efficacy; RTS; S/AS01 malaria vaccine; vaccine development

Vaccines would be the ideal tool for control, prevention, elimination, and eradication of many infectious diseases. However, developing of parasites vaccines such as malaria vaccine is more complex than developing vaccines for viruses and bacteria in terms of their biology including their much larger genomes than viruses and bacteria and they having multiple stages of life cycles.[2]

There are many different approaches for development of malaria vaccines. Malaria vaccines can be categorized into 3 broad categories representing the 3 life-cycle stages in the human host: pre-erythrocytic, blood-stage and transmission-blocking vaccines.[3]

The current vaccine development pipeline is relatively diverse in each stage of parasite lifecycle[4] (Table 1).

Several candidate malaria vaccines are progressing through clinical trials[5,6] and many more are in pre-clinical development. The most advanced malaria vaccine candidate RTS,S, a pre-erythrocytic vaccine, has been recommended for licensure by EMEA and is the first vaccine to undergo large-scale phase 3 evaluation in Africa.[7-12]

This vaccine, RTS,S/AS, is based on the hepatitis B surface antigen virus-like particle (VLP) platform, genetically-engineered which include the carboxy terminus (amino acids 207–395) of the *P. falciparum* circumsporozoite (CS) antigen.[13] The hybrid malaria-hepatitis B VLP is formulated with GlaxoSmithKline's AS01 adjuvant, a mixture of liposomes, MPL and QS21.[14] This vaccine induces humoral and cellular immune responses to the CSP present on the surface of sporozoites and liver stage schizonts.[15]

In a phase 3 randomized, controlled trials in children and young infants at 11 African sites from March 27, 2009, through January 31, 2011, overall, 8,923 children and 6,537 young infants were enrolled. All randomized children and young infants were included in the ITT population, while 6,885 (77%) children and 6,003 (92%) young infants were included in the per-protocol population.[16]

The range of RTS,S/AS01 vaccine efficacy (VE) against all episode of clinical malaria in per- protocol population aged 5–17 months was 39–50% that was higher than children aged 6–12 mo (23–30%). In addition, the VE in intention-to-treat (ITT) population in this age was higher in children aged 5–17 (38–49%) than 6–12 mo groups (23–30%) (Table 2, Table 3). The range of RTS,S/AS01 VE against all episode of severe malaria in per- protocol population aged 5–17 months was 35–47% that was higher than children aged 6–12 mo (15–38%). In addition, the VE in intention-to-treat population in this age was higher in children aged 5–17 (34–44%) than 6–12 mo groups (8–28%) (Table 4, Table 5).

VE against clinical malaria in both per- protocol and intention- to- treat population aged 5–17 mo was 39–50% and 23–30%, respectively. Its efficacy against severe malaria in both populations was 39–50% and 23–30%, respectively. However, lower VE against clinical malaria and severe malaria in both populations in children aged 6–12 mo was seen (Tables 2-5).

There are several malaria vaccine candidates either pre-erythrocytic stages or the blood stage of the parasite life cycle are under clinical development.[1]

RTS,S has demonstrated clinical efficacy against both infection and clinical malaria in several well-designed phase II field efficacy trials in both adults and children.[10-12,17-19] In July 2015, RTS,S/AS01 was recommended for licensure approved by the European Medicines Agency for immunization of children aged 6 weeks to 17 months against malaria.[20]

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Table 1. Status of vaccine research and development of vaccines for malaria.

Vaccine	Phase I	Phase II	Pivotal
Pre-erythrocytic stage			
RTS,S/AS01	X	X	X
ChAd63/MVA ME-TRAP	X	X	
PfSPZ attenuated sporozoite	X	X	
Polyepitope DNA EP1300	X		
PfCelTOS FMP012	X		
CSVAC	X		
R21/AS01B	X		
Adenovirus (Ad35) and adenovirus 26 (Ad26) vectored CS	X		
PfCelTOS FMP012/AS01B	X		
PfCelTOS FMP012/GLA-SE	X		
RTS,S/AS01B + ChAd63/MVA (ME-TRAP)	X		
rCSP/GLA-SE	X		
Blood-stage			
EBA175 RII/aluminum phosphate	X		
FMP2.1/AS01B (AMA-1 3D7 E. coli)	X		
ChAd63/AMA MVA/AMA1	X		
ChAd63 MSP1/MVA MSP1	X		
GMZ2	X		
GMZ2 field	X	X	
pfAMA1-DiCo	X		
P27A	X		
MSP3	X		
MSP3 field		X	
SE36	X		
NMRC-M3V-Ad-PfCA	X	X	
PfPEBS	X		
ChAd63 RH5 +/− MVA RH5	X		
PRIMVAC	X		
Sexual stage			
Pfs25 VLP	X		
Pfs25-EPA/Alhydroge	X		
Pfs230D1M-EPA/Alhydrogel and/or Pfs25-EPA/Alhydrogel	X		
ChAd63 Pfs25-IMX313/MVA Pfs25-IMX313 P. vivax Project	X		
ChAd63/MVA PvDBP	X		

*This information is derived from "Tables of malaria vaccine projects globally, WHO," Ref#3, and that the source of references for all these vaccines may be found in that reference.

Table 2. Vaccine efficacy against all episodes of clinical malaria in children aged 5–17 mo at enrollment.

	RTS,S/ASO1 Vaccine		Control Vaccine				
Population	No. of Events	Person-Yr	No. of Events	Person-Yr	Risk ratio	Vaccine efficacy	Ref.
Per-protocol	1834	2495	1854	1263	0.50	0.50	21
Per-protocol	4257	61860	3639	31004	0.59	0.41	18
Per-protocol	6616	60945	5409	30318	0.61	0.39	18
Intention-to-treat	2343	4243	2289	2110	0.51	0.49	21
Intention-to-treat	5106	90591	4305	44844	0.59	0.41	18
Intention-to-treat	8207	89391	6482	44006	0.62	0.38	18
Month 0 to study end	6616	9957.6	9585	9994.9	0.69	0.31	20
Months 0–32	4078	7099.7	6768	7088.5	0.60	0.40	20
Months 0–20	5106	9059.1	4305	4484.4	0.59	0.41	20
Months21–32	1592	2601	2442	2609.9	0.65	0.35	20
Months 33 to study end	2539	2862.2	2817	2912	0.92	0.08	20
Months 21 to study end	4130	5458.9	5259	5516.3	0.79	0.21	20

In the per-protocol analysis, participants have received 3 doses of RTS,S/AS01 or control vaccine and 3 doses of co-administered vaccine (DTPwHepB/Hib and OPV) according to protocol procedures.

Case definition for clinical malaria: Documented fever as defined by axillary temperature measurement $\geq$ 37.5 ° C and parasite density above threshold derived using recent historical data appropriate to age by logistic regression method with sufficiently high specificity for all sites in a multi-site trial (a minimum of 80%).

RTS,S/AS01 provided protection against clinical and severe malaria, over an 18-mo follow-up period among infant and children at first vaccination across a wide range of malaria transmission settings.[16,21-23]

Although the efficacy of most common vaccines is in excess of 70–80%, the worldwide magnitude of the malaria problem justifies the pursuit of such vaccines, even if the efficacy of these vaccines is only about 30–50%.[3] The big challenge currently exist is the development of a malaria vaccine. Vaccine developers are faced with several problems with malaria due to residing of this organism in the peripheral-blood compartment and its circulation alongside of immune cells and proteins,[24] the antigenic variability of the parasite and the lack of reliable and predictive animal models.[25]

RTS,S/AS01 vaccination provides relatively little protection in infants and the higher rate of efficacy noted in older children decreases rapidly.[20,21] Possible reasons for the lower efficacy of RTS,S/AS01 include immunologic immaturity in neonates, interference from maternal antibodies, and prior exposure to malaria.[24]

Many reviewers agree that the formidable task of malaria eradication will not be accomplished with RTS,S vaccine alone.[26] As previously stated, the prospect of a lack of enduring protection remains a major disadvantage of this vaccine approach.[26] It was reported that sterile immunity can elicit through a vaccine due to the lack of real natural immunity to malaria. Therefore, these vaccines might be suitable for cases with before-quoted clinical immunity to decrease the burden of disease.[26,27]

On the other hand, from an economic point of view, this vaccine might not attain wide approvals worldwide due to its low efficacy. This approach is much less cost effective compare with scaling up malaria treatment and vector control programs.[26] Moreover, it seems unlikely that a vaccine intervening at one stage of the parasite's life cycle will successfully disrupt the entire life cycle each.[26]

Moreover, there are some issues about safety of the vaccine. An unexplained excess of meningitis cases has been reported in the RTS,S group.[28] Since the sex differences in all-cause mortality both clinical trials and experimental animal models have been reported, further reports into how the RTS,S vaccine is associated with greater mortality in girls should be rigorously studied.[29]

Due to the lack of highly efficacious vaccine approach to date, vector control programs, including insecticide-treated bed nets, artemisinin combination therapies and insecticides, should continue apply.[26]

It has been reported that Transmission-blocking vaccines (TBVs) in combination with poorly efficacious pre-erythrocytic vaccines or blood-stage vaccines might increase the efficacy of the RTS,S vaccine by blocking of infection from mosquito to human. (TBVs) target the entry of sexual stage into the *Anopheles stephensi* mosquito thereby preventing transmission.[30] However, they would not block disease in the vaccine recipients directly and can reduce the prevalence of malaria in a population complementing current vector control strategies.[30,31]

Although the performance of RTS,S/AS01 vaccine was disappointing in sub-Saharan African children, the potential

Table 3. Vaccine efficacy against all episodes of clinical malaria in children aged 6–12 mo at enrollment.

Population	RTS,S/ASO1 Vaccine		Control Vaccine		Risk ratio	Vaccine efficacy	Ref.
	No. of Events	Person-Yr	No. of Events	Person-Yr			
Per-protocol	2301	3604	1626	1790	0.70	0.30	19
Per-protocol	3848	53968	2464	26740	0.77	0.23	18
Per-protocol	5781	53214	3718	26246	0.77	0.23	18
Intention-to-treat	2615	4688	1864	2345	0.70	0.30	19
Intention-to-treat	4252	65836	2751	32736	0.77	0.23	18
Intention-to-treat	6564	64946	4221	32164	0.77	0.23	18
Month 0 to study end	4993	6156.4	6170	6147.3	0.81	0.19	20
Months 0–32	3842	5173.3	4916	5162.4	0.78	0.22	20
Months 0–20	4252	6583.6	2751	3273.6	0.77	0.23	20
Months21–32	1671	1888.4	2156	1889.3	0.78	0.22	20
Months 33 to study end	1154	984.9	1254	986.1	0.92	0.08	20
Months 21 to study end	2822	2871.5	3410	2874.2	0.83	0.17	20

In the per-protocol analysis, participants have received 3 doses of RTS,S/AS01 or control vaccine and 3 doses of co-administered vaccine (DTPwHepB/Hib and OPV) according to protocol procedures.

Case definition for clinical malaria: Documented fever as defined by axillary temperature measurement $\geq$ 37.5 ° C and parasite density above threshold derived using recent historical data appropriate to age by logistic regression method with sufficiently high specificity for all sites in a multi-site trial (a minimum of 80%).

of short-term efficacy of this vaccine could be used in other regions and other age groups. There are global efforts on elimination of malaria particullarly in Southeast Asian areas with high antimalarial drug resistance.[20] Therefore, integration of RTS,S/AS01 into elimination strategies might be useful to improve the chances of success.

Table 4. Vaccine efficacy against all episodes of severe malaria in children aged 5–17 mo at enrollment.

Population	RTS,S/ASO1 Vaccine		Control Vaccine		Risk ratio	Vaccine efficacy	Ref.
	No. of Events	Person-Yr	No. of Events	Person-Yr			
Per-protocol	120	4557	95	2328	0.65	0.35	18
Per-protocol (primary)	57	2830	56	1466	0.53	0.47	21
Per-protocol (secondary)	74	2830	72	1466	0.53	0.47	21
Intention-to-treat	156	5949	118	2974	0.66	0.34	18
Intention-to-treat (primary)	81	3997	74	2003	0.55	0.45	21
Intention-to-treat (secondary)	102	3997	92	2003	0.56	0.44	21
Month 0 to study end	116	2976	171	2974	0.68	0.32	20
Months 0–32	99	2976	152	2974	0.65	0.35	20
Months 0–20	156	5949	118	2974	0.66	0.34	20
Months21–32	43	2679	42	2701	1.03	−0.03	20
Months 33 to study end	23	2236	20	2309	1.19	−0.19	20
Months 21 to study end	64	2681	62	2702	1.04	−0.04	20

In the per-protocol analysis, participants have received 3 doses of RTS,S/AS01 or control vaccine and 3 doses of co-administered vaccine (DTPwHepB/Hib and OPV) according to protocol procedures.

Case definition for severe malaria: a proposed case definition for malaria for malaria vaccine trials *P. falciparum* parasitaemia and one or more of the following criteria: prostration, respiratory distress, blantyre coma score $\leq$ 2, seizures; 2 or more hypoglycaemia $<$ 2.2 mmol, a naemia $<$ 5 g/dl and without any of the following pneumonia (clinical assessment and CXR), meningitis (based on CSF examination), bacteraemia (based on blood culture) and astroenteritis (clinical assessment).

Table 5. Vaccine efficacy against all episodes of severe malaria in children aged 6–12 mo at enrollment.

Population	RTS,S/ASO1 Vaccine		Control Vaccine		Risk ratio	Vaccine efficacy	Ref.
	No. of Events	Person-Yr	No. of Events	Person-Yr			
Per-protocol	58	3995	46	2008	0.63	0.37	19
Per-protocol	63	3995	51	2008	0.62	0.38	19
Per-protocol	100	3996	59	2007	0.85	0.15	18
Intention-to-treat	77	4358	52	2179	0.74	0.26	19
Intention-to-treat	83	4358	58	2179	0.72	0.28	19
Intention-to-treat	121	4358	66	2179	0.92	0.08	18
Month 0 to study end	96	2180	116	2179	0.83	0.17	20
Months 0–32	89	2180	101	2179	0.88	0.12	20
Months 0–20	121	4358	66	2179	0.92	0.08	20
Months21–32	29	1966	43	1976	0.68	0.32	20
Months 33 to study end	12	1654	16	1657	0.75	0.25	20
Months 21 to study end	39	1966	58	1976	0.68	0.32	20

In the per-protocol analysis, participants have received 3 doses of RTS,S/AS01 or control vaccine and 3 doses of co-administered vaccine (DTPwHepB/Hib and OPV) according to protocol procedures.

Case definition for severe malaria: a proposed case definition for malaria for malaria vaccine trials *P. falciparum* parasitaemia and one or more of the following criteria: prostration, respiratory distress, blantyre coma score $\leq$ 2, seizures; 2 or more hypoglycaemia $<$ 2.2 mmol, a naemia $<$ 5 g/dl and without any of the following pneumonia (clinical assessment and CXR), meningitis (based on CSF examination), bacteraemia (based on blood culture) and astroenteritis (clinical assessment).

In conclusion, the efficacy of RTS, S/AS01 vaccine in infants is relatively low, and the vaccine apparently will not meet the goal of malaria eradication by itself. A malaria vaccine would be an important tool for preventive and treatment measures, but it needs further well-designed long-term studies before it's introduce as a vaccine in the Expanded Programme for Immunizations. Since there are many vaccine candidates in the pipeline[1] that are being evaluated in vaccine trials, further study on using of alternative parasite targets and vaccination strategies are highly recommended.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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