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REVIEW

Systematic Review of Safety of RTS,S with AS01 and AS02 Adjuvant Systems Using Data from Randomized Controlled Trials in Infants, Children, and Adults

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Background: Emergence of antimalarial drugs and insecticides resistance alarms scientists to develop a safe and effective malaria vaccine. A pre-erythrocytic malaria vaccine called RTS,S has made great strides.

Aim: The review was aimed to assess the safety of the candidate malaria vaccine RTS,S with AS01 and AS02 adjuvants using data from Phase I–III randomized controlled clinical trials (RCTs).

Methods: This systematic review was conducted based on PRISMA 2020. Regardless of time of publication year, all articles related with safety of RTS,S, RCTs published in the English language were included in the study. The last search of databases, and registry was conducted on 30 May, 2022. Pubmed, Google Scholar, Cochrane Library, Wiley Online Library, and Clinical trials.gov were thoroughly searched for accessible RCTs on the safety of RTS,S malaria vaccine. The studies were screened in three steps: duplicate removal, title and abstract screening, and full-text review. The included studies' bias risk was assessed using the Cochrane risk of bias tool for RCTs. This systematic review is registered at Prospero (registration number: CRD42021285888). The qualitative descriptive findings from the included published studies were reported stratified by clinical trial phases.

Findings: A total of thirty-five eligible safety studies were identified. Injection site pain and swelling, febrile convulsion, fever, headache, meningitis, fatigue, gastroenteritis, myalgia, pneumonia, reactogenicity, and anemia were the most commonly reported adverse events. Despite few clinical trials reported serious adverse events, none of them were related to vaccination.

Conclusion: Most of the adverse events observed from RTS,S/AS01 and RTS,S/AS02 malaria vaccines were reported in the control group and shared by other vaccines. Hence, the authors concluded that both RTS,S/AS01 and RTS,S/AS02 malaria vaccines are safe.

Keywords: RTS,S/AS01, RTS,S/AS02, safety, systematic review, randomized controlled trials

Introduction

Malaria cases increased from 227 million in 2019 to 241 million in 2020. In the same year, 627000 malaria-related deaths were estimated. Sub-Saharan Africa accounts for the majority of cases and fatalities. *Plasmodium falciparum* is the most lethal of the five *Plasmodium* parasite species that cause human malaria.[1] To prevent infection, reduce morbidity, and treat malaria, World Health Organization (WHO) recommends use of vector control, chemoprevention, diagnostic testing, and treatment.[2]

The bulk of pesticides is now ineffective against mosquitoes, putting malaria prevention efforts in jeopardy.[3] In addition, *Plasmodium* parasites become resistant to the antimalarial drugs that are now available. The use of antimalarial drugs kills sensitive *plasmodium* parasites leaving resistant ones. Hence, resistance *plasmodium* parasites could be passed

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on to succeeding people and cause antimalarial drug resistance.[4,5] Making malaria vaccinations is thus one way to eradicate the disease.[6] RTS,S is the pre-erythrocytic malaria vaccine candidate that has currently made the most strides.[7,8]

GlaxoSmithKline (GSK) and the Walter Reed Army Institute of Research (WRAIR) developed the RTS,S malaria vaccine in 1987. The National Institutes of Health and WRAIR discovered the genetic structure of the CSP antigen, sequenced it, and created a genetic clone.[9–12] The C terminals of the CSP were added, which carry epitopes for both B and T cells, and the Hepatitis B surface antigen was used as a CSP carrier matrix for the NF54 strain of P. falciparum.[13] The "R" in the RTS,S vaccine is the core repeat region, which is made up of one chain of N-acylneuraminate-9-phosphatase (NANP) amino acid tandem repeat tetrapeptides. T cells' immunodominant segregated epitopes and hepatitis B surface antigen are represented by the letters "T" and "S", respectively.[14–16] These antigens were created by expressing a genetically altered yeast strain in Saccharomyces cerevisiae yeast cells that already contained a "S" expression cassette. As a result, the strain produced RTS and S at a 1:4 ratio.[17]

Researchers at GSK exposed the RTS,S vaccine to a broad variety of adjuvants, and nearly every one of them was successful. RTS,S had been tested with a variety of adjuvants like ASO2A, which is a combination of oil-in-water emulsion (AS02, AS03),[18] and AS01, which is the combination of QS-21, liposomes, and Monophosphoryl lipid A (MPL).[19]

Any vaccine candidate must have its safety profile evaluated by pre-clinical and clinical trial investigations before being approved for human use. This systematic review aimed to provide updated information on the safety of RTS,S/AS01 and RTS,S/AS02 malaria vaccines. In order to investigate the safety of the RTS,S/AS01 and RTS,S/AS02 malaria vaccines, this systematic review looked at papers from phases I, II, and III of randomized controlled trials (RCT) in infants, children, and adults.

Methods

This complete overview of the key findings from the studies carried out to assess the safety of the RTS,S malaria vaccine with AS01 and 02 adjuvants was provided by the systematic review, which was conducted based on PRISMA 2020.[20] (Supplementary File 1).

Prospero Registration and Amendments to the Protocol

(Supplementary File 2).

Eligibility Criteria

Inclusion Criteria

Study setting: This study incorporated researches conducted world wide.

Study units: The study included studies on the safety of RTS,S with AS01 and AS02 adjuvants.

Publication status: The research included published articles.

Language: In this review, researches written in English were incorporated.

Study type: RCTs were included.

Publication year: Regardless of time of publication year, all articles related with safety of RTS,S with AS01 and AS02 adjuvants were included.

Type of article: In this review, only full-text articles were included.

Exclusion Criteria

The analysis rejected studies that did not report the safety of RTS,S with AS01 and AS02 adjuvants, were not available in full text, were not published in English, and were conducted in vitro or on animals.

Information Sources

The last search of databases and registry was performed on 30 May 2022 EC. The studies were discovered using databases such as Pubmed, Google Scholar, Cochrane Library, Wiley Online Library, and Clinical trials.gov registry.

Search Strategy

The articles were searched by WY, BK, BA, MG, DA, YA, HB, and BH using the keywords of ("RTS" OR "RTS,S" OR "RTS,S/AS01" OR "RTS,S/AS02" OR "RTS,S/SBAS2" AND "Vaccine" OR "malaria vaccine" OR "Vaccination" OR "Vaccines" OR "Malaria vaccines'). The same search strategy was used on all the databases.

Risk of Bias Assessment

The Cochrane risk of bias tool for RCTs[21,22] was used to evaluate the quality of the included studies. Procedures such as the randomization process, deviations from the intended interventions, measurement of the outcome data, gaps in the outcome analysis, and reported result selection.

Data Selection, and Collection Process

The search results were first filtered using the study title and abstract followed by full texts. The chosen studies were scanned in accordance with the inclusion criteria before the finished papers were included in this review. Reference lists of pertinent publications were also looked through in order to locate further applicable studies. All of the duplicates were removed, but if more than one published study was found on the same current trial, they were all included because the outcomes were evaluated differently in each published study. The finalized articles, were independently screened and extracted the pertinent information. In the screened studies, disagreements were discussed and resolved. Data extraction was done using Microsoft Excel 16 and tables were created using Microsoft Word.

Data Items (Outcomes)

All results related to safety of RTS,S malaria vaccine with AS01 and AS02 adjuvants were sought for screening.

Results

Systematic Search and Study Characteristics

A literature search on different databases and registry (1st April –30th May 2022) yielded a total of 4118 articles. 118 articles were sought after reviewing the titles and abstracts of the articles. Further 83 articles were removed after a full-length review. Finally, 35 RCTs were selected to be included in the review (Figure 1).

All of the 35 articles, were studies on RCTs categorized under phases I, I/II, II, III clinical trials with 3 (8.57%), 4 (11.43%), 21 (60.00%), and 7 (20.00%) studies respectively. The studies were conducted on RTS,S/AS01 (16 studies), RTS,S/AS02 (14 studies), and on both vaccines simultaneously (5 studies). The majority of the studies were conducted in Sub-Saharan Africa followed by USA, UK, and Belgium with a total of 26, 927 infants, children and adults. (Table 1)

Quality Assessment

The studies that we used underwent a quality assessment. All of the selected studies had low risks of selection, performance, detection, and reporting biases due to the proper execution of these RCTs, which included the randomization process, deviations from the intended interventions, measurement of the outcome data, gaps in the outcome analysis, and reported result selection. In conclusion, the included studies had high methodological quality and a small likelihood of bias (Figure 2).

Safety Results of RTS,S/AS01 and RTS,S/AS02

The safety profiles of RTS,S/AS01 and RTS,S/AS02 were examined and published in a total of 35 articles. Each vaccination schedule was well-tolerated and had respectable safety profiles. The RTS,S/AS01 and RTS,S/AS02 safety results have been divided into Phase I, phase I/II, Phase II, and Phase III clinical trials for convenience of understanding. Adverse events reported by over two studies were categorized under clinical trial phases and summarized in Table 2. (Table 2)

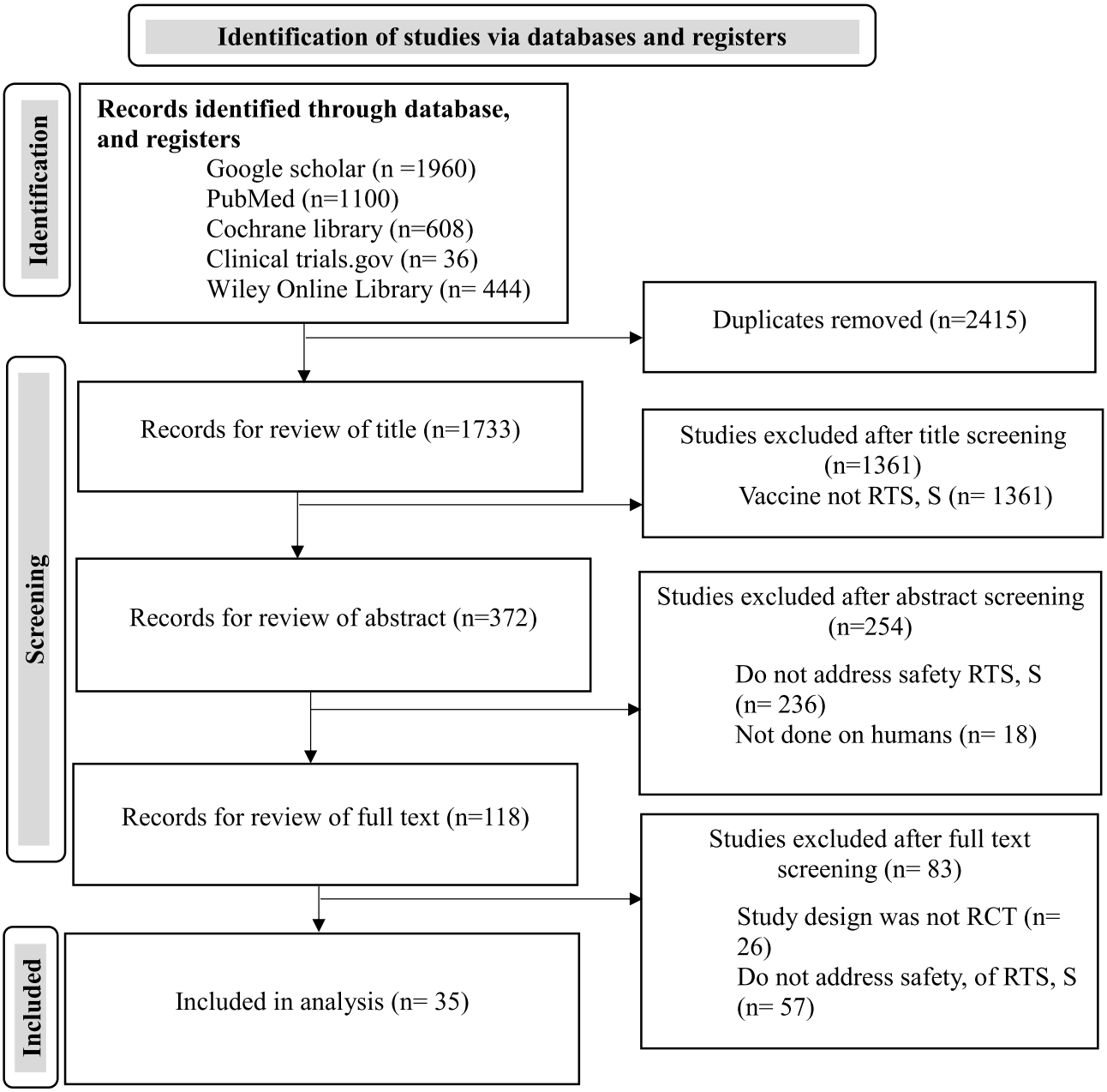

Figure 1 Flow diagram of the study selection to assess the safety of RTS,S malaria vaccine.
Notes: PRISMA figure adapted from Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *Syst Rev.* 2021;10(1):89. Creative Commons.[20]

Safety of RTS,S from Phase I and Phase I/II Clinical Trial Studies

All phase I and Phase I/II clinical trials aimed to study the safety of RTS,S were conducted on AS02 (formerly called SBAS2) adjuvant system. A total of 7 phase I and phase I/II studies were conducted on 564 children aged 1–11 years and 183 adults in USA, Belgium, Gambia, Mozambique, and Kenya. (Table 1)

Kester et al[23,24] demonstrated that none of the immunization schedules were found to have caused any major adverse events. The incidence of local and general solicited symptoms was not statistically different between the RTS,S/AS02 and control groups, according to phase I and phase I/II clinical studies carried out in Sub-Saharan African nations, the United States, and Belgium. The local symptoms that were most frequently reported were discomfort and/or edema at the

Table 1 Characteristics of the Included Randomized Controlled Clinical Trial Studies on the Safety of RTS,S

Study Reference	Year	Phases of RCT	Adjuvant	Country	Sample Size	Age Range	Doses	Comparator
Kester et al[23]	2001	I/IIa-	SBAS2	USA	80	18–45 years	3	Hepatitis B vaccine and the adjuvant only
Kester et al[24]	2007	I/IIa-	AS02	USA	40	18–45 years	2	Infectivity control
Alonso et al[39]	2005	IIb-	AS02	Mozambique	2202	1–4 years	3	Seven-valent pneumococcal conjugate vaccine
Bojang et al[42]	2001	II	AS02	Gambia	306	18–45 years	3	Rabies vaccine
Alonso et al[40]	2004	IIb	AS02	Mozambique	1605	1–4 years.	3	Seven-valent pneumococcal conjugate vaccine
Macete et al[25]	2007	I/IIb-	AS02	Mozambique	200	3 to 5 years	3	Each formulation
Bojang et al[43]	2009	II	AS02	Gambia	306	18–45 years	4	Rabies vaccine
Aide et al[41]	2011	IIB	AS02	Mozambique	2022	1–4 years	3	Hepatitis B Vaccine
Kester et al[45]	2008	IIB	AS02	USA	52	18–45 years		Infectivity control
Abdulla et al[44]	2008	IIB	AS02	Tanzania	340	7.8 weeks mean age	3	Hepatitis B vaccine
Macete et al[26]	2007	I	AS02	Mozambique	60	1–4 years	3	Hepatitis B vaccine
Bojang et al[27]	2005	I	AS02	Gambia	90	1–11 years	3	Rabies vaccine
Aide et al[28]	2010	I/IIb	AS02	Mozambique	214	6–12 weeks	3	Hepatitis B vaccine
Kester et al[29]	2014	I &II	AS02	Belgium & USA	43	18–45 years	3	TRAP/AS02
Moon et al[30]	2020	IIa,	AS01	USA	154	18–55years	3	Adjuvants only
Lell et al[48]	2009	II	AS01&AS02	Gabon	180	18 months to 4 years	3	AS01 vs AS02
RTS,S Clinical Trials Partnership[55]	2015	III	AS01	Seven Sub-Saharan countries	15,459	6–12 weeks and 5–17 months	4	Rabies vaccine and meningococcal sero group C conjugate vaccine
Olotu et al[37]	2011	IIB-	AS01	Kenya, and Tanzania	894	children	3	Rabies vaccine
Polhemus et al[49]	2009	IIb	AS02 & AS01	Kenya	255	18–35 years	3	Rabies vaccine
Leroux-Roels et al[14]	2014	II	AS01&AS02	Belgium	36	18–45 years	3	RTS,S/saline
Agnandji et al[38]	2010	II	AS01	Ghana, Tanzania, and Gabon	511	6–12 weeks and 5–17 months	3	EPI vaccines only
The RTS,S Clinical Trials Partnership[53]	2011	III	AS01	Seven Sub-Saharan countries	15,460	6 to 12 weeks and 5 to 17 months	3	Rabies vaccine for children and Meningococcal C conjugate vaccine for infants
Asante et al[50]	2020	IIIb	AS01	Gana	709	6–9 months	4	YF and combined MR vaccines
Owusu-Agyei et al[47]	2009	II	AS02 & AS01	Gana	540	5–17 months	3	Rabies vaccine
Kester et al[46]	2009	IIa	AS02 & AS01	USA	138	18–45 years	3	Infectivity control
Rampling et al[31]	2018	IIa	AS01	UK	45	18–45 years	3	ME- ME-TRAP
Asante et al[32]	2011	II	AS01	Gana, Gabon and tanzania	511	6–10 weeks	3	EPI vaccinesalone
Rampling et al[33]	2016	IIa	AS01	UK	48	18–45 years	3	Unvaccinated controls
Otieno et al[51]	2016	III	AS01	Kenya	200	6 weeks to 17 months	3	Rabies vaccine
Witte et al[34]	2018	II	AS01	Malawi	480	1 to 7 days	3	Hepatitis B vaccine
Lusingu et al[35]	2010	IIb	AS01	Kenya & Tanzania	894	5–17 month	3	Rabies vaccine
Olotu et al[36]	2016	II	AS01	Kenya & Tanzania	447	5 to 17 months	3	Rabies vaccine
Otieno et al[52]	2020	III	AS01	Seven Sub-Saharan countries	153	6–12 weeks and 5–17 months	4	Meningococcal C CRM197 conjugate vaccine and rabies vaccine
RTS,S Clinical Trials Partnership[56]	2020	III	AS01	Seven Sub-Saharan countries	15,460	6–12 weeks and 5–17 months	3	Rabies vaccine and Meningococcal C conjugate vaccine
RTS,S Clinical Trials Partnership[54]	2012	III	AS01	Seven Sub-Saharan countries	6537	6–12 weeks	3	Meningococcal serogroup C conjugate vaccine

Notes: NB: Seven Sub-Saharan countries: Mozambique, Malawi, Tanzania, Kenya, Gabon, Gana, and Burkina Faso SBAS2: former name for AS02.

injection site.[23–29] Additionally, myalgia was the most often reported general complaint in the Phase 1 investigation, according to Kester et al[29] Further, Aide et al[28] found that participants in both RTS,S/AS02 and control groups reported upper respiratory tract infections. Furthermore, Bojang et al[27] showed that headache and fever were more frequently reported in the RTS,S/AS02 group as compared to control vaccine.

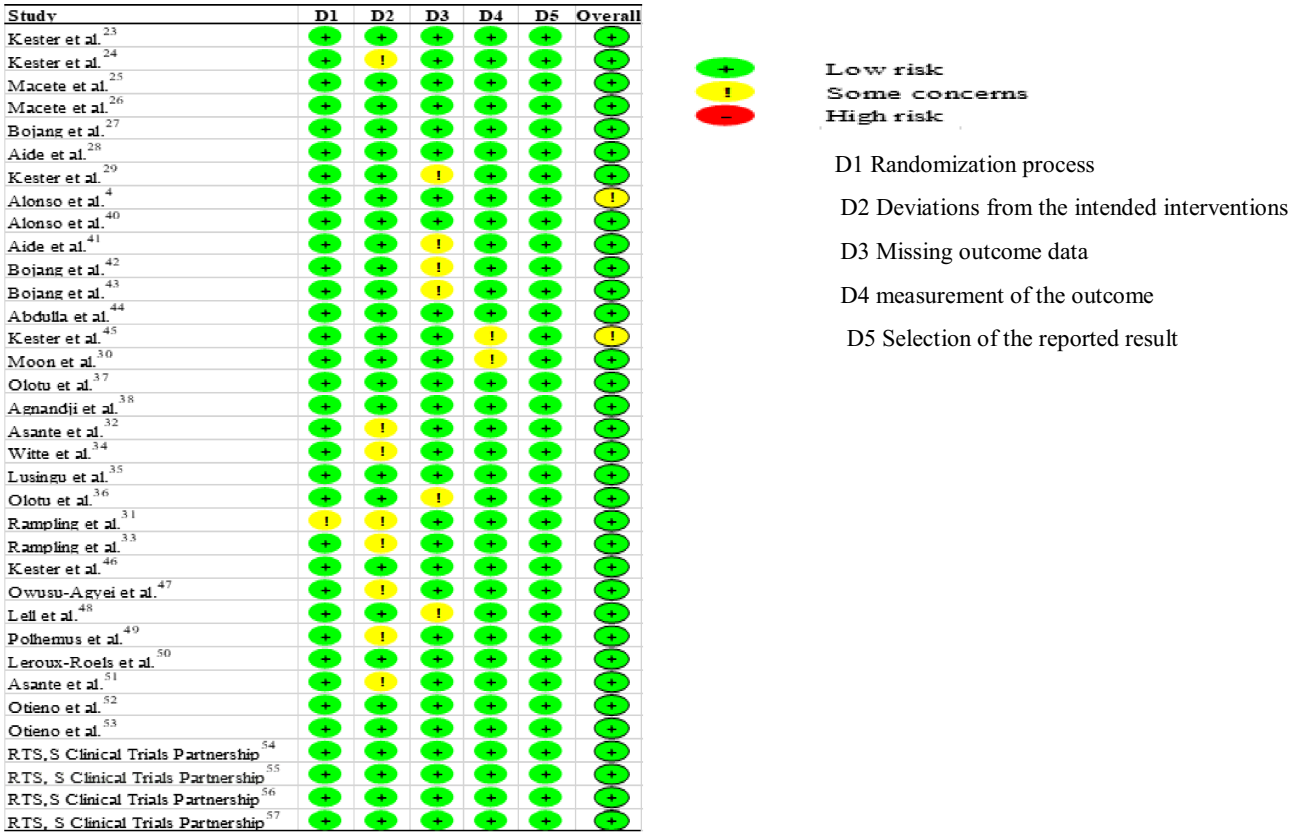

Figure 2 Risk of bias assessment of the studies, RTS,S.

Safety of RTS,S from Phase II Clinical Trial Studies

Both RTS,S/AS01 and RTS,S/AS02 were the subject of phase II clinical trials to examine the safety of the RTS,S malaria vaccine. Phase II clinical trials constituted the majority of the studies examining the safety of RTS,S. (Table 1)

Table 2 Commonly Reported Adverse Events Reported by Studies Following RTS,S/AS01 and RTS,S/AS02 Administration

Type of Adverse Event	Number of Studies Reporting Adverse Events (N = 38)						
	Phase I and I/II		Phase II		Phase III		Total
	n (%)	References	n (%)	References	n (%)	References	n (%)
Injection site pain and/or swelling	7 (20.00)	[23–29]	14 (40.00)	[14,30,31,34,37,38,40,42,44–49]	3 (8.57)	[50,51,53]	24 (68.57)
Headache	1 (2.85)	[27]	6 (17.14)	[14,30,31,42,45,46]	NA	–	7 (20.00)
Fever	1 (2.85)	[27]	4 (11.43)	[31,38,40,47]	2 (5.71)	[50,53]	7 (20.00)
Febrile convulsion /Seizure	NA	–	3 (8.57)	[33,35,37,38]	3 (8.57)	[51–53]	7 (20.00)
Fatigue	NA	–	5 (14.23)	[14,30,31,40,46]	NA	–	5 (14.23)
Meningitis	NA	–	NA	–	5 (14.23)	[52–56]	5 (14.23)
Gastroenteritis	NA	–	3 (8.10)	[35,37,44]	2 (5.41)	[50,51]	5 (14.23)
Pneumonia	NA	–	3 (8.57)	[35,37,44]	1 (2.85)	[51]	4 (11.43)
Reactogenicity	NA	–	NA	–	4 (11.43)	[51,53–55]	4 (11.43)
Myalgia	1 (2.85)	[29]	2 (5.71)	[14,30]	NA	–	3 (8.57)
Upper respiratory tract infections.	1 (2.85)	[28]	1 (2.85)	[35]	1 (2.85)	[50]	3 (8.57)
Anemia	NA	–	3 (8.57)	[32,35,44]	NA	–	3 (8.57)

Abbreviations: N, Total number of studies addressing the outcome; n, number of studies reported the specified outcome; NA, not available.

RTS,S/As01

A number of phase II clinical trials were conducted in Sub-Saharan Africa (Gabon, Kenya, Tanzania, Gana, and Malawi), USA (in Walter Reed Army Institute of Research (WRAIR)), and in United Kingdom. (Table 1)

Majority of the studies revealed that all vaccination regimens were well tolerated. The proportions of solicited and unsolicited AEs reported following each dosage of the vaccination were comparable between groups. There were no known vaccine-related serious adverse events (SAEs) or suspected unanticipated significant adverse events. No serious adverse event was determined to be linked to vaccination, and no individual incident occurred with a greater incidence that was clinically significant as compared to the control group in the RTS,S/AS01 vaccine group.[30–36]

Moreover, the majority of the studies indicated that injection site adverse effects were the most frequently reported solicited local AEs and considered causally related to vaccination.[30,31,34,37,38] In addition, Lusingu et al[35] reported that drowsiness and loss of appetite were occasionally reported and similar in both RTS,S/AS01, and rabies vaccine groups. Phase II clinical trials conducted on adults in the USA, and UK showed that fatigue and headache,[30,31] feverishness, malaise, and myalgia[31] were the most frequently reported solicited general AEs. Moreover, Agnandji et al[38] found fever was reported more frequently in participants who received RTS,S/AS01 with EPI vaccines, measles, and yellow fever vaccines compared with participants who received EPI vaccines, measles, and yellow fever vaccines without RTS,S/AS01, respectively. Furthermore, studies conducted in Sub-Saharan Africa showed that serious adverse events reported during the study period were pneumonia,[35,37] febrile convulsion,[32,35,37] gastroenteritis,[35,37] *P. falciparum* malaria,[35,37] and upper respiratory tract infections.[35]

On the other hand, fewer people in the RTS,S/AS01 group than in the rabies group, according to Olotu et al,[37] experienced at least one severe adverse event. Three seizures were documented within one month of vaccination, according to Agnandji et al;[38] two occurred in RTS,S/AS01 (0, 1, 7) group individuals, and one occurred in a control group subject. In addition, anemia was recorded as a significant adverse event that happened with a similar frequency across groups, according to studies by Asante et al[32] and Lusingu et al.[35]

RTS,S/As02

A total of 7 Phase II clinical trials to study the safety of RTS,S/AS02 were conducted, 3 studies in Mozambique,[39–41] 2 studies in Gambia,[42,43] 1 study in each Tanzania[44] and USA[45] with a total participant of 6527 of whom 340 infants, 5829 1–4 years children and 358 adults. (Table 1)

The malaria vaccine RTS,S/AS02 demonstrated good safety profiles, according to a Phase II experiment conducted by Kester et al[45] on the 0, 1, and 3 month and 0, 7, and 28 day immunization schedules. Additionally, other investigations carried out in Sub-Saharan Africa revealed that no fatality or significant adverse event was thought to be connected to vaccination.[39,40,42–44] Moreover, numerous investigations revealed that throughout the four-day follow-up period in both cohorts and overall doses, discomfort and/or swelling at the injection site was the most commonly reported local adverse event.[40,42,44,45]

Additionally, Bojang et al[42] and Kester et al[45] found that the RTS,S/AS02 group experienced headache more frequently than the control group did. Moreover, Alonso et al[40] found that fever, irritability, sleepiness, and anorexia were more common in the RTS,S/AS02 group as compared to the control. Furthermore, Abdulla et al[44] found that in both the RTS,S/AS02 and hepatitis B vaccine groups, pneumonia, gastroenteritis, and anemia were the most commonly reported adverse events; though none of the serious adverse effects were linked to vaccination.

RTS,S/AS01 vs RTS,S/AS02

A total of 5 safety studies were conducted in both RTS,S/AS01 and RTS,S/AS02 in Gabon, Kenya, Gana, USA, and Belgium with 720 children and 429 adults.(Table 1) A study of RTS,S/AS01 and RTS,S/AS02 in USA and Ghana by Kester et al[46] and Owusu-Agyei et al[47] indicated that both vaccines had acceptable safety profiles. On the other hand, different phase II RCT studies on RTS,S/AS01 and RTS,S/AS02 in 1113 children and adults in Gabon, Kenya, Gana, and USA showed that pain and swelling were reported more commonly on RTS,S/AS02 than RTS,S/AS01.[14,46–49] Furthermore, a research by Polhemus et al[49] on healthy individuals in Kenya revealed that the RTS,S/AS01 and RTS,S/AS02 vaccines had a higher incidence of discomfort and edema than the control. In addition, Leroux-Roels et al[14]

found that incidences of AEs tended to be lower in RTS,S without the adjuvant system as compared with the adjuvanted vaccine. Furthermore, myalgia which was reported by participants in RTS,S/AS01 group, went away after two days.[14]

Fatigue and headache were the most often reported general AEs in both groups, according to other investigations by Kester et al[46] and Leroux-Roels et al[14] conducted in Kenya and the USA. Additionally, Owusu-Agyei et al[47] found that fever was reported by participants in RTS,S with both AS01 and AS02 adjuvant systems. Although; deviations of normal hematological and biochemical values were recorded, no grade 3 abnormalities were seen.[48] Moreover, Owusu-Agyei et al[47] and Leroux-Roels et al[14] reported no AEs that were clinically significant alterations in clinical laboratory values.

Safety of RTS,S from Phase III Clinical Trials

Phase III clinical studies on RTS,S/AS01 including 16,521 infants and children were carried out in Sub-Saharan Africa on 16, 521 infants and children. An equal percentage of participants in both the RTS,S/AS01, and the control group reported at least one major adverse event. Overall, both immunization groups had few grade 3 solicited adverse events with similar incidence.[50–52]

As other phase I and II clinical trial studies, in phase III studies, pain at the RTS,S/AS01 injection site was the most frequently reported AE.[50,52,53] A Phase III clinical trial on infants and children by the RTS,S Clinical Trials Partnership,[54] conducted in eleven locations across seven African countries, revealed that meningitis of any cause was reported as a serious adverse event in infants more frequently in participants in the RTS,S/AS01 group as compared to the control group. In addition, the studies indicated that meningitis was also recorded as a SAE in both age groups.[54] Meningitis occurred more frequently in the RTS,S/AS01 group compared to the control group, although not being temporally linked to vaccination. Meningitis cases were also significantly imbalanced between the RTS,S/AS01 and control groups among children, but not in infants.[53,55,56]

A Safety study of RTS,S/AS01 in HIV- positive infants and children by Otieno et al,[52] revealed that meningitis was more commonly reported in the RTS,S/AS01 than the control in children as compared to infants.

A study conducted by the RTS,S Clinical Trials Partnership[53] showed that one of the significant adverse events recorded that was thought to be connected to a study vaccine and more common in the older age group was seizure. Another study by Otieno et al,[51] revealed that among the most common serious adverse events in both RTS,S/AS01, and rabies-vaccine recipients was febrile convulsions, with similar events noted in both groups. Furthermore, a study done on HIV-infected infants and children by Otieno et al[52] revealed febrile convulsion was reported more commonly in children taking RTS,S/AS01 than the control and it was judged to be associated with vaccination. It also reported that a higher number of deaths was seen in RTS,S/AS01 vaccinated female participants as compared with the control; though it was not observed in males.[52]

Studies conducted in sub-Saharan African countries showed that pyrexia was another serious adverse event, reported more frequently in the RTS,S/AS01 group than the control group more in children than infants.[50,53] In addition, the RTS, S Clinical Trials Partnership[53] indicated that Myositis was reported as a serious adverse event in children and it was thought to be connected to vaccination.

In a study carried out in Kenya by Otieno et al[51] reported that the most frequent major adverse events were pneumonia and gastroenteritis, with equal percentage of occurrences reported in both groups. Furthermore, Asante et al[50] showed that upper respiratory tract infections and diarrhea were reported in the RTS,S coad, RTS,S alone, and Control groups in children; however, none of these events were linked to the study vaccine.

A study conducted in seven sub-Saharan countries revealed that the RTS,S/AS01 booster dose was more reactogenic than the comparator vaccine in both children and young infants.[55] Different studies indicated that RTS,S/AS01 vaccine was more reactogenic than the control.[51,53,54]

Discussion

Antimalarial drugs, and insecticides resistance, pave the way for malaria to claim hundreds of thousands of lives each year, calling attention to develop safe, and effective vaccines.[1,3–5] Among different malaria vaccine candidates, RTS,S, is the pre-erythrocytic vaccine that is most progressed.[8] Studying the safety of vaccines has to be given high priority at all stages of vaccine development.[57] Therefore, This systematic review was aimed to assess the safety of RTS,

S with AS02 and AS01 adjuvant systems from RCT studies. RCTs would eliminate concerns about confounding factors, both known and unknown.[58]

An adverse event following immunization (AEFI), such as an unpleasant or unexpected sign, abnormal laboratory test findings, symptoms, or disease, is an indicator of the safety of a vaccine.[59] Unpleasant effects of vaccines can be ascribed to vaccines themselves and their components.[60] As a result, it is a must to ensure the safety of the RTS,S malaria vaccine before its approval.

This study tried its best to qualitatively describe the safety of RTS,S malaria vaccine with AS01 and AS02 adjuvant systems from the 35 published RCTs. As a result, the review found that RTS,S/AS01 and RTS,S/AS02 vaccines are safe to humans. Moreover, in most RCT studies, the reported AEFI were comparable between RTS,S and the control. The common AEFI were injection-site pain and swelling, febrile convulsion, fever, headache, meningitis, fatigue, gastroenteritis, myalgia, pneumonia, reactogenicity, and anemia. Injection site pain and/or swelling was the most frequently reported local symptom in all vaccine groups. Four studies conducted in seven sub-Saharan countries revealed that the RTS,S/AS01 three dose and booster dose was more reactogenic than the comparator rabies vaccine in both children and young infants[51,53–55] These adverse effects are also common to other types of vaccines as identified in the investigational phase of clinical trials.[58]

No matter what components are in a vaccination, all vaccines generate some level of inflammation at the injection site, which is likely to contribute to the symptoms of pain, redness, and swelling. When pyrogenic chemicals are released into the systemic circulation, a series of immunological and neurological system interactions are thought to be activated, including an increase in body temperature.[61]

Furthermore, in this systematic review, AEs were reported more commonly with the adjuvanted antigen than with the unadjuvanted RTS,S. This demonstrates that adjuvants have their own adverse events. Moreover, studies confirmed that adjuvants are immunostimulants that enhance the immune response to the antigen.[62,63]

Vaccine antigens set up an immune response that may provide specific disease protection. Immune system stimulation results in a complicated cascade of innate immunological processes, including as phagocytosis, the creation of inflammatory mediators like chemokines and cytokines, complement activation, and cellular recruitment. These inflammatory reactions followed immune system stimulation may lead to the development of signs and symptoms of injection-site reaction (pain, redness, and swelling) in the vaccinated person. The mediators and products of inflammation in the circulation may have systemic negative effects, such as fever, weakness, and headache.[61] Fever was reported more frequently in participants who received RTS,S/AS01 in combination with EPI vaccines and measles and yellow fever vaccines compared with participants who received EPI vaccines and measles and yellow fever vaccines alone, respectively.[38] This may be due to additive adverse effect of combination of vaccines.

Different phase II RCT studies on RTS,S/AS01 and RTS,S/AS02 in 1113 children and adults in Gabon, Kenya, Gana, and USA showed that pain and swelling were reported more frequently on RTS,S/AS02 than RTS,S/AS01.[46–49] Furthermore, AS01's immunogenicity superiority to AS02,[64–66] this strengthened to prefer RTS,S/AS01 to RTS,S/AS02 for further studies (phase III clinical trials[8] and pilot implementation[67]).

In addition, a study carried out on HIV-positive children reported that a higher number of deaths was seen in female children taking RTS,S/AS01 compared with female children in the control group; though it was not observed in male children.[52] Furthermore, this was supported by other studies.[68,69]

A pilot implementation of the four-dose schedule of RTS,S/AS01 was started in Gana, Malawi and Kenya in 2019 to further characterize vaccine safety in the context of a routine immunization program, paying special attention to the safety signals observed in the Phase III trial (meningitis, cerebral malaria, excess mortality in female compared to male children).[68] No proof of a connection between the RTS,S/AS01 vaccination and the three potential safety signals from phase III clinical trials was discovered, according to the report.[70,71] Following the findings of favorable safety and efficacy profiles from the RTS,S/AS01 malaria vaccine pilot program in Ghana, Kenya, and Malawi, WHO recommended that the RTS,S/AS01 be used widely among children in Sub-Saharan Africa and other regions with moderate to high P. falciparum malaria transmission.[72]

Strengths and Limitations

This study covered the assessment of the safety of RTS,S with both AS01 and AS02 adjuvant systems in infants, children and adults world-wide. Moreover, it included all RCTs from Phase I–III. However, we have not access to some search engines due to lack of subscription by our affiliate university. In addition, some articles were not full-text and were rejected.

Conclusion

This systematic review was conducted using data from randomized controlled trials. Most of the adverse events observed from RTS,S/AS01 and RTS,S/AS02 malaria vaccines were also shared by other vaccines. Moreover, the safety signals (meningitis, cerebral malaria, excess mortality in female compared to male children), from phase III clinical trials were chance only. Hence, the authors concluded that both RTS,S/AS01 and RTS,S/AS02 malaria vaccines are safe.

Amendments to the Protocol

See Supplementary File 2.

Abbreviations

AE, Adverse Events; AEFI, Adverse Events Following Immunization; CSP, Circumsporozoite protein; GSK, GlaxoSmithKline; NANP, N-acylneuraminate-9-phosphatase; WRAIR, Walter Reed Army Institute of Research; WHO, World Health Organization.

Data Sharing Statement

Unless there are legal or ethical reasons to the contrary, the data will be made available upon request from the corresponding author.

Disclosure

The authors declared that they have no competing interests.

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