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[Intervention Review]

Vaccines for preventing malaria (SPf66)

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ABSTRACT

Background

A malaria vaccine is badly needed. SPf66 was one of the earliest vaccines developed. It is a synthetic peptide vaccine containing antigens from the blood stages of malaria linked together with an antigen from the sporozoite stage, and is targeted mainly against the blood (asexual) stages.

Objectives

To assess the effect of SPf66 malaria vaccines against *Plasmodium falciparum*, *P. vivax*, *P. malariae,* and *P. ovale* in preventing infection, disease, and death.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (March 2008), CENTRAL (*The Cochrane Library* 2008, Issue 1), MEDLINE (1966 to March 2008), EMBASE (1980 to March 2008), LILACS (1982 to March 2008), Science Citation Index (1981 to March 2008), and reference lists of articles. We also contacted organizations and researchers in the field.

Selection criteria

Randomized and quasi-randomized controlled trials comparing SPf66 vaccine with placebo or routine antimalarial control measures in people of any age receiving an artificial challenge or natural exposure to malaria infection (any species).

Data collection and analysis

Two people independently assessed trial quality and extracted data, including adverse events. Results were expressed as risk ratios (RR) with 95% confidence intervals (CI).

Main results

Ten efficacy trials of SPf66 involving 9698 participants were included. Results with SPf66 in reducing new episodes of *P. falciparum* malaria were heterogeneous: it was not effective in four African trials (RR 0.98, 95% CI 0.90 to 1.07; 2371 participants) or in one Asian trial (RR 1.06, 95% CI 0.90 to 1.25; 1221 participants). In four trials in South America the number of first attacks with *P. falciparum* was reduced by 28% (RR 0.72, 95% CI 0.63 to 0.82; 3807 participants). It did not reduce episodes of *P. vivax* malaria or admission to hospital with severe malaria. Trials have not indicated any serious adverse events with SPf66 vaccine.

Authors' conclusions

There is no evidence for protection by SPf66 vaccines against *P. falciparum* in Africa. There is a modest reduction in attacks of *P. falciparum* malaria following vaccination with SPf66 in South America. There is no justification for further trials of SPf66 in its current formulation. Further research with SPf66 vaccines in South America or with new formulations of SPf66 may be justified.

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23 April 2019

No update planned

Intervention not in general use or been superseded

This intervention is no longer available.

PLAIN LANGUAGE SUMMARY

The SPf66 vaccine has little or no effect on preventing malaria

The SPf66 vaccine was one of the first malaria vaccines to be tested extensively in endemic areas. SPf66 is a synthetic peptide vaccine containing antigens from the blood stages of malaria linked together with an antigen from the sporozoite stage. SPf66 has had 10 trials in Africa, Asia, and South America. Results were initially promising, but further trials showed only a small effect in some trials, and no effect in Africa. There is no evidence that SPf66 is effective enough to be introduced on a routine basis for prevention of malaria.

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BACKGROUND

Malaria is caused by four species of the parasitic protozoan *Plasmodium,* which are transmitted by many species of anopheline mosquitoes. *Plasmodium falciparum* is the most widespread and also the most serious form. Recent estimates of the annual number of clinical malaria cases worldwide range from 214 to 397 million (WHO 2002; Breman 2004), although a higher estimate of 515 million (range 300 to 660 million) clinical cases of *P. falciparum* in 2002 has been proposed (Snow 2005). Estimates of annual mortality (nearly all from *P. falciparum* malaria) are thought to be around 1.1 million (WHO 2002; Breman 2004). Malaria deaths are believed to account for 3% of the world's total Disability Adjusted Life Years (DALYs) lost and 10% of DALYs in Africa (Breman 2004). Malaria also significantly increases the risk of childhood death from other causes (Snow 2004). Almost half of the world's population is exposed to the risk of malaria where they live (Hay 2004), as are the increasing numbers of visitors to malarious areas.

Despite continued efforts to control malaria it remains a major health problem in many regions of the world, and new ways to prevent the disease are urgently needed. Early optimism for vaccines was tempered as the problems caused by genetic (hence, antigenic) variability of the parasite and the difficulty of generating high levels of durable immunity emerged. Recently, hope has been renewed by the development of several new vaccine candidates and delivery systems, as well as new formulations and adjuvants for previously existing candidates (Richie 2002; Ballou 2004). Vaccines currently under evaluation include recombinant proteins, synthetic peptides (including multiple antigen peptides), DNA vaccines, inactivated whole parasites, and vaccines comprising mixtures of a large variety of potential antigens.

To be effective, a malaria vaccine could either prevent infection altogether or mitigate against severe disease and death in those who become infected despite vaccination. Four stages of the malaria parasite's life cycle (Figure 1) have been the targets of vaccine development efforts. The first two stages are often grouped as 'pre-erythrocytic stages' (ie before the parasite invades the human red blood cells): these are the sporozoites inoculated by the mosquito into the human bloodstream, and the parasites developing inside human liver cells. The other two targets are the stage when the parasite is invading or growing in the red blood cells (blood, merozoite, or erythrocytic stage); and the gametocyte stage, when the parasites emerge from red blood cells and fuse to form a zygote inside the mosquito vector (gametocyte, gamete or sexual stage). Vaccines based on the pre-erythrocytic stages usually aim to completely prevent infection, while blood stage vaccines aim to reduce (and preferably eliminate) the parasite load once a person has been infected. Gametocyte vaccines would prevent the parasite being transmitted to others through mosquitoes. An ideal vaccine would be effective against all parasite stages (Richie 2002).

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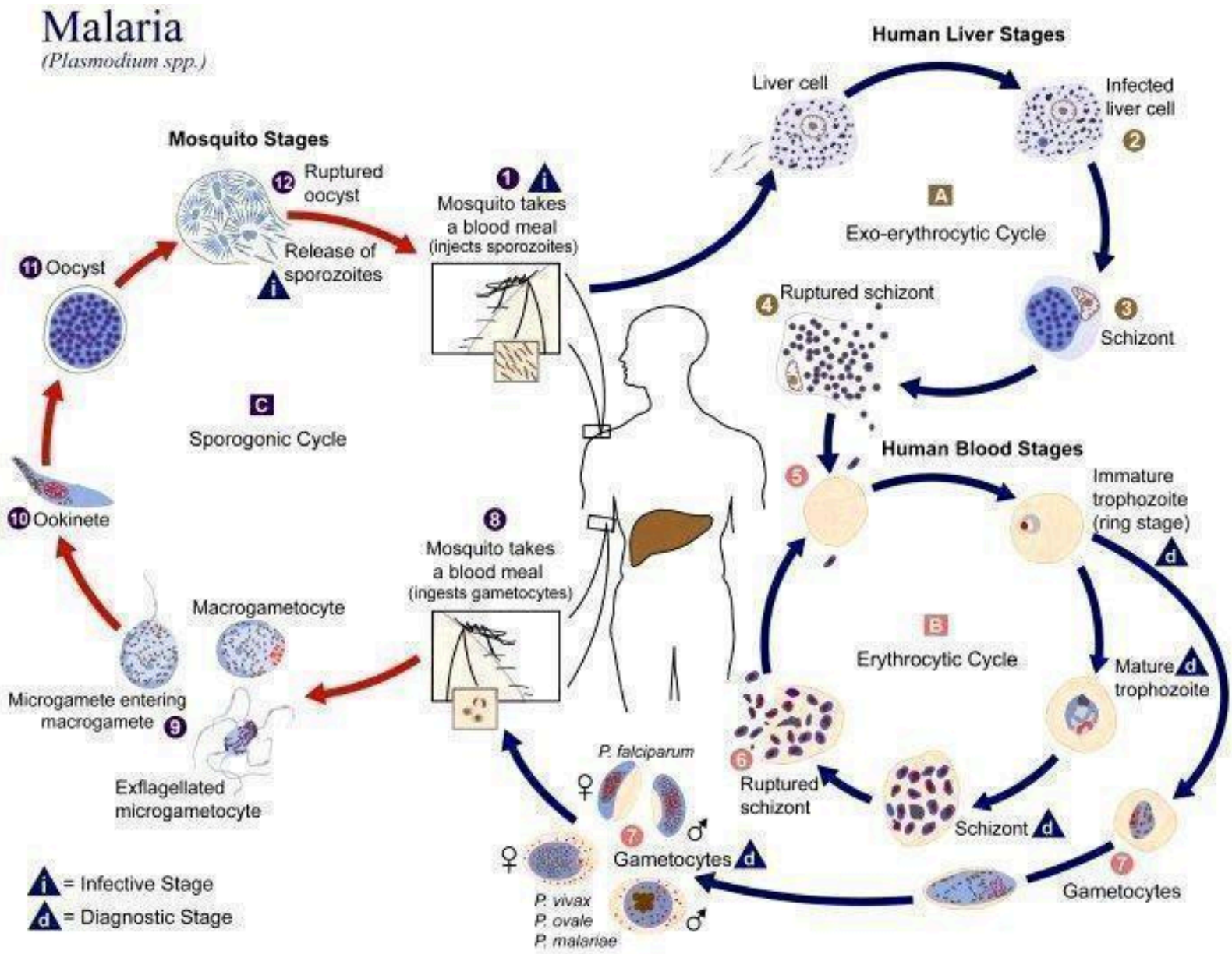
Figure 1. Plasmodium life cycle (CDC/Alexander J. da Silva, PhD/Melanie Moser)



The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host ❶. Sporozoites infect liver cells ❷ and mature into schizonts ❸, which rupture and release merozoites ❹. (Of note, in *P. vivax* and *P. ovale* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years later.) After this initial replication in the liver (exo-erythrocytic schizogony A), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony B). Merozoites infect red blood cells ❺. The ring stage trophozoites mature into schizonts, which rupture releasing merozoites ❻. Some parasites differentiate into sexual erythrocytic stages (gametocytes) ❼. Blood stage parasites are responsible for the clinical manifestations of the disease.

The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an *Anopheles* mosquito during a blood meal ❽. The parasites' multiplication in the mosquito is known as the sporogonic cycle C. While in the mosquito's stomach, the microgametes penetrate the macrogametes generating zygotes ❾. The zygotes in turn become motile and elongated (ookinetes) ❿ which invade the midgut wall of the mosquito where they develop into oocysts ⓫. The oocysts grow, rupture, and release sporozoites ⓬, which make their way to the mosquito's salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle ❶.

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Given the complexity and wide range of malaria vaccines under development, we have chosen to consider them in three categories: (1) the SPf66 vaccine; (2) pre-erythrocytic vaccines (Graves 2006a); and the (3) blood-stage vaccines (Graves 2006b). This review considers trials of SPf66 vaccine, while other types of malaria vaccine are covered in separate forthcoming reviews; reviews of multi-stage and transmission-blocking vaccines will also be prepared when they have reached the trial stage.

The SPf66 vaccine was first formulated and tested in Colombia (Patarroyo 1988) and later also manufactured in the USA. SPf66 is a synthetic hybrid peptide polymer containing amino acid sequences derived from three *P. falciparum* asexual blood stage proteins (83, 55, and 35 kilodaltons) linked by repeat sequences from a protein found on the *P. falciparum* sporozoite surface (circumsporozoite protein). Therefore it is technically a multistage vaccine. SPf66 was one of the first types of vaccine to be tested in randomized controlled trials in endemic areas and is the vaccine that has undergone the most extensive field testing to date.

We have systematically reviewed the trials conducted to estimate the efficacy of SPf66 vaccine. Trials of SPf66 have been subgrouped by area of the world because the transmission rate of malaria is generally more intense in Africa than in South America and Asia. In this way we explore possible variation in efficacy dependent on the level of exposure of the host to infective mosquito bites, the age of the participants, and the seasonality of transmission, all of which contribute to the immune status of people living in the areas, which, in turn, can affect the response to a vaccine.

OBJECTIVES

To assess the effect of SPf66 malaria vaccines against *P. falciparum*, *P. vivax*, *P. malariae,* and *P. ovale* in preventing infection, disease, and death.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

People of any age who are challenged by a malaria infection. The challenge infection could be either a natural malaria infection (ie residents of malaria endemic areas) or a laboratory-induced infection (either from infected blood or bites of infected mosquitoes).

Types of interventions

Intervention

- SPf66 vaccine.

Control

- Placebo or routine antimalarial control measures.

Types of outcome measures

Primary

- New malaria infection.
- Clinical malaria episodes.
- Fever episodes.

Secondary

- Death.
- Severe malaria.
- Admission to hospital.
- Admission to hospital with diagnosis of malaria.
- Parasite density.
- Prevalence of malaria.
- Anaemia.

Adverse events

- Local and systemic.

Search methods for identification of studies

We have attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (March 2008); CENTRAL (March 2008); MEDLINE (1966 to March 2008); EMBASE (1980 to March 2008); LILACS (1982 to March 2008); and Science Citation Index (1981 to March 2008).

Conference proceedings

We checked the proceedings of the annual meetings of the American Society for Tropical Medicine and Hygiene for 2002 to 2004, the MIM Malaria Pan-Africa Conference, 18 to 22 November 2002, Arusha, Tanzania, and the third Pan-African Malaria Conference, 22 to 24 June 1998, Nairobi, Kenya. We also accessed the proceedings of the Global Vaccine Research Forum, Montreux, Switzerland, 7 to 10 June 2004, and Bahia, Brazil 12 to 15 June 2005, organized by the WHO Initiative for Vaccine Research.

Researchers and organizations

In preparing earlier versions of this review (Graves 2003) we contacted the following researchers working in the field: M Patarroyo, M Urdaneta, B Greenwood, and P Alonso. In 2005 we also contacted R Rabinovich and the website of the Malaria Vaccine Initiative at the Program for Appropriate Technology in Health (PATH) as well as the Malaria Vaccine Technology Roadmap site. Other web sources included the European Malaria Vaccine Initiative, the European Malaria Vaccine Consortium, and the African Malaria Network Trust. We also accessed the documents 'Portfolio of candidate malaria vaccines currently in development' (March 2005) and 'New vaccines against infectious diseases: research and development status' (April 2005) from the Initiative for Vaccine Research, WHO.

Reference lists

We checked the reference lists of all studies identified by the above methods.

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Data collection and analysis

Selection of studies

Two people independently applied the inclusion criteria to all identified trials (Patricia Graves and an Editor of the Cochrane Infectious Diseases Group, or both authors). Differences were discussed until consensus was reached.

Data extraction and management

Each author independently extracted all data for analyses. Differences were resolved by discussion.

Assessment of risk of bias in included studies

Each author independently assessed the trials for four dimensions of quality: (1) method of generation of allocation sequence and (2) allocation concealment (both as adequate, inadequate, not done, or unclear according to Juni 2001); (3) blinding (double, ie investigators and participants were blinded; single, ie only participants blinded; neither blinded; or unclear), and (4) loss to follow up (proportion of those randomized who completed all doses and who completed follow up, if stated). Differences were resolved by discussion.

Data synthesis

We analysed the data using Review Manager 4.2. A fixed-effect model was used. Heterogeneity between trials in the outcomes was dealt with by subgrouping trials into geographical areas of the world.

Results for dichotomous data are expressed as risk ratios (RR) of an outcome occurring in the vaccine group compared to the placebo group. The risk ratio may be converted to an estimate of vaccine efficacy by the following formula:

Efficacy = (1-RR) x 100%

Similarly, the 95% confidence interval (CI) for the vaccine efficacy may be obtained by substituting the upper and lower 95% CIs of the RR into the formula.

This review includes outcomes only for those participants who received the full course of vaccine (usually three doses), if this was stated in the trials. Some trials did not report this information. Some trials included adjusted incidence rates, such as by village or the distance from a health facility, or performed survival analysis. This meta-analysis uses only unadjusted incidence rates based on the number of participants in each arm of the trial.

RESULTS

Description of studies

See the ' Characteristics of included studies ' for more detailed information.

Ten trials involving 9698 participants aged from one month to 86 years met the inclusion criteria. These trials were done during the years 1990 to 1998. Four of the SPf66 vaccine trials were conducted in South America (Valero 1993; Sempertegui 1994; Valero 1996; Urdaneta 1998), five in Africa (Alonso 1994; D'Alessandro 1995; Leach 1995; Masinde 1998; Acosta 1999), and one in Asia (Nosten 1996). All the included SPf66 trials were conducted in situations of natural challenge.

The decision about which age group to include in a vaccine trial is based partly on epidemiological considerations and partly on safety concerns. Different areas vary greatly in endemicity, and this has consequences for the age-specific incidence of infection, and of severe disease and death. Repeated malarial infections and inoculations of sporozoites from mosquitoes (even if not causing clinical disease) gradually result in the development of what is referred to as 'partial' immunity, and as a result, fewer full-blown infections become likely. When an infection does become established, the numbers of parasites are generally lower than they are in people with no experience of infection, hence no immunity. Because clinical manifestations are related to the parasite density, clinical manifestations are generally less serious (or absent) in people with partial immunity than in immune 'naïve' individuals. In most of sub-Saharan Africa, malaria infection begins early in life. Very young children, who have yet to develop any immunity to malaria, suffer the most infections and the most severe consequences of infection. However in Brazil, Colombia, Ecuador, and Thailand, there are non-immune people (and therefore, symptomatic infections) among all age groups. As a result, most African trials have involved young children while other trials have included older children, all ages, or adults only. The exception in Africa was Masinde 1998, which was conducted with adults.

Vaccine source

Of the 10 trials, seven used vaccine prepared in Colombia (Valero 1993; Alonso 1994; Sempertegui 1994; D'Alessandro 1995; Valero 1996; Urdaneta 1998; Acosta 1999), one used vaccine manufactured in the USA (Nosten 1996), one compared vaccine from both sources (Leach 1995), and one did not state the source (Masinde 1998). In all preparations, the peptide vaccine was adsorbed to alum, which served as an adjuvant. The placebos were tetanus toxoid vaccine in five of the trials (Valero 1993; Alonso 1994; Sempertegui 1994; Valero 1996; Urdaneta 1998), injected polio vaccine in two trials (D'Alessandro 1995; Leach 1995), hepatitis B vaccine in two trials (Nosten 1996; Masinde 1998), and alum alone in one trial (Acosta 1999).

Participants

Three of the SPf66 trials were carried out in all age groups (Valero 1993; Sempertegui 1994; Valero 1996), and one was with adults only (Masinde 1998). The Urdaneta 1998 trial included people aged seven to 60 years. The Nosten 1996 trial included children aged two to 15 years. Four trials were in children in areas of high endemicity: age at first dose was one to five years in Alonso 1994; six to 11 months in Leach 1995 and D'Alessandro 1995; and one month in Acosta 1999.

Dose

All but one trial used doses of 0.5 to 2 mg of SPf66 vaccine given at day zero, and one and six months; the Masinde 1998 trial gave doses at day zero, four months, and seven to eight months, but the doses are not stated. In all trials except one, experimental and placebo vaccines were given at visits specifically for that purpose. In Acosta 1999, the trial was designed to coincide with the Expanded Program on Immunization (EPI) vaccine schedule, so the first two doses of vaccine or placebo were given at the same time as the first and second diphtheria, tetanus, and acellular pertussis (DTP) vaccine

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(injected into the opposite thigh); oral polio vaccine was also given at both visits. The third dose was given at a specialized visit except for 39 children (3%), who received dose three concurrently with measles vaccine.

Definition of a clinical malaria case

Because of the differing levels of endemicity, trials used different definitions of a clinical malaria case. In the Alonso 1994 trial and both trials in The Gambia (D'Alessandro 1995; Leach 1995), the trials used fever together with a defined level of malaria parasites as a case definition, after having determined a cut-off level using the percentage of fevers which were likely attributable to malaria. In the Acosta 1999 trial, the primary outcome was the incidence of fever with any level of parasitaemia, although secondary analyses requiring at least certain levels of parasitaemia to define a case were also performed. In other endemic areas, the presence of parasitaemia alone, parasitaemia with fever, or parasitaemia with clinical symptoms defined a case. Case definitions are noted under 'Outcomes' in the 'Characteristics of included studies'.

Use of antimalarial drugs

In three of the five African trials of SPf66, parasites were cleared from all participants by chemotherapy before or shortly after vaccination (before each dose in the Alonso 1994 trial, before the first and third doses in the D'Alessandro 1995 trial, and one week after the second and third doses in the Masinde 1998 trial). This was done because of the high prevalence of parasitaemia in the target population and the difficulty this created for determining the incidence of new infections. In the Nosten 1996 trial in Thailand, children found to be parasitaemic at surveys conducted before vaccination or on the day of vaccination were treated.

Detecting malaria cases

Some trials detected malaria cases when participants reported for treatment (passive case detection), some conducted population-based surveys at regular intervals (active case detection), and most used a combination of the two. The Nosten 1996 trial conducted the most intensive active surveillance (daily home visitation for 15 months) combined with cross-sectional surveys and detection of self-reported cases. In this review, for outcomes that include clinical malaria episodes (cases), both self-reported cases and results of population-based surveys have been combined, where possible.

Incidence and prevalence of malaria

All trials reported on the incidence or prevalence of *P. falciparum* malaria after vaccination. Incidence of *P. vivax* was also reported in all five trials conducted outside Africa. *P. malariae* is present at a low level in the African sites of trials, but incidence of this species after vaccination was not reported.

Length of follow up

Total length of follow up in the SPf66 trials ranged from eight months to two years. The two Gambian trials continued follow up into the second year after vaccination, although intensive surveillance was only conducted during 18 weeks of the malaria season in the second year of each trial (D'Alessandro 1995; Leach 1995). In this review, the results of the first and second malaria seasons are reported separately.

Outcomes

The outcomes that we were able to extract from the trials were as follows: new malaria episode (*P. falciparum*) − by year of follow up in two trials; new malaria episode (*P. vivax*); death; admission to hospital; admission to hospital with diagnosis of malaria; prevalence of malaria; and adverse events. Definitions of a new malaria episode varied by trial and are given in the 'Characteristics of included studies'.

Risk of bias in included studies

Generation of allocation sequence

The randomization method was described explicitly in four trials, in which it was regarded as adequate (Nosten 1996; Valero 1996; Urdaneta 1998; Acosta 1999). The rest were unclear.

Allocation concealment

Seven trials described adequate methods of allocation concealment, using central randomization and vials or syringes that were identical, masked, or placed in coded envelopes. In three trials allocation concealment was not done or unclear (Leach 1995; Masinde 1998; Urdaneta 1998).

Blinding

All trials were stated to be double blind with the exception of Masinde 1998, which was stated to be blinded but did not specify double blind.

Loss to follow up

The proportion of participants lost to follow up was high in five of the 10 SPf66 trials (Valero 1993; Sempertegui 1994; Valero 1996; Masinde 1998; Urdaneta 1998). In three of the South American trials, more than 20% of participants receiving the first vaccine dose withdrew before completion of the vaccine schedule (Valero 1993; Valero 1996; Urdaneta 1998). In Valero 1993, of those failing to complete the doses, one third were excluded because of "fever, allergy, pregnancy or malaria treatment" although the number due to each cause and breakdown by group is not provided. The rest were excluded because of absence, migration, or refusal. The high level of post-randomization exclusions led to an imbalance in numbers between vaccine and placebo groups in this trial and is a potential source of bias. This potential bias seemed to be less of a problem in Urdaneta 1998 since the losses were of similar proportion in the two trial arms, and analysis showed that the losses were independent of malaria parasitaemia or adverse reactions to vaccine.

The Masinde 1998 trial had initially 85 participants randomized and more than 20% of participants dropped out of the trial post-randomization (balanced between trial arms), but apparently none left the trial after the first dose.

In the D'Alessandro 1995 trial, although the dropout rate was small, a mistake in coding syringes necessitated exclusion of a large number of the placebo group who wrongly received vaccine, leading to an imbalance in numbers between groups. In both Leach 1995 and D'Alessandro 1995, the dropout rate in the first year was very low, but greater than 10% of the participants could not be traced for follow up in the second year.

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Effects of interventions

1. New malaria episode (P. falciparum)

Nine trials used new episodes of *P. falciparum* malaria as their primary outcome and reported data on the incidence of the first or only attack of clinical malaria. One trial reported prevalence as the major outcome (Masinde 1998).

Considering the trials individually, two trials showed significant protective effect against a new malaria infection (Valero 1993; Valero 1996) and the rest did not (Analysis 1.1). The combined RR from all nine trials was 0.90 (95% CI 0.84 to 0.96), giving an estimated vaccine efficacy of 10% (95% CI 4% to 16%). However, there was large heterogeneity between trials (chi-squared 29.10, df 8, I^2 72.5%), indicating that a combined estimate may not be a fair representation of the 'typical' effect of the vaccine.

The endemicity of malaria is greater in Africa than in the other sites of trials, and all the trials in Africa that used incidence as an outcome were performed in young children. To investigate whether the observed heterogeneity was related to endemicity levels, we subgrouped trials into those taking place in Africa, South America, or Asia (Analysis 1.1). In African trials, the combined RR was 0.98 (95% CI 0.90 to 1.07), showing no evidence of efficacy. In South American trials, the combined RR was 0.72 (95% CI 0.63 to 0.82), suggesting that in this area of the world the vaccine was significantly protective against *P. falciparum* with an efficacy of 28% (95% CI 18% to 37%). There was no evidence for efficacy in one trial from Asia (Nosten 1996).

Two trials in The Gambia followed children during the second malaria season after vaccination, but there was no evidence of efficacy in the second year (Analysis 1.2).

2. New malaria episode (P. vivax)

Five trials reported new malaria infections with *P. vivax*. As for *P. falciparum*, these trials were subgrouped according to area of the world. In South American trials, there was a suggestion that the vaccine increased the incidence of *P. vivax* infections (Analysis 1.3). The combined RR for the four trials in South America was 1.16 (95% CI 1.01 to 1.32). The one trial in Asia showed the opposite trend (RR 0.90, 95% CI 0.83 to 0.98).

3. Serious outcomes: death, admission to hospital, and admission to hospital with a diagnosis of malaria

These serious outcomes were reported only in some of the African trials (Analysis 1.4, Analysis 1.5, and Analysis 1.6). Total deaths and admissions are included in these trials because the cause of death or admission to hospital may not have been correctly ascribed, and also because malaria may have been a secondary factor in deaths from other causes. The SPf66 vaccine had no statistically significant effect on these serious outcomes in the few trials that reported them (Alonso 1994; D'Alessandro 1995; Acosta 1999).

4. Prevalence

One trial reported prevalence as the major outcome (Masinde 1998). There was no evidence for reduction in prevalence of *P. falciparum* in adults by the vaccine in this trial (Analysis 1.7).

5. Systemic and local adverse events

The frequency of local and systemic adverse events after vaccination with SPf66 was recorded after time periods varying from one hour to two weeks. The results are reported in Figure 2 (systemic adverse events) and Figure 3 (local adverse events). The intensity of surveillance varied among trials and there is little standardization in the definitions of symptoms.

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Figure 2. Number of systemic reactions[1] in each group of participants after each dose of SPf66 vaccine or placebo

Trial	Dose	SPf66		Placebo	
		n/N	%	n/N	%
Acosta 1999: all participants[2]	1	49/604	8.1	39/603	6.5
	2	38/594	6.4	24/582	4.1
	3	35[3]/553	6.3	38/543	7.0
Acosta 1999: intense monitoring[4]	1	17/48	35.4	21/50	42.0
	2	18/48	37.5	22/47	46.8
	3	30/45	66.7	32/46	69.6
Nosten 1996[5]	1	106/680	15.6	80/668	12.0
	2	100/659	15.2	84/654	12.8
	3	70/610	11.5	64/611	10.5
Sempertegui 1994	-	0/230	0.0	1[6]/232	0.4
Urdaneta 1998	1	24/361	6.6	12/356	3.4
	2	4/361	1.1	3/354	0.8
	3	3/210	1.4	3/201	1.5
Valero 1993	1	0	0.0	0	0.0
	2	0	0.0	0	0.0
	3	0/738	0.0	0/810	0.0
Valero 1996[7]	-	2[8]/634	0.3	1[8]/623	0.2

[1] Systemic reactions include fever, headache, gastric symptoms, muscle pain, dizziness, rash, wheeze, difficultybreathing, cough, itching, diarrhoea, and vomiting
[2] Within 1 hour
[3] Includes 1 serious reaction, facial oedema 20 minutes after vaccination, requiring antihistamine injection
[4] Subgroup of the first 98 infants recruited: systemic reactions occurring after the first day post-vaccination up to the seventh day
[5] These numbers are for fever only; 4 cases of mild wheezing in 3 children were also reported, but dose not specified
[6] Rash after second dose
[7] Only effects after third dose reported
[8] Cases of hypotension, diagnosed as vagal presyncope, resolved by postural treatment alone

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Figure 3. Number of local reactions[1] in each group of participants occurring after each dose of SPf66 vaccine or placebo

Trial	Dose	SPf66		Placebo	
		n/N	%	n/N	%
Alonso 1993	1	12	-	13	-
	2	0	-	2[2]	
	3	16[3]/274	5.8	7/312	2.2
Acosta 1999	1[4]	27/604	4.5	23/603	3.8
	2[5]	10/594	1.7	9/582	1.5
	3[6]	7/553	1.3	6/543	1.1
Leach 1995	3	14/48	29.2	0/50	0
Nosten 1996[7]	1	428/680	62.9	148/668	22.2
	2	356[8]/659	54.0	83/654	12.7
	3	266[9]/610	43.6	48/611	7.9
Sempertegui 1994	1	16/259	6.2	5/278	1.8
	2	49/252	19.4	10/268	3.7
	3	32/230	13.9	6/232	2.6
Urdaneta 1998	1	31/361	8.6	57/356	16.0
	2	122/361	33.8	45/354	12.7
	3	42/210	20.0	24/201	11.9
Valero 1993	1	13	1.3	13	1.3
	2	3	-	0	-
	3	0/738	0.0	0/810	0.0
Valero 1996	3	29/634	10.1	18/623	2.9

[1] Local reactions include mild inflammation, nodules, pain, erythema, pruritis, induration, and warmth at the site of injection
[2] Both had contralateral induration
[3] One had contralateral induration
[4] Contralateral erythema or induration: 11 in vaccine group and 12 in placebo group
[5] Contralateral erythema or induration: 1 in vaccine group and 3 in placebo group
[6] Contralateral erythema or induration: 0 in vaccine group and 1 in placebo group
[7] These numbers are for induration, erythema, and warmth; pain, pruritis, and subcutaneous nodules also reported, but amount of overlap in numbers with other local reactions is not clear
[8] 2 had contralateral reactions
[9] 22 had contralateral reactions

In the overall trial groups given non-intensive surveillance for adverse events, there were a total of three severe systemic adverse events in the vaccine group (two hypotension, one facial oedema) and two in the placebo (alum) group (one hypotension, one rash). There was also a higher proportion of allergic reactions in the vaccinated group, particularly in the Nosten 1996 trial where a large number of SPf66 recipients reported bilateral cutaneous reactions at the second or third dose, suggesting sensitization by the vaccine. This reaction had been observed previously in phase one non-randomized trials of SPf66 (Gordon 1996; Migasena 1997; Nosten 1997), which are not included in this review. These bilateral cutaneous reactions resolved within 24 hours with symptomatic treatment. Three cases of contralateral induration were also observed in the Alonso 1994 trial at the second or third dose, but two of these were in the placebo group (tetanus toxoid plus alum). In the Acosta 1999 trial, bilateral cutaneous reactions were also observed after the first dose of vaccine or placebo (which was alum), presumably at the site of DTP vaccination that was given in the other thigh. Frequencies of these reactions were no different between vaccine and placebo groups.

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Intense surveillance of the initial vaccinated group in the Acosta 1999 trial (48 children given vaccine and 50 given placebo) resulted in high frequencies of reported systemic adverse events, but the proportions were higher in the placebo than the vaccine group after each dose. The proportion of children with fever after vaccination was higher in the Nosten 1996 trial (11% to 16%) than in most of the other trials, although 10% to 13% of the placebo group also reported fevers after vaccination with the Engerix-B hepatitis vaccine in this trial.

DISCUSSION

SPf66 malaria vaccine was not efficacious in five good quality trials in Africa. Four of these trials (which assessed incidence of new *P. falciparum* episodes) were in young children. The one trial in African adults assessed prevalence. In South America, four trials suggested that the vaccine has a low but statistically significant efficacy of 28% (95% CI 18% to 37%) against new episodes of *P. falciparum*. However, all four South American trials suffered from a high frequency of dropouts and losses to follow up. The four trials in South America also suggested a slightly elevated incidence of *P. vivax* in the vaccine groups, possibly demonstrating competition between the two malaria species. No effect of the vaccine was apparent in Asia against either malaria species, but this was studied in only one trial.

No significant effect of the vaccine on serious outcomes of malaria such as death or admission to hospital was apparent. However the trials were not designed to have sufficient power to evaluate vaccine efficacy against these rarer events. Although some allergic and bilateral cutaneous reactions were reported, the frequency of serious adverse events after immunization with SPf66 was not significantly higher than for the 'placebo' vaccines (mainly hepatitis B and tetanus toxoid for the first doses, and adjuvants alone for the second and third).

The SPf66 malaria vaccine did not work as well as had been hoped. In the 1990s, much attention focused on this vaccine, and there was controversy about its effectiveness. It is apparent from this review that SPf66 is not effective enough for routine use, and attention has moved on to other vaccine types which are described in separate reviews. It is possible that re-formulations of SPf66 to improve its effectiveness may lead to further trials of this vaccine outside Africa. For example, the adjuvant QS21 is being tested in an attempt to improve the immunogenicity of SPf66 (Kashala 2002).

The trials described here used a wide range of different definitions of a malaria case, and different methods and frequencies of surveillance. Close attention should be paid to these issues in trial design, and their potential effects on estimation of vaccine efficacy. In deciding on a case definition, there is a trade-off between the high sensitivity required for statistical power and the high specificity required to determine vaccine efficacy. Intensive population-based surveillance for case detection could lead to inclusion of more mild and possibly self-limiting cases of malaria. This might underestimate the effect of the vaccine compared to trials that relied more heavily on self-referral for treatment. It appears unlikely, however, that these factors are responsible for the lack of demonstrated efficacy of the SPf66 vaccine in Africa. Most trials in Africa used a case definition based on clinical symptoms as well as demonstration of parasitaemia, and used a mixture of active and passive surveillance.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support the introduction of SPf66 vaccine for routine use in prevention of malaria, either in Africa or in other regions of the world.

Implications for research

There is no justification for further trials of SPf66 in its current formulation for protection against malaria in Africa. The modest efficacy observed against *P. falciparum* in South America suggests that further research on new formulations of SPf66 with increased immunogenicity may be justified in areas outside Africa.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Acosta 1999

Methods	Randomized controlled trial Generation of allocation sequence: vials were assigned letters A to F, three letters designating vaccine and three placebo; random sequence was generated and children got vaccinated from the next available lettered vial Allocation concealment: coded vials, with doses drawn up independent of administrators Blinding: double blind Inclusion of all randomized participants: 1096/1207 (90.8%) received all 3 doses Length of follow up: up to 2 years after third dose
Participants	1207 infants Inclusion criteria: age 1 month Exclusion criteria: requiring admission to hospital at time of first dose; twins (to avoid misidentification)
Interventions	1. 3 doses of SPf66 0.5 mg adsorbed onto 0.312 g alum in 0.125 mL; dosing planned to coincide with Expanded Programme on Immunization (EPI) vaccinations 2. Alum alone
Outcomes	1. Incidence of first or only episode of clinical malaria after 3 doses (case definition: axillary temperature ≥ 37.5 °C together with slide positive (any density) for *Plasmodium falciparum*) 2. Adverse events
Notes	Location: Ifakara, Kilombero district, southern Tanzania Date: 1997 to 1998

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Acosta 1999 *(Continued)*

	Method of surveillance: active follow up by cross-sectional surveys at 8, 10, and 24 months of age; passive follow up from local clinic records

Alonso 1994

Methods	Randomized controlled trial Generation of allocation sequence: method not reported Allocation concealment: code held by monitors Blinding: double blind Inclusion of all randomized participants 586/631 (92.9%) received all 3 doses Length of follow up: 12 months after third dose
Participants	586 children Inclusion criteria: age 1 to 5 years; resident in study area Exclusion criteria: history of allergies leading to medical consultation or treatment; acute conditions warranting hospital admission; chronic conditions; packed cell volume < 25%
Interventions	1. 3 doses of SPf66, 2 mg per dose to > 5 year olds, 1 mg to under 5 year olds, at weeks 0, 4, and 25 2. Tetanus toxoid plus aluminium hydroxide on same schedule Blood stage parasitaemia cleared with Fansidar (25 mg sulfadoxine/0.75 mg pyrimethamine per kg body weight) before each vaccination
Outcomes	1. Incidence of first clinical malaria episode after (a) at least 2 doses, (b) 3 doses of vaccine (case definition: axillary temperature ≥ 37.5 °C together with *Plasmodium falciparum* density > 20,000/µL) 2. Total number of clinical malaria episodes (by active or passive case detection) after (a) at least 2 doses (b) 3 doses of vaccine 3. Prevalence of *P. falciparum* parasitaemia 4. Incidence of *P. falciparum* parasitaemia 5. Density of *P. falciparum* parasitaemia 6. Hospitalization 7. Hospitalization with a diagnosis of malaria 8. Death 9. Death from malaria 10. Packed cell volume 11. Geometric mean anti-SPf66 and anti-*P. falciparum* antibody titre 12. Chloroquine in urine 13. Adverse events
Notes	Location: Idete, Southern Tanzania, an area of intense perennial transmission Date: 1993 to 1994 Method of surveillance: active follow up by weekly home visits by field assistants for a pre-selected (randomized) subgroup; passive follow up from records of Idete dispensary

D'Alessandro 1995

Methods	Randomized controlled trial

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D'Alessandro 1995 *(Continued)*

	Generation of allocation sequence: method not reported Allocation concealment: not reported Blinding: double blind Inclusion of all randomized participants: 630/669 (94.2%) infants received all 3 doses, but because of coding errors, only 547 were included in the analysis; 532/630 (84.4%) children were re-enrolled in the second year Length of follow up: 3.5 months after third dose (until end of malaria transmission season) in first year; 18 weeks of active follow up in second year
Participants	669 infants Inclusion criteria: aged 6 to 11 months Exclusion criteria: weight for age 60% or less; chronic disease (eg heart disease or sickle cell anaemia)
Interventions	1. 3 doses of SPf66 (1 mg per dose) given subcutaneously at weeks 0, 4, and 26 2. Imovax polio given on same schedule Fansidar given 1 to 2 weeks before the first and third doses
Outcomes	1. Incidence of clinical malaria (case definition: axillary temperature > 37.5 °C plus *Plasmodium falciparum* parasitaemia ≥ 6000/µL) 2. Total number of episodes of clinical malaria 3. Adverse events
Notes	Location: 210 villages in Upper River Division, The Gambia, an area of seasonal malaria with moderate transmission Date: 1993 to 1995 Method of surveillance: active follow up by twice weekly visits from field workers; passive follow up by records from 6 health centers in area

Leach 1995

Methods	Randomized controlled trial Generation of allocation sequence: method not reported Allocation concealment: not specified Blinding: double blind Inclusion of all randomized participants: 147/150 (98%) received all 3 doses; 127 children (84.7%) were located and followed in the second year Length of follow up: 9 months in first year, then 18 weeks in the second year
Participants	150 infants Inclusion criteria: age 6 to 11 months Exclusion criteria: none stated
Interventions	1. 3 doses of SPf66 on days 0, 30, and 180 in 4 groups: 1 mg Colombian vaccine (25 participants); 0.5 mg Colombian vaccine (25 participants); 1 mg American vaccine (25 participants); 0.5 mg American vaccine (25 participants)

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Leach 1995 *(Continued)*

	2. Inactivated polio vaccine (50 participants)
Outcomes	1. Incidence of first episode of malaria, after 2 and 3 doses of vaccine (case definition: fever of ≥ 37.5 °C and *Plasmodium falciparum* parasitaemia of ≥ 6000/µL) 2. Total number of episodes of malaria 3. Death 4. Severe anaemia 5. Cerebral malaria 6. Admission to hospital with malaria 7. Antibodies to SPf66 by ELISA 8. Adverse events
Notes	Location: villages near Basse, The Gambia Date: 1993 to 1995 Method of surveillance: active by home visits every 2 weeks during rainy season; passive by attendance at clinic Adverse effects assessed on days 1, 2, and 6

Masinde 1998

Methods	Randomized controlled trial Generation of allocation sequence: not stated Allocation concealment: not stated Blinding: 'blinded', not explicitly stated to be double blind Inclusion of all randomized participants: 69/85 (81.2%) received all 3 doses Length of follow up: 3 months after third dose
Participants	85 adults Inclusion criteria: age 18 to 50 years; resident in study area Exclusion criteria: thrombocytopenia; granulocytopenia, anaemia; pregnancy; gastritis; abnormal liver function; pelvic mass; cholelithiasis; hypertension; asthma; respiratory infection; heart murmur; chest pain
Interventions	1. 3 doses of SPf66 given at 3 to 4 month intervals either intramuscularly (27 participants) or subcutaneously (28 participants) 2. Hepatitis B Engerix, given intramuscularly (30 participants) Quinine (10 mg/kg 3 times a day for 3 days) and doxycycline (100 mg twice a day for 7 days) given 1 week after doses 2 and 3
Outcomes	1. Prevalence of parasitaemia, 2 and 3 months after immunization 2. Infection with specific *Plasmodium falciparum* types as detected by polymerase chain reaction (PCR)
Notes	Location: Siaya district, Nyanza province, Kenya, a highly endemic area with EIR of 6 to 30 infective bites per month during April to August Date: 1995 Method of surveillance: weekly blood slides

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Nosten 1996

Methods	Randomized controlled trial Generation of allocation sequence: valid complex scheme requiring balance of pre-specified characteristics; randomization within households, then evaluated and repeated 3 times to achieve age/sex balance Allocation concealment: not used Blinding: double blind Inclusion of all randomized participants: 1221/1348 (90.6%) participants received all 3 doses Length of follow up: 15 months after third dose
Participants	1348 children of Karen ethnicity Inclusion criteria: age 2 to 15 years Exclusion criteria: serious underlying illness; pregnancy; splenectomy; epilepsy; anaemia (packed cell volume (PCV) < 25%); uncontrolled asthma; thalassemia with anaemia; any other condition deemed to increase risk
Interventions	1. 3 doses of SPf66 vaccine (MPS, San Diego, CA) adsorbed onto aluminium hydroxide (2 mg in 0.5 mL for children ≥ 5 years; 1 mg in 0.25 mL for children < 5 years) subcutaneously on days 0, 30, and about 180 2. Engerix-B recombinant hepatitis B vaccine subcutaneously on same schedule Those with parasites at cross-sectional surveys before first and third vaccine doses were treated with artesunate/mefloquine; children sick and parasitaemic on day of vaccination were also treated and not vaccinated until free of symptoms
Outcomes	1. First episode of symptomatic *Plasmodium falciparum* malaria (case definition: slide positive - any density - for *P. falciparum* (alone or mixed with *Plasmodium vivax*) together with at least 1 of the following: oral temperature > 38 °C or history of fever within 3 days; chills; headache; myalgia; arthralgia; nausea) 2. Severe malaria (case definition: World Health Organization (WHO) definition or parasitaemia > 4%) 3. Symptomless malaria, detected at cross-sectional surveys (case definition: positive slide with no symptoms in preceding 4 days or subsequent 14 days 4. Time to first episode of symptomatic *P. falciparum* infection 5. SPf66 seroconversion
Notes	Location: Shoklo refugee camp, in North-West Thailand, where malaria transmission is low, unstable, seasonal, and highest in May to September and November to January Date: 1993 to 1995 Method of surveillance: active follow up: case detection (daily surveillance and cross-sectional surveys every 2 to 3 months); passive follow up by case detection

Sempertegui 1994

Methods	Randomized controlled trial Generation of allocation sequence: method not reported; randomization within 5 age-groups Allocation concealment: coded vials; codes kept by Ethical Committee (Ministry of Health) until end of study

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Sempertegui 1994 *(Continued)*

	Blinding: double blind Inclusion of all randomized participants: 462/537 (86.0%) received all 3 doses Length of follow up: 1 year after third dose
Participants	537 persons Inclusion criteria: age > 1 year; resident in study area Exclusion criteria: pregnancy; history of allergy; acute infection; renal, cardiovascular or endocrine chronic disease
Interventions	1. 3 doses of SPf66 adsorbed onto aluminium hydroxide (2 mg in 0.5 mL for persons ≥ 5 years; 1 mg in 0.25 mL for children < 5 years) on days 0, 30, and 180 2. Tetanus toxoid adsorbed onto aluminium hydroxide for dose 1; aluminium hydroxide alone for doses 2 and 3
Outcomes	1. Number of malaria cases (case definition: malaria parasites in a thick blood slide, with or without clinical symptoms) 2. Prevalence of anti-SPf66 antibody titre
Notes	Location: La T, Ecuador, an area 'highly endemic' for malaria Date: 1991 to 1992 Method of surveillance: bi-monthly cross-sectional surveys

Urdaneta 1998

Methods	Randomized controlled trial Generation of allocation sequence: numbers 1 to 800 randomly assigned; even numbers got one intervention, odd got the other Allocation concealment: not used Blinding: double blind Inclusion of all randomized participants: 572/800 (71.5%) participants received all 3 doses Length of follow up: 18 months after third dose
Participants	800 persons Inclusion criteria: age 7 to 60 years; resident in study area Exclusion criteria: acute or severe diseases; history of allergies; pregnancy
Interventions	1. 3 doses of SPf66 (0.5 mL) on days 0, 30, and 180 2. Tetanus toxoid for the first dose and aluminium hydroxide for the second and third doses
Outcomes	1. Incidence of first, second, and all *Plasmodium falciparum* and *Plasmodium vivax* cases, total and by person-weeks at risk (case definition: positive slide in a participant previously free of parasitaemia for at least 30 days) 2. Death 3. Parasite density per cubic mm 4. Spleen size

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Urdaneta 1998 *(Continued)*

Notes	Location: rural settlements in Costa Marques, State of Rondonia, Brazil (incidence of malaria 500 per 1000 persons per year) Date: 1991 to 1993 Method of surveillance: blood slide on days 0, 30, 45, 90, 180, 195, 240, 300, 360, 450, 540, 630, and 720; passive surveillance records from four diagnostic and treatment stations

Valero 1993

Methods	Randomized controlled trial Generation of allocation sequence: method not reported Allocation concealment: coded vials at vaccination site: codes kept in Bogota until final analysis Blinding: double blind Inclusion of all randomized participants: it appears that 2496 were randomized prior to applying exclusion criteria; 2033 received first dose and 1548/2033 (76.1%) received all 3 doses Length of follow up: 1 year, starting 1 month after third dose
Participants	2496 persons Inclusion criteria: age > 1 year; resident in study area Exclusion criteria: pregnancy; history of allergy or other chronic disease (tuberculosis, asthma, rickets, marasmus)
Interventions	1. 3 doses of SPf66 on days 0, 30, and 180; 0.5 mL if > 5 years, 0.25 mL if 1 to 4 years (adsorbed onto aluminium hydroxide, 4 mg/mL) 2. Tetanus toxoid for first dose, saline in aluminium hydroxide for second and third doses
Outcomes	1. Number of episodes of *Plasmodium falciparum* malaria 2. Incidence of first episode of malaria by person weeks at risk, by age group and sex (case definition: axillary temperature ≥ 37.5 °C, symptoms of malaria and positive blood slide) 3. Incidence of second episode of malaria by person weeks at risk, by age group and sex 4. Density of parasitaemia 5. Cases of *Plasmodium vivax* 6. Incidence by antibody titre group 7. Adverse events
Notes	Location: La Tola, Colombia, which has perennial transmission with fluctuating incidence (20 to 500/ cases per 1000 person per year) Date: 1990 to 1991 Method of surveillance: active follow up by monthly home visits; blood slides if fever or other symptoms present; passive from records of 4 village-based malaria control posts and the health center

Valero 1996

Methods	Randomized controlled trial Generation of allocation sequence: "pseudorandom numbers generated in a program written in dBase III"; randomization within 5 age groups and by sex (10 strata)

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Valero 1996 *(Continued)*

	Allocation concealment: codes kept by clinical monitor in sealed envelopes until end of study Blinding: double blind Inclusion of all randomized participants: 1257/1825 (68.9%) participants received all 3 doses Length of follow up: 22 months after second dose
Participants	1825 persons Inclusion criteria: age 1 to 86 years; resident in study area Exclusion criteria: pregnancy; positive blood slide at time of vaccination; history of allergy; acute infection; renal, cardiovascular, or endocrinological chronic infection
Interventions	1. 3 doses of SPf66, adsorbed onto aluminium hydroxide (2 mg per dose, 1 mg for those < 5 years) given subcutaneously at days 0, 30, and 180 2. Tetanus toxoid at first dose, aluminium hydroxide at doses 2 and 3
Outcomes	1. First cases of *Plasmodium falciparum* and *Plasmodium vivax* (case definition: positive blood slide in persons free of parasitaemia for previous 30 days) 2. Subsequent cases of *P. falciparum* and *P. vivax* 3. Density of parasitaemia
Notes	Location: 14 villages along Rio Rosario, Colombia, an area endemic for malaria Date: 1992 to 1994

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amador 1992	Volunteers were randomized to two different groups, within each of which were vaccinees and controls; no randomization into vaccine and control groups
Gordon 1996	Nonrandomized open label phase 1 trial; no placebo group
Migasena 1997	Nonrandomized open label phase 1 study; no placebo group
Nosten 1997	Open label phase 1 trial; no placebo group
Noya 1994	Nonrandomized study
Patarroyo 1988	Nonrandomized study
Patarroyo 1992	Nonrandomized study, no placebo group

DATA AND ANALYSES

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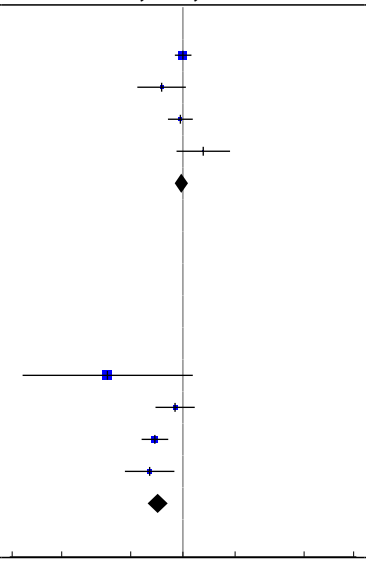
Comparison 1. SPf66 vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 New malaria episode (P. falciparum)	9	7399	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.84, 0.96]
1.1 Africa	4	2371	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.90, 1.07]
1.2 South America	4	3807	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.63, 0.82]
1.3 Asia	1	1221	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.90, 1.25]
2 New malaria episode (P. falciparum): year 2	2	600	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.19]
3 New malaria episode (P. vivax)	5	5028	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.93, 1.08]
3.1 South America	4	3807	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.01, 1.32]
3.2 Asia	1	1221	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.83, 0.98]
4 Death	3	2224	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.35, 1.22]
5 Admission to hospital	3	2224	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.08]
6 Admission to hospital with diagnosis of malaria	2	1133	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.53, 1.35]
7 Prevalence of P. falciparum	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 SPf66 vaccine versus placebo, Outcome 1 New malaria episode (P. falciparum).

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Africa					
Acosta 1999	294/550	288/541		25.92%	1[0.9,1.12]
Alonso 1994	49/274	74/312		6.18%	0.75[0.55,1.04]
D'Alessandro 1995	160/316	121/231		12.48%	0.97[0.82,1.14]
Leach 1995	56/97	22/50		2.59%	1.31[0.92,1.87]
Subtotal (95% CI)	**1237**	**1134**		**47.16%**	**0.98[0.9,1.07]**
Total events: 559 (Vaccine), 505 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.35, df=3(P=0.15); I^2=43.91%					
Test for overall effect: Z=0.49(P=0.62)					
1.1.2 South America					
Sempertegui 1994	4/230	11/232		0.98%	0.37[0.12,1.14]
Urdaneta 1998	76/269	85/271		7.56%	0.9[0.69,1.17]
Valero 1993	152/738	242/810		20.6%	0.69[0.58,0.82]
Valero 1996	53/634	81/623		7.29%	0.64[0.46,0.89]
Subtotal (95% CI)	**1871**	**1936**		**36.43%**	**0.72[0.63,0.82]**
Total events: 285 (Vaccine), 419 (Placebo)					



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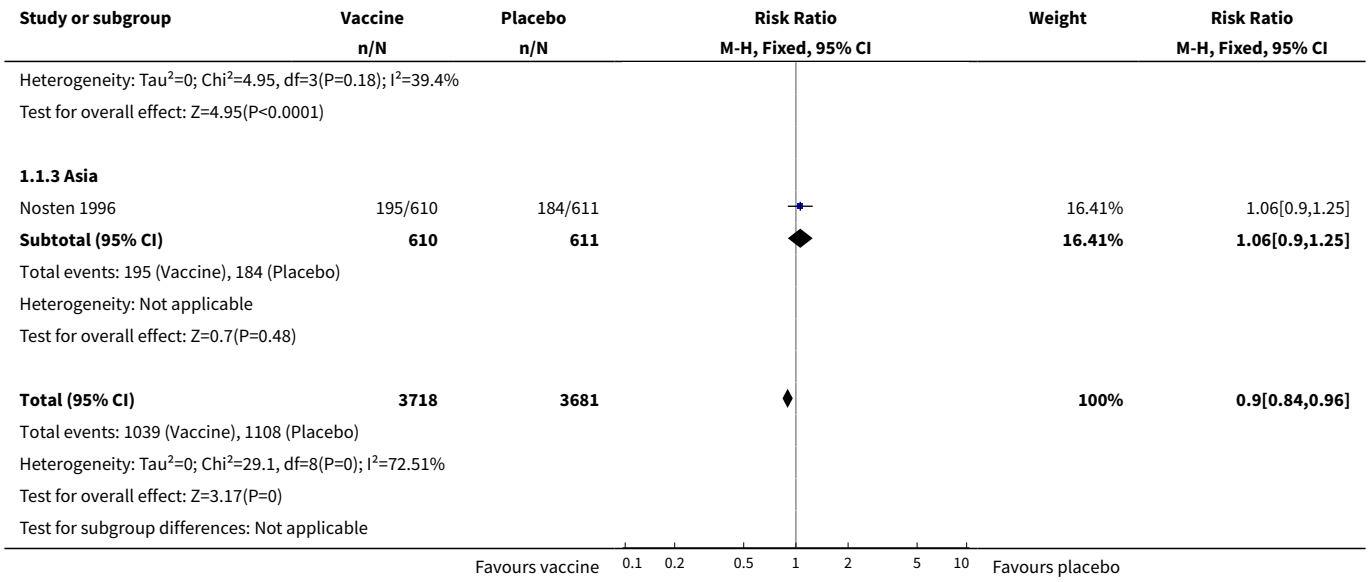
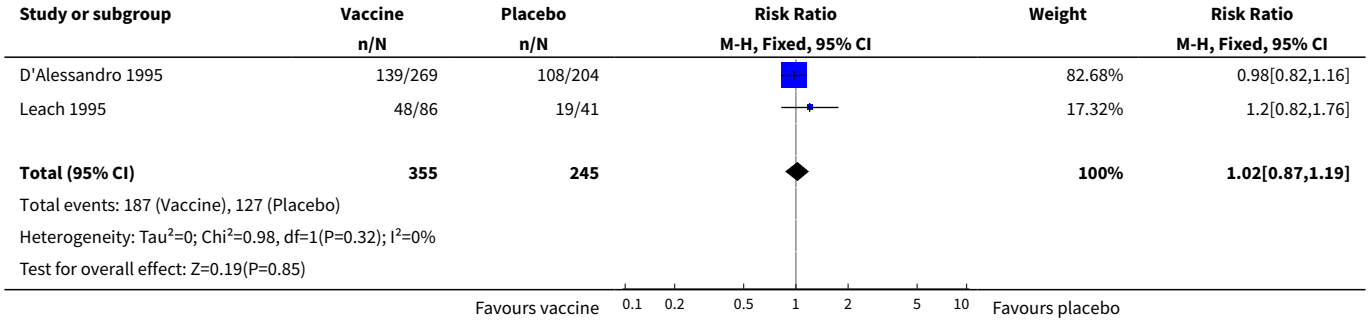
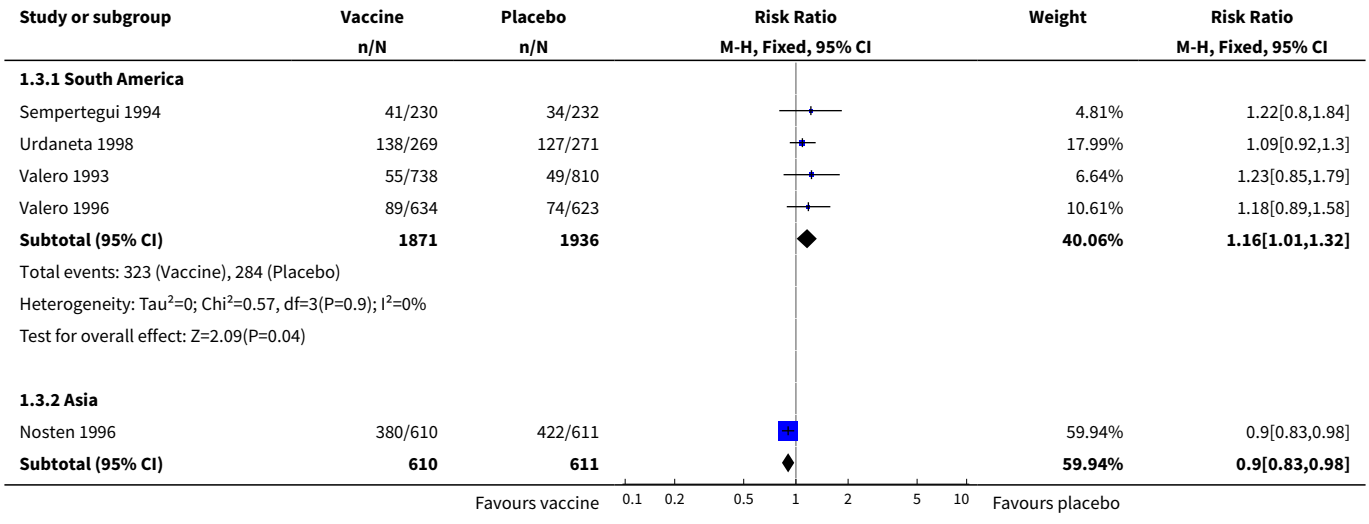


Analysis 1.2. Comparison 1 SPf66 vaccine versus placebo, Outcome 2 New malaria episode (P. falciparum): year 2.



Analysis 1.3. Comparison 1 SPf66 vaccine versus placebo, Outcome 3 New malaria episode (P. vivax).



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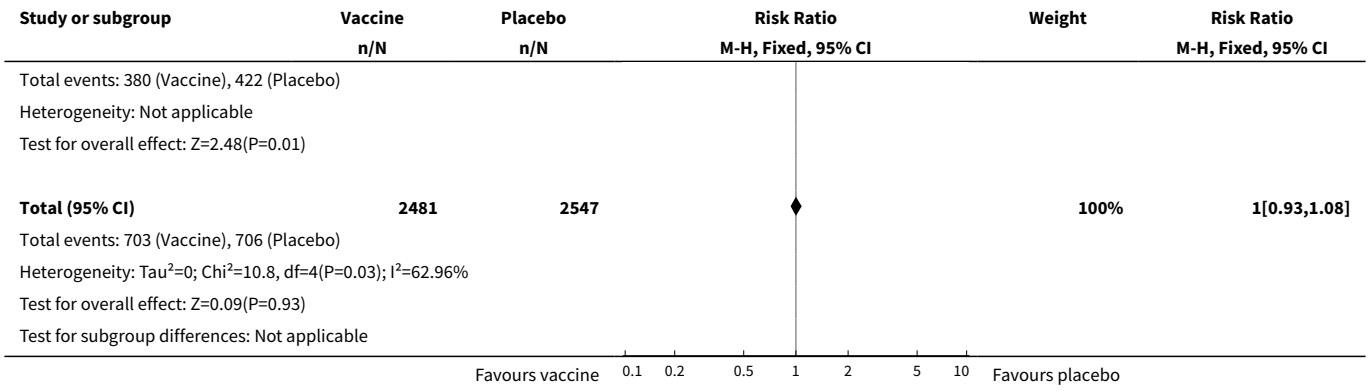
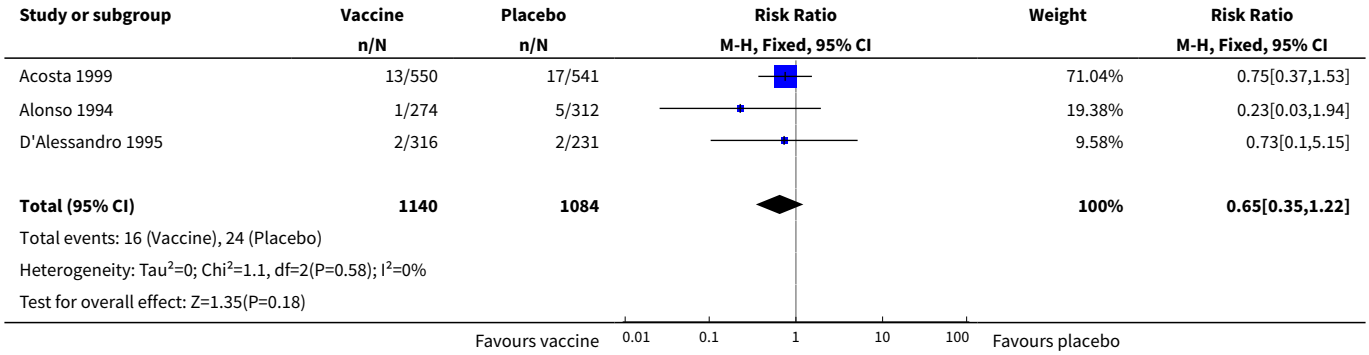
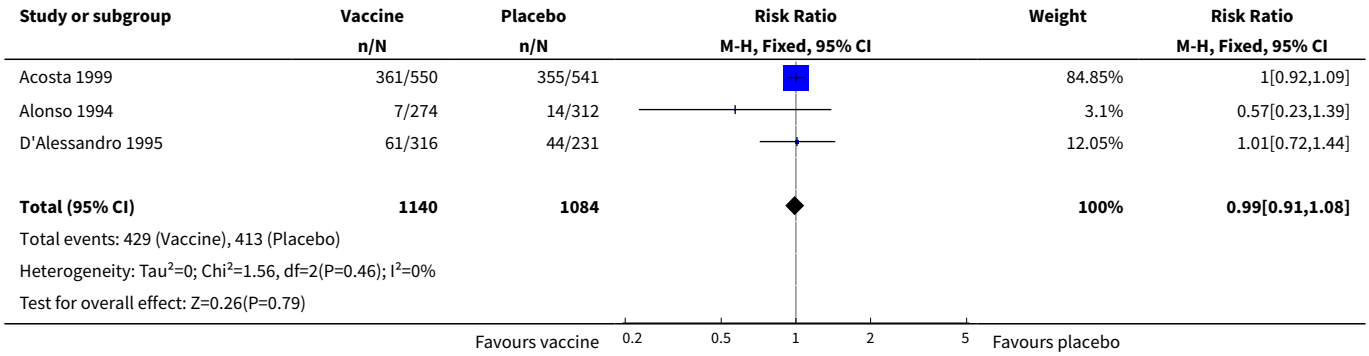


Analysis 1.4. Comparison 1 SPf66 vaccine versus placebo, Outcome 4 Death.



Analysis 1.5. Comparison 1 SPf66 vaccine versus placebo, Outcome 5 Admission to hospital.



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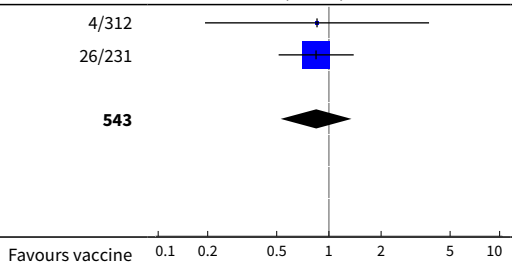
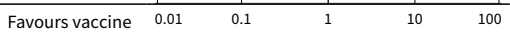
Analysis 1.6. Comparison 1 SPf66 vaccine versus placebo, Outcome 6 Admission to hospital with diagnosis of malaria.

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alonso 1994	3/274	4/312		11.07%	0.85[0.19,3.78]
D'Alessandro 1995	30/316	26/231		88.93%	0.84[0.51,1.39]
Total (95% CI)	**590**	**543**		**100%**	**0.84[0.53,1.35]**
Total events: 33 (Vaccine), 30 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.7(P=0.48)					



Analysis 1.7. Comparison 1 SPf66 vaccine versus placebo, Outcome 7 Prevalence of P. falciparum.

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Masinde 1998	19/43	12/26		0.96[0.56,1.63]



APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]	Science Citation Index
1	malaria	malaria	malaria	malaria	malaria	malaria
2	Plasmodium	Plasmodium	Plasmodium	Plasmodium	Plasmodium	Plasmodium
3	1 or 2	1 or 2	1 or 2	1 or 2	1 or 2	1 or 2
4	vaccin*	vaccin*	vaccin*	vaccin*	vaccin*	vaccin*
5	3 and 4	3 and 4	3 and 4	3 and 4	3 and 4	3 and 4
6	—	MALARIA VACCINES	MALARIA VACCINES	MALARIA VACCINES	—	—
7	—	5 or 6	5 or 6	5 or 6	—	—
8	—	—	Limit 7 to human	Limit 7 to human	—	—

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2005); Upper case: MeSH or EMTREE heading; Lower case: free text term.

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WHAT'S NEW

Date	Event	Description
18 March 2008	New search has been performed	New studies sought but none found

HISTORY

Protocol first published: Issue 1, 1995
Review first published: Issue 2, 1996

Date	Event	Description
21 July 2008	Amended	Converted to new review format with minor editing.
15 August 2006	New search has been performed	2006, Issue 4: References to the Cochrane Reviews for pre-erythrocytic vaccines and blood-stage vaccines added.
6 February 2006	New citation required and conclusions have changed	2006, Issue 2: The original review of malaria vaccines (Graves 2003) has been divided into three parts: SPf66, pre-erythrocytic, and blood-stage vaccines. This review includes only SPf66 trials; because of this change the text of the review has been completely rewritten. No new trials of SPf66 have been added since the original review, although additional publications from previously included trials have been added. The SPf66 trials have been subgrouped into Africa, South America, and Asia, instead of just the former two categories, for some outcomes. The second year of follow up for two trials in The Gambia has been added. Risk ratio is used as the default measure of effect.

CONTRIBUTIONS OF AUTHORS

Patricia Graves wrote the protocol, extracted and analyzed data, and drafted the review. Hellen Gelband extracted data and edited the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.
- European Commission (Development Directorate XII), Belgium.

INDEX TERMS

Medical Subject Headings (MeSH)

Malaria [*prevention & control]; Malaria Vaccines [immunology] [*therapeutic use]; Protozoan Proteins [immunology] [*therapeutic use]; Randomized Controlled Trials as Topic; Recombinant Proteins [immunology] [*therapeutic use]; Vaccines, Synthetic [immunology] [therapeutic use]

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MeSH check words

Humans

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