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[Intervention Review]

Vaccines for preventing malaria (blood-stage)

Patricia M Graves[1], Hellen Gelband[2]

[1]EpiVec Consulting, Atlanta, Georgia, USA. [2]Resources for the Future, Washington, DC, USA

Contact: Patricia M Graves, EpiVec Consulting, Atlanta, Georgia, GA 30341, USA. epivec@comcast.net, pmgraves@aol.com.

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ABSTRACT

Background

A malaria vaccine is needed because of the heavy burden of mortality and morbidity due to this disease. This review describes the results of trials of blood (asexual)-stage vaccines. Several are under development, but only one (MSP/RESA, also known as Combination B) has been tested in randomized controlled trials.

Objectives

To assess the effect of blood-stage malaria vaccines in preventing infection, disease, and death.

Search methods

In March 2006, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2006, Issue 1), MEDLINE, EMBASE, LILACS, and the Science Citation Index. We also searched conference proceedings and reference lists of articles, and contacted organizations and researchers in the field.

Selection criteria

Randomized controlled trials comparing blood-stage vaccines (other than SPf66) against *P. falciparum*, *P. vivax*, *P. malariae*, or *P. ovale* with placebo, control vaccine, or routine antimalarial control measures in people of any age receiving a challenge malaria infection.

Data collection and analysis

Both authors independently assessed trial quality and extracted data. Results for dichotomous data were expressed as risk ratios (RR) with 95% confidence intervals (CI).

Main results

Five trials of MSP/RESA vaccine with 217 participants were included; all five reported on safety, and two on efficacy. No severe or systemic adverse effects were reported at doses of 13 to 15 µg of each antigen (39 to 45 µg total). One small efficacy trial with 17 non-immune participants with blood-stage parasites showed no reduction or delay in parasite growth rates after artificial challenge. In the second efficacy trial in 120 children aged five to nine years in Papua New Guinea, episodes of clinical malaria were not reduced, but MSP/RESA significantly reduced parasite density only in children who had not been pretreated with an antimalarial drug (sulfadoxine-pyrimethamine). Infections with the 3D7 parasite subtype of MSP2 (the variant included in the vaccine) were reduced (RR 0.38, 95% CI 0.26 to 0.57; 719 participants) while those with the other main subtype, FC27, were not (720 participants).

Authors' conclusions

The MSP/RESA (Combination B) vaccine shows promise as a way to reduce the severity of malaria episodes, but the effect of the vaccine is MSP2 variant-specific. Pretreatment for malaria during a vaccine trial makes the results difficult to interpret, particularly with the relatively small sample sizes of early trials. The results show that blood-stage vaccines may play a role and merit further development.

23 April 2019

No update planned

Other

Although the CIDG conducted a new search up to 8 Aug, 2018 for potentially relevant studies, these studies have not yet been incorporated into this Cochrane Review as this review is not a current priority for update by CIDG.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing malaria in the blood phase

Malaria is a parasitic disease spread by mosquitoes. It affects millions of people worldwide and causes significant illness and mortality. Uncomplicated malaria presents with symptoms such as fever, headache, muscle pain, and vomiting, and children commonly present with rapid breathing, cough, and convulsions. Severe malaria causes unconsciousness and death. Vaccines are widely considered a necessary component for the complete success of malaria control. The parasite moves through several life-cycle stages in the human body, during which its molecular makeup changes, at least partially. Vaccines specific for each stage (ie targeting different antigens) are under development. This review looked at vaccinations targeted at the asexual (blood) phase of the parasite's life, when the parasites are in red blood cells. One vaccine for this phase, MSP/RESA (also known as Combination B), has been tested in field trials in Papua New Guinea. It reduced the density of parasites in the blood, but it did not prevent malaria attacks. Blood-stage vaccines are being actively pursued in further research.

BACKGROUND

Malaria is a severe and debilitating disease caused by four species of the parasitic protozoan *Plasmodium* that are transmitted by many species of anopheline mosquitoes. *Plasmodium falciparum* is the most widespread and also the most serious and potentially fatal 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). Annual mortality (nearly all from *P. falciparum* malaria) is thought to be around 1.1 million (WHO 2002; Breman 2004). Malaria is 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 lives in areas where they are exposed to risk of malaria (Hay 2004), and the increasing numbers of visitors to endemic areas are also at risk.

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 (Ballou 2004; Moorthy 2004). Improved methods for screening the numerous vaccine candidates for efficacy have been developed (Druilhe 2005). 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 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. Ideally, a vaccine effective at all these parasite stages is desirable (Richie 2002).

Given the complexity and wide range of malaria vaccines under development, we have chosen to consider them in separate categories: blood-stage vaccines (the subject of this review); SPf66 vaccine; and pre-erythrocytic vaccines. Multi-stage vaccines, such as combined pre-erythrocytic and blood-stage vaccines (Reber-Liske 1995; Sturchler 1995), and transmission-blocking vaccines will be included in future reviews.

The SPf66 vaccine was the first to be tested extensively (Graves 2006a). SPf66 was ineffective in Africa (five trials) and Asia (one trial). It had marginal efficacy in South America (four trials). SPf66 is no longer being tested, and development towards commercialization is not taking place. However, it is possible that new formulations of SPf66 or combinations with other antigens will be developed in the future. Results with one pre-erythrocytic vaccine, RTS,S, were more encouraging. In four trials, it was effective in preventing a significant number of clinical malaria episodes, including good protection against severe malaria in children, with no serious adverse effects (Graves 2006b).

This review includes trials of blood (asexual)-stage vaccines. The first blood-stage vaccine to be tested in challenge trials is MSP/RESA, known as Combination B. This vaccine is a mixture of three recombinant asexual blood-stage antigens: parts of two merozoite surface proteins (MSP1 and MSP2) together with a part of the ring-infected erythrocyte surface antigen (RESA), which is found on the inner surface of the infected red cell membrane. The MSP1 antigen is a 175 amino acid fragment of the relatively conserved blocks 3 and 4 of the K1 parasite line; it also includes a T-cell epitope from the *P. falciparum* circumsporozoite (CS) protein as part of the MSP1 fusion protein. The MSP2 protein includes the nearly complete sequence from one allelic form (3D7) of the polymorphic MSP2 protein. The RESA antigen consists of 70% of the native protein from the C-terminal end of the molecule.

Many other potential asexual stage vaccines are currently undergoing preclinical evaluation (*see* WHO 2005). The proteins from which they are derived include:

- AMA1: recombinant apical membrane antigen 1 from the merozoite.
- MSP1, MSP2, MSP3, MSP4, and MSP5: merozoite surface proteins or portions thereof (eg MSP1(19), MSP1(42)), either recombinant or synthetic peptides.
- GLURP: glutamate-rich protein, recombinant or synthetic peptide, alone or combined with MSP3.
- RAP2: recombinant rhoptry-associated protein 2 (the rhoptry is an organelle in the merozoite).
- EBA-175, EBP2, MAEBL, and DBP: erythrocyte binding proteins involved in parasite invasion.
- PfEMP1: recombinant erythrocyte membrane protein, an antigen present on the surface of infected red blood cells.

Of these blood-stage antigens, a few also occur in pre-erythrocytic stages (GLURP, EBA-175, and MAEBL). Several antigens (AMA1, MSP1(19), MSP1(42), and a MSP peptide) have been tested in Phase 1 safety and immunogenicity trials excluded from this review. A Phase 2 trial of MSP1(42) (also known as FMP1) is in progress in Kenya (Stoute 2006). Trials with these other blood-stage vaccines will be included as the results of randomized efficacy trials become available. MSP1-based and AMA-1 based antigens are also being tested in combination with antigens from pre-erythrocyte stages (Heppner 2005).

OBJECTIVES

To assess the effect of blood-stage malaria vaccines in preventing infection, disease, and death.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

People of any age.

Types of interventions

Intervention

Recombinant, synthetic peptide, parasite-derived, or other vaccines containing antigens from blood (asexual) stages of any species of malaria parasite tested in humans in artificial or natural challenge trials.

Control

Placebo, control vaccine, or routine antimalarial control measures.

Types of outcome measures

Primary

- Clinical malaria episodes.
- Parasite density.

Secondary

- New malaria infection.
- Prevalence of parasitaemia.
- Fever episodes.
- Anaemia.
- Cerebral malaria.
- Severe malaria.
- Admission to hospital.
- Admission to hospital with diagnosis of malaria.
- Death.
- Adverse events.

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 2006); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2006, Issue 1); MEDLINE (1966 to March 2006); EMBASE (1980 to March 2006); LILACS (1982 to March 2006); and Science Citation Index (SCI; 1981 to March 2006).

Conference proceedings

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

Researchers and organizations

We contacted the following researchers working in the field: A Saul; B Genton; B Greenwood; and A Thomas. We also contacted R Rabinovich and searched the websites of the Malaria Vaccine Initiative at Program for Appropriate Technology in Health (PATH) and the Malaria Vaccine Technology Roadmap (January 2006). Other web sources included the European Malaria Vaccine Initiative, the European Malaria Vaccine Consortium, and the African Malaria Network Trust (November 2005).

Reference lists

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

Data collection and analysis

Selection of studies

Both authors independently applied the inclusion criteria to all identified trials. Differences were discussed until consensus was reached.

Data extraction and management

Both authors independently extracted data from the included trials using a pre-designed form. Differences found were discussed between the authors and errors corrected. Data that were not clear were checked with the authors for Saul 1999a, Saul 1999b, and Genton 2002.

Assessment of risk of bias in included studies

Both authors independently assessed the trials for four dimensions of quality using a pre-specified form: method of generation of allocation sequence and allocation concealment (adequate, inadequate, not done, or unclear as defined by Jüni 2001); blinding (described who was blinded, eg participants, investigators, and outcome assessors); and completion of follow up (proportion of those randomized who completed all doses and who completed follow up, if stated). Differences were discussed until consensus was reached. Trial details were checked with the authors for Saul 1999a, Saul 1999b, and Lawrence 2000.

Data synthesis

We analysed the data using Review Manager 5. Results for dichotomous data were 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 (also known as risk ratio reduction): efficacy = (1 - RR) x 100%. Similarly, the 95% confidence interval (CI) for the vaccine efficacy (risk ratio reduction) may be obtained by substituting the upper and lower 95% confidence interval of the risk ratio into the formula.

Continuous results (parasite density) were expressed as mean differences (MD), using the geometric mean parasite density in positive blood samples.

If trials continued for more than one year (with or without booster dose), we separated the analysis of these results according to the year of follow up. It was prespecified that subgroup analysis could be performed according to geographical area or intensity of transmission, if appropriate. It was not prespecified that subgrouping would be done based on whether or not the participants were pretreated with antimalarial drugs. However this had an important effect on the results in one trial and therefore such subgrouping was done.

RESULTS

Description of studies

Five trials of MSP/RESA vaccine (Combination B) including 217 participants met the inclusion criteria; see the 'Characteristics of included studies' for more detailed information. Six trials were excluded; see the 'Characteristics of excluded studies'. One safety and immunogenicity trial of MSP1 in Kenya is in press (Stoute 2006). We will include it in an update of this review if and when an efficacy trial of the vaccine is completed.

Of the five included trials, three assessed safety (and immunogenicity) only, and two tested efficacy as well as safety. Three were small trials in non-immune adults: two of these assessed safety only (Saul 1999a; Saul 1999b); and one assessed safety and efficacy against experimental challenge (Lawrence 2000). The two other trials had immune participants in Papua New Guinea: one was a small safety trial in 12 immune adults (Genton 2000), and the largest trial (120 participants) assessed safety and efficacy in semi-immune children aged five to nine years exposed to natural challenge (Genton 2002). All trials used vaccine in Montanide ISA 720 adjuvant.

Safety trials

The first two randomized controlled trials, Saul 1999a and Saul 1999b, were small dose-finding studies that reported on safety and immunogenicity in non-immune adults (32 and 36 participants respectively). The first dose tested was 100 µg of each antigen, either mixed in one injection site or divided into three sites. Because of adverse effects in initial participants (see below) the dose was reduced to 50 µg (20 µg in the second dose) for remaining participants in the first trial, and to 50 µg, 13 µg, or 4 µg of each antigen per dose in the second trial. A dose of 13 to 15 µg of each antigen was used in the three subsequent trials.

The safety trial of Genton 2000 included 12 semi-immune adults in Papua New Guinea who were moved to a non-endemic area for the duration of the trial (six weeks) to monitor adverse events. This trial used 15 µg of each antigen (total 45 µg) in each of two doses.

Safety and efficacy trials

The first MSP/RESA efficacy trial, Lawrence 2000, was in 17 non-immune adult Australians using experimental challenge with blood-stage parasites. In this trial, the primary outcome measure was the growth rate of the parasites after artificial challenge with blood-stage parasites injected intravenously, assessed by polymerase chain reaction (PCR). All participants had malaria parasites detected by PCR by day eight after the challenge, when they were all treated even though symptoms had not yet developed.

The second safety and efficacy trial, Genton 2002, was in 120 Papua New Guinea children aged five to nine years exposed to natural challenge. The primary outcome measures were parasite density (geometric mean in positive samples) and change in ratio of different parasite variants (response to the variants whose genetic material was included in the vaccine was expected to be better than response to other variants). Active surveillance was by weekly home visits from week eight to 76 for suspected cases, with blood samples taken from all children every two weeks from weeks eight to 18. Passive surveillance for clinical episodes reporting to health facilities was also done. Extensive safety data were also collected. Because of debate over whether children should be pretreated for malaria before vaccination, half of the participants were treated with sulfadoxine-pyrimethamine (an effective drug in that population), and the results analysed separately by these subgroups.

Risk of bias in included studies

The method of randomization (allocation sequence) was by computer-generated random assignment in all trials. In the Saul 1999a trial, participants were initially randomly divided into three groups that were vaccinated sequentially, but screening and scheduling arrangements led to some reassignment between groups. Two in each group were randomly chosen to receive placebo. The Genton 2002 trial used randomization within age-stratified blocks of 12 so that vaccines could be given in a staggered manner while assessing safety. The Genton 2002 trial was also adequate for allocation concealment, while this was unclear in the other trials.

The three trials that only examined safety and immunogenicity blinded only the participants (Saul 1999a; Saul 1999b; Genton 2000), and the two trials that also assessed efficacy were double blind (Lawrence 2000; Genton 2002).

All the MSP/RESA trials were high quality in terms of losses to follow up. All participants completed the initial safety trials (Saul 1999a; Saul 1999b; Genton 2000) and the experimental challenge trial (Lawrence 2000). However, one participant in the placebo group in the Saul 1999a trial inadvertently received vaccine instead of placebo at the first dose. This person received vaccine at the second dose and was subsequently treated as a member of that group. Two participants in the Saul 1999b trial did not receive the second dose of vaccine due to adverse effects after the first dose but completed all the follow up. In the larger natural challenge trial (Genton 2002), 91% of all clinical assessments (7532 visits) and all but one of the planned 1080 blood samples (99.9%) were completed over a period of 76 weeks. The analysis was based on the total number of children randomized into the trial (120).

Effects of interventions

Criteria for judging the effectiveness of blood-stage vaccines are different from the pre-erythrocytic vaccines. With the latter, the aim is to prevent a patent infection from occurring at all, while with blood-stage vaccines, the aim is to reduce parasite density, which should translate to a reduction in number of clinical attacks or symptom severity.

1. Efficacy

Lawrence 2000 and Genton 2002 measured efficacy, but only Genton 2002 provided data that could be reported in the review. Genton 2002 is the only trial to date that has assessed a blood-stage vaccine with natural challenge. The results showed extreme heterogeneity between groups of children who were or who were not pretreated with an antimalarial (sulfadoxine-pyrimethamine). As a result, these two subgroups could not be combined in the meta-analyses for most outcome measures.

1.1. Parasite density

Parasite density was significantly lower in the vaccine group than in the placebo group, in the group that was not pretreated with sulfadoxine-pyrimethamine (MD -238.00, 95% -238.95 to -237.05; 31 participants, Analysis 1.1). The opposite trend was observed in the group that was treated with sulfadoxine-pyrimethamine (MD 432.30, 95% 429.99 to 434.61; 16 participants, Analysis 1.1), but this was complicated by the fact that in this sub-arm of the trial at baseline the vaccine group had a ten-fold higher parasite density than the placebo group.

1.2. Clinical malaria episodes

There was no evidence for an effect of the vaccine against episodes of clinical malaria in either the group pretreated with the antimalarial (60 participants) or the group with no antimalarial (60 participants) (Analysis 1.2); the results for these subgroups tended in the opposite direction.

1.3. New malaria infections

The trialists reported the effect of the vaccine on different parasite subtypes (detected by PCR); see Analysis 1.3. The vaccine was of the 3D7 MSP2 allelic type and vaccinees had a significantly fewer new malaria infections with the 3D7 type (RR 0.52, 95% CI 0.28 to 0.99; 120 participants). The number of infections measured with FC27, the other allelic type (not included in the vaccine), was not reduced by vaccination (120 participants). These effects were seen in both the groups with and without pretreatment with sulfadoxine-pyrimethamine (combined results are given in the analyses).

1.4. Prevalence of parasitaemia

Prevalence of parasitaemia (as assessed by blood slide) was lower in the group that was not pretreated with an antimalarial (60 participants) than the group that used sulfadoxine-pyrimethamine (60 participants), but neither result was statistically significant (Analysis 1.4).

In an analysis of the effect of the vaccine on different parasite subtypes (detected by PCR) (see Analysis 1.5), the vaccinees had a significantly lower prevalence of the 3D7 type (included in the vaccine) than did placebo recipients (RR 0.38, 95% CI 0.26 to 0.57; 719 participants). The prevalence of FC27, the other allelic type (not included in the vaccine), was not reduced by vaccination (720 participants). These effects were seen in both the groups with and without pretreatment with sulfadoxine-pyrimethamine (combined results are given in the analyses).

2. Safety

All five trials contributed safety data to the review. The plan in the first MSP/RESA trial was to give 100 µg of each antigen at each of two doses (Saul 1999a). However, due to adverse effects at these doses, only the first two-thirds of the 32 participants received this amount at the first dose. Significant pain and swelling in the injected thigh in one of these participants developed 12 days after first vaccination. The second dose was reduced to 20 µg of each antigen and even at that dose a hard painful lump developed at the injection site in the same volunteer six weeks after the second dose, causing difficulty in walking. Two other participants developed moderately severe delayed reactions to the vaccine, even when antigens were given in separate sites.

In the second trial (Saul 1999b), doses were reduced to 4, 25, or 50 µg of each antigen or equivalent amount of placebo. In the 50 µg group, one vaccine participant developed severe pain in the injected thigh and one other developed a severe delayed reaction of pain and swelling in the injected leg.

Overall in the two trials using 50 to 100 µg doses (Saul 1999a; Saul 1999b), there were four severe and four moderate local reactions, all in participants receiving vaccine rather than placebo. All the severe reactions resolved and there were no severe systemic reactions or sequelae. All three subsequent trials used a lower dose of 13 to 15 µg of each antigen per dose (Lawrence 2000; Genton 2000; Genton 2002).

For the purposes of this review, we have tabulated only adverse events occurring in the three trials using the 13 to 15 µg doses, shown graphically in Analysis 1.6 and Analysis 1.7. The results represent the sum of events occurring after each of two doses. There were no significant differences between vaccine and placebo groups in the frequency of local or systemic adverse events of any severity (Analysis 1.6) or events of moderate severity including fever and pain or swelling at the injection site (Analysis 1.7). The most frequent adverse events reported were injection site pain, tenderness, and swelling. No serious or severe adverse events occurred in these three trials using 13 to 15 µg doses.

DISCUSSION

This review describes the results of several relatively small trials of safety and efficacy of a blood-stage malaria vaccine. A small efficacy trial in non-immune adults with experimental challenge showed no effect (Lawrence 2000). In the single natural-challenge efficacy trial of MSP/RESA vaccine (Combination B) in semi-immune children (Genton 2002), no effect on clinical malaria infections was detected. However, parasite density was significantly reduced in the vaccinated children who were not pretreated with sulfadoxine-pyrimethamine. Also, in these children there was a reduction in the proportion of children with medium and high parasitaemia levels. The necessity of subgrouping by pretreatment status, together with imbalance in parasite density at baseline and heterogeneity, reduced the expected power of this trial.

The MSP/RESA vaccine (Combination B) contains three blood-stage antigens – MSP1, MSP2, and RESA. MSP2 has two major allelic forms (3D7 and FC27). Vaccinees in the Genton 2002 trial had a lower incidence and prevalence of parasites with the 3D7 type of MSP2 (the type included in the vaccine) than the placebo group, and a higher incidence of malaria episodes were associated with the FC27 type of MSP2. The investigators noted that efforts should be made to include all significant allelic types in a future vaccine. Also, the relative role of the three vaccine constituents cannot be assessed when based on the trials that have been carried out to date.

An issue explored by the Genton 2002 trial is the advisability of clearing parasitaemia with drug treatment before a trial commences. In this trial, significant efficacy was only observable in the group who were not pretreated with sulfadoxine-pyrimethamine. Since pretreatment with this antimalarial clearly reduces infection it enables incidence of new infections to be more easily determined, but this strategy also reduces power to detect changes in prevalence.

The results from the Genton 2002 trial have had a large impact on the design of blood-stage vaccine trials. In particular, the observation that the frequency of high or medium density infections was reduced by vaccination (in children not pretreated with sulfadoxine-pyrimethamine) has led to the likely inclusion of a similar outcome in future trials.

The results from trials of vaccines from other malaria life stages are described in separate Cochrane Reviews. In brief, the SPf66 vaccine showed early promise, but eventually it was determined to be ineffective in African children and only marginally effective in South America (Graves 2006a). The pre-erythrocytic vaccine RTS,S is showing encouraging results, with approximately 26% efficacy against malaria episodes and an estimated 58% efficacy against severe malaria in children (Graves 2006b). There is not enough evidence yet to determine whether MSP/RESA or other blood-stage vaccines currently being tested will be superior or equal to the now obsolete SPf66 vaccine or to the pre-erythrocytic vaccine RTS,S. Prevailing opinion today is that multi-stage vaccines, with antigens from several stages combined, are likely to be most effective. Results of multi-stage vaccine trials will be covered in a separate Cochrane Review as they become available.

AUTHORS' CONCLUSIONS

Implications for practice

Blood-stage malaria vaccines are not currently licensed for use. It is thus too early to evaluate implications for practice.

Implications for research

Based on the MSP/RESA results, blood-stage vaccines show promise. Further development of the vaccine should include adding the other main allelic form of MSP2, and the relative contribution of the other antigens in the vaccine should be clarified. Pretreatment of the participants during a vaccine trial has a large effect on the results, and the desirability of this practice for blood-stage vaccine trials needs to be resolved.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Genton 2000

Methods	Randomized controlled trial
	Generation of allocation sequence: computer-generated list
	Allocation concealment: unclear
	Blinding: participants blinded

Genton 2000 *(Continued)*

	Inclusion of all randomized participants: 100% completed trial Length of follow up: 6 weeks after second dose
Participants	Number: 12 adults Inclusion criteria: age 18 to 50 years Exclusion criteria: allergic predisposition; acute illness on day of screening; chronic illness; impaired liver or kidney function; human immunodeficiency virus (HIV) infection
Interventions	1. MSP1/MSP2/RESA vaccine in adjuvant Montanide ISA720: 2 doses at 4-week intervals; 0.55 mL per dose containing 15 µg of each antigen 2. Adjuvant only: 0.55 mL All participants given sulfadoxine-pyrimethamine before first dose to clear parasites
Outcomes	1. Adverse events (local or systemic) 2. Immunologic outcomes
Notes	Location: Goroka and Wosera, Papua New Guinea; participants were moved to Goroka (non-endemic area) during immunization Method of surveillance: observation by physician for 6 h after immunization, daily visits for 2 weeks; weekly observation for 6 weeks

Genton 2002

Methods	Randomized controlled trial Generation of allocation sequence: computer generated; randomized in blocks of 12 within age group (5 to < 7.5 and 7.5 to < 10 years), 3 into each of 4 groups (vaccine/placebo, pretreated/not treated with sulfadoxine-pyrimethamine) Allocation concealment: code generated externally; vials indistinguishable and labelled only with code by independent preparers Blinding: double blind Inclusion of all randomized participants: 99.9% participation in blood sampling to week 18; 91% participation in morbidity surveillance to week 76 Length of follow up: 68 weeks after second immunization
Participants	Number: 120 children Inclusion criteria: age 5 to 9 years; parental consent Exclusion criteria: allergic predisposition; acute illness on day of screening; chronic illness; impaired liver or kidney function
Interventions	1. MSP1/MSP2/ RESA vaccine in adjuvant Montanide ISA720: 2 doses at 4-week intervals; 0.55 mL per dose containing 15 µg of each antigen 2. Adjuvant only Half the children were given sulfadoxine-pyrimethamine before first dose to clear parasites Children in the older group were vaccinated first

Genton 2002 *(Continued)*

Outcomes	1. Geometric mean parasite density, calculated from blood taken every 2 weeks from week 8 to week 18 2. Prevalence of infection detected by microscopy 3. Prevalence of infection and MSP2 subtype detected by polymerase chain reaction (PCR) 3. Incidence of new infections 4. Clinical malaria attacks (case definition: fever or history of fever in last 3 days plus parasite density >= 8000/µL) 5. Adverse events: mild, moderate, or severe
Notes	Location: 4 villages in South Wosera District, East Sepik province, Papua New Guinea where the entomological inoculation rate is 35, 12, and 10 per year for *Plasmodium falciparum*, *P. vivax* and *P. malariae* respectively Method of surveillance: bi-weekly parasitologic and haematologic surveillance for 18 weeks and weekly clinical surveillance for 76 weeks; for adverse events, visits daily for 3 days, every other day for 2 weeks, weekly for 68 weeks, plus health facility-based surveillance at nearby health subcentre

Lawrence 2000

Methods	Randomized controlled trial Generation of allocation sequence: computer-generated randomization Allocation concealment: unclear Blinding: double blind Inclusion of all randomized participants: 100% completed trial Length of follow up: 8 days after challenge
Participants	Number: 17 adults Inclusion criteria: healthy adults Exclusion criteria: visit to malaria endemic region in last 12 months; acute illness or immunization with live vaccine in previous 4 weeks; current hepatitis B or HIV infection; seronegativity to Epstein-Barr virus or cytomegalovirus; taking corticosteroids, anti-inflammatory drugs, or anticoagulants; smoking > 20 per day; pregnancy; antinuclear antibody titre > 640
Interventions	1. MSP1/MSP2/RESA vaccine in Montanide ISA720 adjuvant: 2 doses at 6-week intervals; 13 µg of each component in 0.5 mL 2. Adjuvant only Treatment for challenge infection given on day 8
Outcomes	1. Parasite growth rates 2. Adverse events
Notes	Location: Brisbane, Australia Artificial challenge by injection of blood stage parasites 4 weeks after dose 2 Method of surveillance: daily sample of 10 mL blood

Saul 1999a

Methods	Randomized controlled trial Generation of allocation sequence: computer-generated randomization; participants were randomly divided in 3 groups that were vaccinated sequentially, but screening and scheduling arrangements led to some reassignment between groups; 2 in each group were randomly chosen to receive placebo Allocation concealment: unclear Blinding: participants blinded; immunological assessors also blinded Inclusion of all randomized participants: 100% completed trial, although 1 participant in placebo group was inadvertently given vaccine instead Length of follow up: 12 months for immunologic outcomes; unclear for adverse events
Participants	Number: 32 adults Inclusion criteria: medical or veterinary student at University of Queensland Exclusion criteria: history of malaria; visit to malaria endemic region in last 12 months; acute illness or immunization with live vaccine in last 4 weeks; markers of current hepatitis B or HIV infection; current medication with corticosteroids, anti-inflammatory drugs, or anticoagulants; current smoking > 10/day; pregnancy; elevated antinuclear antibodies
Interventions	1. Mixture of 3 antigens (MSP1, MSP2, RESA) plus adjuvant: 2 doses; each 1.8 mL in 1 site 2. Placebo (adjuvant in saline): 2 doses; each 1.8 mL in 1 site 3. MSP1, MSP2, RESA plus adjuvant: 2 doses in separate sites; each 0.6 mL 4. Placebo (adjuvant in saline): 2 doses in separate sites; each 0.6 mL The planned dose schedule was 2 doses at 4-week intervals with 100 µg each antigen each dose, but adverse reactions in first two-thirds of vaccinees resulted in drop to 50 µg of antigen at first dose for the remaining one third of participants and a delay between doses of approximately 6 weeks. The second dose was 20 µg each antigen in 0.36 mL at single site or 0.12 mL at each of 3 separate sites
Outcomes	1. Adverse events, classified as mild, moderate, or severe 2. Immunological outcomes
Notes	Location: Brisbane, Australia This trial reported in same publication as Saul 1999b

Saul 1999b

Methods	Randomized controlled trial Generation of allocation sequence: computer-generated randomization; participants were randomly assigned into 3 groups of 12; 2 in each group were randomly chosen to receive placebo Allocation concealment: unclear Blinding: participants blinded; immunological assessors also blinded Inclusion of all randomized participants: 2/10 participants in highest dose vaccine group did not receive second dose due to adverse events, but all completed follow up Length of follow up: 12 months for immunologic outcomes; unclear for adverse events
Participants	Number: 36 adults Inclusion criteria: medical or veterinary student at University of Queensland

Saul 1999b *(Continued)*

	Exclusion criteria: history of malaria; visit to malaria endemic region in last 12 months; acute illness or immunization with live vaccine in last 4 weeks; markers of current hepatitis B or HIV infection; current medication with corticosteroids, anti-inflammatory drugs, or anticoagulants; current smoking > 10/day; pregnancy; elevated antinuclear antibodies
Interventions	1. Mixture of 4 µg each of 3 antigens (MSP1, MSP2, RESA) plus adjuvant: 2 doses; each 0.5 mL 2. Placebo (adjuvant in saline): 2 doses; each 0.5 mL 3. Mixture of 13.3 µg each of 3 antigens (MSP1, MSP2, RESA) plus adjuvant: 2 doses; each 0.5 mL 4. Placebo (adjuvant in saline): 2 doses; each 0.5 mL 5. First dose of mixture of 50 µg each of 3 antigens (MSP1, MSP2, RESA) plus adjuvant in 0.9 mL, second dose 20 µg each antigen in 0.36 mL 6. Placebo (adjuvant in saline): 2 doses; 0.9 mL and 0.36 mL Two participants in group 5 did not receive second dose of vaccine due to adverse events The second dose was given 6 months after the first
Outcomes	1. Adverse events, classified as mild, moderate, or severe 2. Immunological outcomes
Notes	Location: Brisbane, Australia This trial reported in same publication as Saul 1999a

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

Study	Reason for exclusion
Keitel 1999	Safety and immunogenicity study; vaccine not yet tested in efficacy studies
Malkin 2005	Nonrandomized dose-finding study; no placebo group
Ockenhouse 2006	Nonrandomized open-label safety and immunogenicity study
Pombo 2002	Nonrandomized study; a trial of repeated infection rather than vaccination
Ramasamy 1995	Nonrandomized study
Saul 2005	Safety and immunogenicity study; vaccine not yet tested in efficacy studies

Characteristics of studies awaiting assessment *[ordered by study ID]*

Stoute 2006

Methods	Safety and immunogenicity trial of MSP1 in Kenya in press
Participants	—
Interventions	—
Outcomes	—
Notes	—

DATA AND ANALYSES

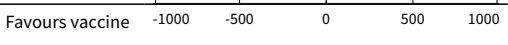
Comparison 1. MSP/RESA vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasite density	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 No sulfadoxine-pyrimethamine pretreatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Sulfadoxine-pyrimethamine pretreatment	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Clinical malaria episodes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 No sulfadoxine-pyrimethamine pretreatment	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Sulfadoxine-pyrimethamine pretreatment	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 New malaria infection, by MSP2 type	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 3D7	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 FC27	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Prevalence (microscopy)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 No sulfadoxine-pyrimethamine	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Sulfadoxine-pyrimethamine	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Prevalence (PCR), by MSP2 type	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 3D7	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 FC27	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Adverse events (any severity)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Pain at injection site	3	295	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.82, 1.20]
6.2 Limping gait	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.41, 1.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Firmness/nodule at injection site	3	297	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.65, 2.79]
6.4 Swelling/induration at injection site	3	297	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.67, 3.74]
6.5 Fever	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.46, 1.45]
6.6 Cough	1	240	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.38, 3.83]
6.7 Headache	1	240	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.34, 4.54]
6.8 Pain	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.11, 3.92]
6.9 Vomiting	1	240	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.45, 35.27]
6.10 Swelling	1	240	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.18, 21.76]
6.11 Conjunctivitis	1	240	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.91]
6.12 Diarrhoea	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.10]
6.13 Difficulty hearing	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.10]
6.14 Earache	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.10]
6.15 Nausea	1	240	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.80]
6.16 Running nose	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.10]
7 Adverse events (moderate severity)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Fever	1	240	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.80]
7.2 Pain at injection site	2	273	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.49, 3.15]
7.3 Swelling at injection site	1	240	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.10]

Analysis 1.1. Comparison 1 MSP/RESA vaccine versus placebo, Outcome 1 Parasite density.

Study or subgroup	Vaccine N	Vaccine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.1.1 No sulfadoxine-pyrimethamine pretreatment						
Genton 2002	13	144.6 (1.3)	18	382.6 (1.4)		-238[-238.95,-237.05]
1.1.2 Sulfadoxine-pyrimethamine pretreatment						
Genton 2002	10	689.5 (2.1)	6	257.2 (2.4)		432.3[429.99,434.61]



Analysis 1.2. Comparison 1 MSP/RESA vaccine versus placebo, Outcome 2 Clinical malaria episodes.

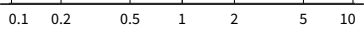
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.2.1 No sulfadoxine-pyrimethamine pretreatment				
Genton 2002	18/30	11/30		1.64[0.94,2.85]
1.2.2 Sulfadoxine-pyrimethamine pretreatment				
Genton 2002	15/30	12/30		1.25[0.71,2.2]

Analysis 1.3. Comparison 1 MSP/RESA vaccine versus placebo, Outcome 3 New malaria infection, by MSP2 type.

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.3.1 3D7				
Genton 2002	11/60	21/60		0.52[0.28,0.99]
1.3.2 FC27				
Genton 2002	11/60	6/60		1.83[0.72,4.64]

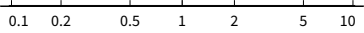
Analysis 1.4. Comparison 1 MSP/RESA vaccine versus placebo, Outcome 4 Prevalence (microscopy).

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.4.1 No sulfadoxine-pyrimethamine				
Genton 2002	13/30	18/30		0.72[0.44,1.19]
1.4.2 Sulfadoxine-pyrimethamine				
Genton 2002	10/30	6/30		1.67[0.69,4]



Analysis 1.5. Comparison 1 MSP/RESA vaccine versus placebo, Outcome 5 Prevalence (PCR), by MSP2 type.

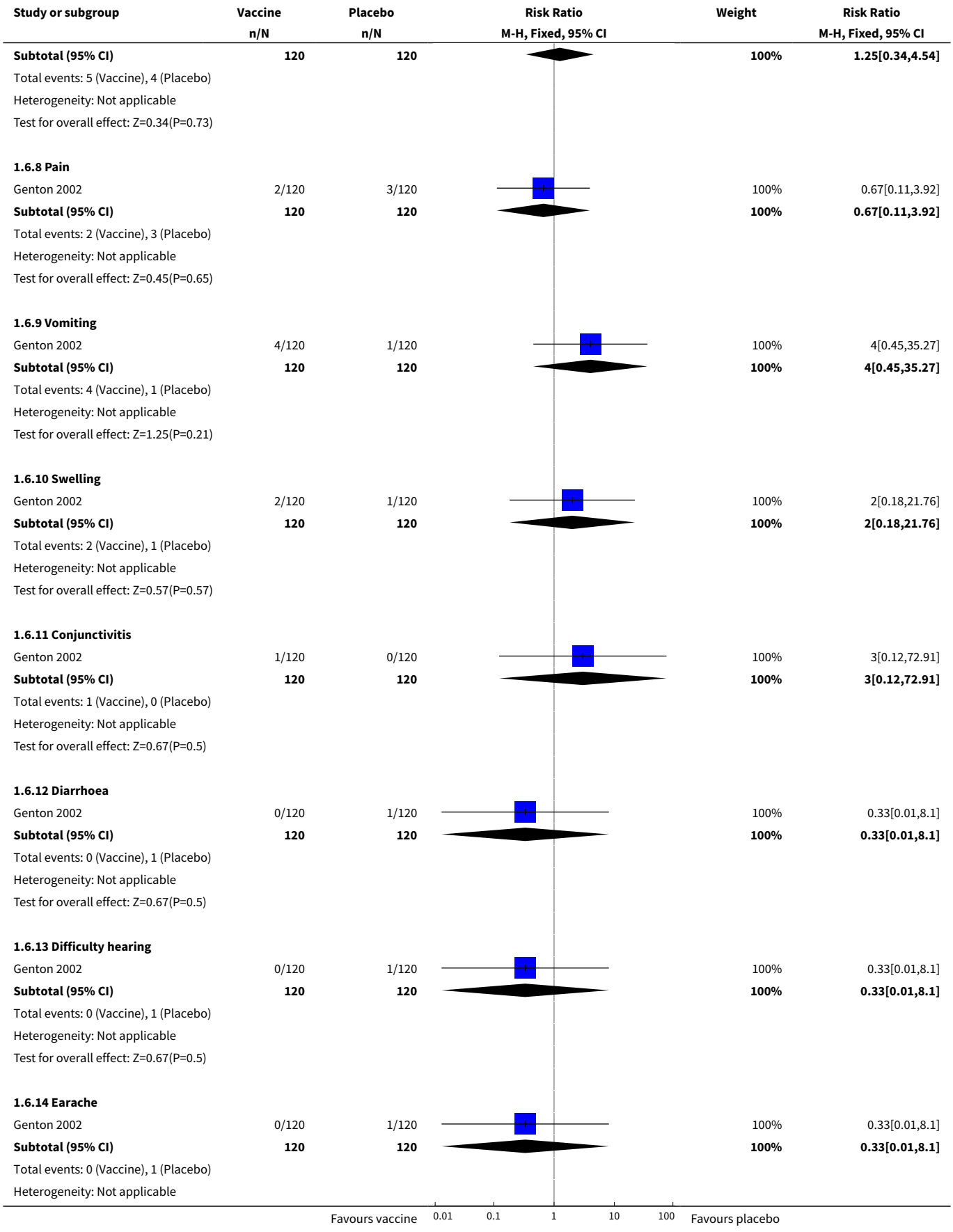
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.5.1 3D7				
Genton 2002	30/360	78/359		0.38[0.26,0.57]
1.5.2 FC27				
Genton 2002	27/360	20/360		1.35[0.77,2.36]

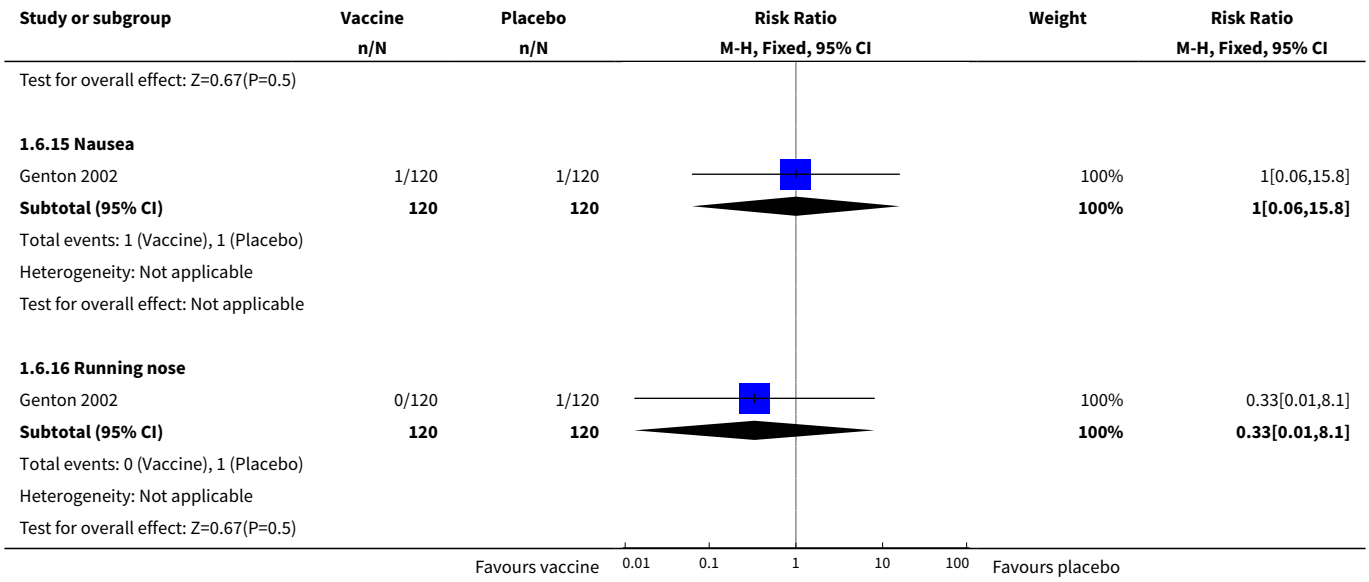


Analysis 1.6. Comparison 1 MSP/RESA vaccine versus placebo, Outcome 6 Adverse events (any severity).

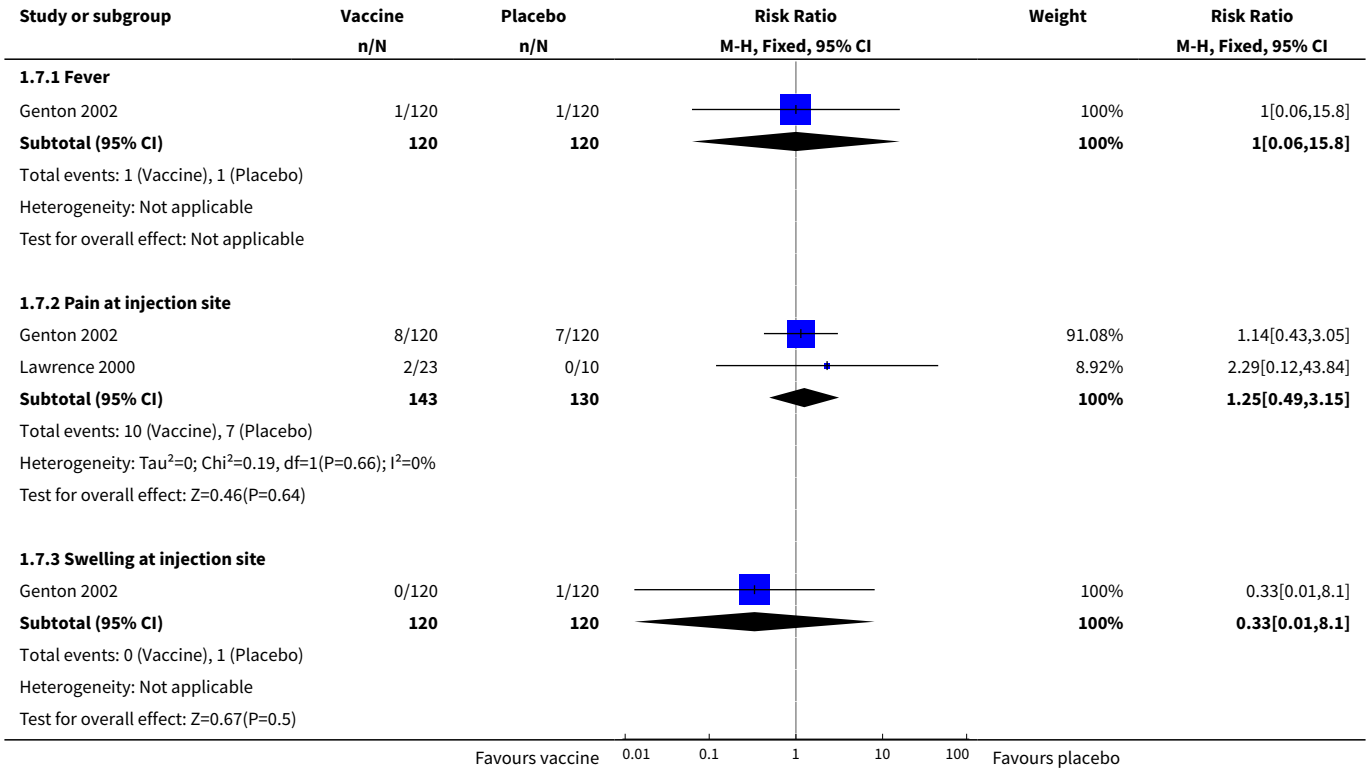
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Pain at injection site					
Genton 2000	11/20	1/2		2.19%	1.1[0.26,4.65]
Genton 2002	73/120	77/120		92.77%	0.95[0.78,1.15]
Lawrence 2000	12/23	3/10		5.04%	1.74[0.62,4.84]
Subtotal (95% CI)	**163**	**132**		**100%**	**0.99[0.82,1.2]**
Total events: 96 (Vaccine), 81 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.37, df=2(P=0.5); I^2=0%					
Test for overall effect: Z=0.09(P=0.93)					
1.6.2 Limping gait					
Genton 2002	13/120	16/120		100%	0.81[0.41,1.61]
Subtotal (95% CI)	**120**	**120**		**100%**	**0.81[0.41,1.61]**
Total events: 13 (Vaccine), 16 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.55)					
1.6.3 Firmness/nodule at injection site					
Genton 2000	1/20	0/4		7.03%	0.71[0.03,15.06]
Genton 2002	14/120	10/120		87.01%	1.4[0.65,3.03]
Lawrence 2000	1/23	0/10		5.97%	1.38[0.06,31.14]
Subtotal (95% CI)	**163**	**134**		**100%**	**1.35[0.65,2.79]**
Total events: 16 (Vaccine), 10 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.18, df=2(P=0.92); I^2=0%					
Test for overall effect: Z=0.81(P=0.42)					
1.6.4 Swelling/induration at injection site					
Genton 2000	3/20	0/4		9.51%	1.67[0.1,27.36]
Genton 2002	8/120	7/120		82.42%	1.14[0.43,3.05]
Lawrence 2000	6/23	0/10		8.07%	5.96[0.37,96.67]
Subtotal (95% CI)	**163**	**134**		**100%**	**1.58[0.67,3.74]**
Total events: 17 (Vaccine), 7 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.29, df=2(P=0.52); I^2=0%					
Test for overall effect: Z=1.05(P=0.3)					
1.6.5 Fever					
Genton 2002	18/120	22/120		100%	0.82[0.46,1.45]
Subtotal (95% CI)	**120**	**120**		**100%**	**0.82[0.46,1.45]**
Total events: 18 (Vaccine), 22 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
1.6.6 Cough					
Genton 2002	6/120	5/120		100%	1.2[0.38,3.83]
Subtotal (95% CI)	**120**	**120**		**100%**	**1.2[0.38,3.83]**
Total events: 6 (Vaccine), 5 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.31(P=0.76)					
1.6.7 Headache					
Genton 2002	5/120	4/120		100%	1.25[0.34,4.54]

Favours vaccine — Favours placebo





Analysis 1.7. Comparison 1 MSP/RESA vaccine versus placebo, Outcome 7 Adverse events (moderate severity).



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.

WHAT'S NEW

Date	Event	Description
21 July 2008	Amended	Converted to new review format with minor editing.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 4, 2006

Date	Event	Description
15 August 2006	New citation required and conclusions have changed	2006, Issue 4: The original review of malaria vaccines (Graves 2003) has been divided into three parts for blood-stage vaccines, SPf66 vaccine, and pre-erythrocytic vaccines. This review includes the trials of blood-stage vaccines. The only vaccine tested in randomized efficacy trials to date is MSP/RESA. In addition to the two efficacy trials of this vaccine, which were previously included in Graves 2003, three safety trials with MSP/RESA have been added. The text of the review has been extensively updated and revised.

CONTRIBUTIONS OF AUTHORS

Patricia Graves wrote the protocol, extracted data, analysed data, and drafted the review. Hellen Gelband extracted data and co-wrote 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.

INDEX TERMS

Medical Subject Headings (MeSH)

Antigens, Protozoan [immunology]; Malaria [blood] [*prevention & control]; Malaria Vaccines [adverse effects] [*therapeutic use]; Merozoites [immunology]; Protozoan Proteins [immunology]; Randomized Controlled Trials as Topic; Vaccines, Combined [adverse effects] [therapeutic use]

MeSH check words

Humans