
BACKGROUND:
An ongoing phase 3 study of the efficacy, safety, and immunogenicity of candidate malaria vaccine RTS,S/AS01 is being conducted in seven African countries.

METHODS:
From March 2009 through January 2011, we enrolled 15,460 children in two age categories—6 to 12 weeks of age and 5 to 17 months of age—for vaccination with either RTS,S/AS01 or a non-malaria comparator vaccine. The primary end point of the analysis was vaccine efficacy against clinical malaria during the 12 months after vaccination in the first 6000 children 5 to 17 months of age at enrollment who received all three doses of vaccine according to protocol. After 250 children had an episode of severe malaria, we evaluated vaccine efficacy against severe malaria in both age categories.

RESULTS:
In the 14 months after the first dose of vaccine, the incidence of first episodes of clinical malaria in the first 6000 children in the older age category was 0.32 episodes per person-year in the RTS,S/AS01 group and 0.55 episodes per person-year in the control group, for an efficacy of 50.4% (95% confidence interval [CI], 45.8 to 54.6) in the intention-to-treat population and 55.8% (97.5% CI, 50.6 to 60.4) in the per-protocol population. Vaccine efficacy against severe malaria was 45.1% (95% CI, 23.8 to 60.5) in the intention-to-treat population and 47.3% (95% CI, 22.4 to 64.2) in the per-protocol population. Vaccine efficacy against severe malaria in the combined age categories was 34.8% (95% CI, 16.2 to 49.2) in the per-protocol population during an average follow-up of 11 months. Serious adverse events occurred with a similar frequency in the two study groups. Among children in the older age category, the rate of generalized convulsive seizures after RTS,S/AS01 vaccination was 1.04 per 1000 doses (95% CI, 0.62 to 1.64).

CONCLUSIONS:
The RTS,S/AS01 vaccine provided protection against both clinical and severe malaria in African children.


BACKGROUND:
The RTS,S/AS01E (malaria candidate vaccine is being developed for immunization of African infants through the Expanded Program of Immunization (EPI).)

METHODS:
This phase 2, randomized, open, controlled trial conducted in Ghana, Tanzania, and Gabon evaluated the safety and immunogenicity of RTS,S/AS01E when coadministered with EPI vaccines. Five hundred eleven infants were randomized to receive RTS,S/AS01E at 0, 1, and 2 months (in 3 doses with diphtheria, tetanus, and whole-cell pertussis conjugate [DTPw]; hepatitis B [HepB]; Haemophilus influenzae type b [Hib]; and oral polio vaccine [OPV]), RTS,S/AS01E at 0, 1, and 7 months (2 doses with DTPwHepB/Hib+OPV and 1 dose with measles and yellow fever), or EPI vaccines only.

RESULTS:
The occurrences of serious adverse events were balanced across groups; none were vaccine-related. One child from the control group died. Mild to moderate fever and diaper dermatitis
occurred more frequently in the RTS,S/AS01(E) coadministration groups. RTS,S/AS01(E) generated high anti-circumsporozoite protein and anti-hepatitis B surface antigen antibody levels. Regarding EPI vaccine responses upon coadministration when considering both immunization schedules, despite a tendency toward lower geometric mean titer to some EPI antigens, predefined noninferiority criteria were met for all EPI antigens except for polio 3 when EPI vaccines were given with RTS,S/AS01(E) at 0, 1, and 2 months. However, when antibody levels at screening were taken into account, the rates of response to polio 3 antigens were comparable between groups.

CONCLUSION:
RTS,S/AS01(E) integrated in the EPI showed a favorable safety and immunogenicity evaluation.


BACKGROUND:
The RTS,S/AS01(E) candidate malaria vaccine is being developed for immunisation of infants in Africa through the expanded programme on immunisation (EPI). 8 month follow-up data have been reported for safety and immunogenicity of RTS,S/AS01(E) when integrated into the EPI. We report extended follow-up to 19 months, including efficacy results.

METHODS:
We did a randomised, open-label, phase 2 trial of safety and efficacy of the RTS,S/AS01(E) candidate malaria vaccine given with EPI vaccines between April 30, 2007, and Oct 7, 2009, in Ghana, Tanzania, and Gabon. Eligible children were 6-10 weeks of age at first vaccination, without serious acute or chronic illness. All children received the EPI diphtheria, tetanus, pertussis (inactivated whole-cell), and hepatitis-B vaccines, Haemophilus influenzae type b vaccine, and oral polio vaccine at study months 0, 1, and 2, and measles vaccine and yellow fever vaccines at study month 7. Participants were randomly assigned (1:1:1) to receive three doses of RTS,S/AS01(E) at 6, 10, and 14 weeks (0, 1, 2 month schedule) or at 6 weeks, 10 weeks, and 9 months (0, 2, 7 month schedule) or placebo. Randomisation was according to a predefined block list with a computer-generated randomisation code. Detection of serious adverse events and malaria was by passive case detection. Antibodies against Plasmodium falciparum circumsporozoite protein and HBsAg were monitored for 19 months. This study is registered with ClinicalTrials.gov, number NCT00436007.

FINDINGS:
511 children were enrolled. Serious adverse events occurred in 57 participants in the RTS,S/AS01(E) 0, 1, 2 month group (34%, 95% CI 27-41), 47 in the 0, 1, 7 month group (28%, 21-35), and 49 (29%, 22-36) in the control group; none were judged to be related to study vaccination. At month 19, anticircumsporozoite immune responses were significantly higher in the RTS,S/AS01(E) groups than in the control group. Vaccine efficacy for the 0, 1, 2 month schedule (2 weeks after dose three to month 19, site-adjusted according-to-protocol analysis) was 53% (95% CI 26-70; p=0.0012) against first malaria episodes and 59% (36-74; p=0.0001) against all malaria episodes. For the entire study period, (total vaccinated cohort) vaccine efficacy against all malaria episodes was higher with the 0, 1, 2 month schedule (57%, 95% CI 33-73; p=0.0002) than with the 0, 1, 7 month schedule (32% CI 16-45; p=0.0003). 1 year after dose three, vaccine efficacy against first malaria episodes was similar for both schedules (0, 1, 2 month group, 61-6% [95% CI 35-67-77-1], p<0.001; 0, 1, 7 month group, 63-8% [40-4-78-0], p<0.001, according-to-protocol cohort).

INTERPRETATION:
Vaccine efficacy was consistent with the target put forward by the WHO-sponsored malaria vaccine technology roadmap for a first-generation malaria vaccine. The 0, 1, 2 month vaccine schedule has been selected for phase 3 candidate vaccine assessment.

Rotavirus is the leading cause of diarrheal disease in children under 5 years of age. It is responsible for more than 450,000 deaths each year, with more than 90% of these deaths occurring in low-resource countries eligible for support by the GAVI Alliance. Significant efforts made by the Alliance and its partners are providing countries with the opportunity to introduce rotavirus vaccines into their national immunization programs, to help prevent childhood illness and death. We projected the cost-effectiveness and health impact of rotavirus vaccines in GAVI-eligible countries, to assist decision makers in prioritizing resources to achieve the greatest health benefits for their populations. A decision-analytic model was used to project the health outcomes and direct costs of a birth cohort in the target population, with and without a rotavirus vaccine. Current data on disease burden, vaccine efficacy, immunization rates, and costs were used in the model.

Vaccination in GAVI-eligible countries would prevent 2.46 million childhood deaths and 83 million disability-adjusted life years (DALYs) from 2011 to 2030, with annual reductions of 180,000 childhood deaths at peak vaccine uptake. The cost per DALY averted is $42 for all GAVI countries combined, over the entire period. Rotavirus vaccination would be considered very cost-effective for the entire cohort of GAVI countries, and in each country individually, as cost-effectiveness ratios are less than the gross domestic product (GDP) per capita. Vaccination is most cost-effective and has the greatest impact in regions with high rotavirus mortality. Rotavirus vaccination in GAVI-eligible countries is very cost-effective and is projected to substantially reduce childhood mortality in this population.


No abstract available.


No abstract available.

Good MF. Our impasse in developing a malaria vaccine. Cell Mol Life Sci. 2011;68(7):1105–1113. Malaria presents a challenge to world health that to date has been beyond the abilities of researchers to conquer. This critique presents some of the strategies employed by the parasite to overcome immunity and the immunological challenges that we face to develop vaccines. A conclusion is that a vaccine must identify novel antigens or epitopes that are not normally immunogenic and which are therefore not under immune pressure and most likely to be conserved between different strains. Such antigens are most likely to be targets of cellular immunity. The case for a whole parasite blood stage vaccine is presented based on these premises.


BACKGROUND: Introduction of human papillomavirus (HPV) vaccination in settings with the highest burden of HPV is not universal, partly because of the absence of quantitative estimates of country-specific effects on health and economic costs. We aimed to develop and validate a simple generic model of such effects that could be used and understood in a range of settings with little external support.

METHODS: We developed the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model to assess cost-effectiveness and health effects of vaccination of girls against HPV before sexual debut
in terms of burden of cervical cancer and mortality. PRIME models incidence according to proposed vaccine efficacy against HPV 16/18, vaccine coverage, cervical cancer incidence and mortality, and HPV type distribution. It assumes lifelong vaccine protection and no changes to other screening programmes or vaccine uptake. We validated PRIME against existing reports of HPV vaccination cost-effectiveness, projected outcomes for 179 countries (assuming full vaccination of 12-year-old girls), and outcomes for 71 phase 2 GAVI-eligible countries (using vaccine uptake data from the GAVI Alliance). We assessed differences between countries in terms of cost-effectiveness and health effects.

FINDINGS:
In validation, PRIME reproduced cost-effectiveness conclusions for 24 of 26 countries from 17 published studies, and for all 72 countries in a published study of GAVI-eligible countries. Vaccination of a cohort of 58 million 12-year-old girls in 179 countries prevented 690,000 cases of cervical cancer and 420,000 deaths during their lifetime (mostly in low-income or middle-income countries), at a net cost of US$4 billion. HPV vaccination was very cost effective (with every disability-adjusted life-year averted costing less than the gross domestic product per head) in 156 (87%) of 179 countries. Introduction of the vaccine in countries without national HPV vaccination at present would prevent substantially more cases of cervical cancer than in countries with such programmes, although the disparity has narrowed since 2012. If 71 phase 2 GAVI-eligible countries adopt vaccination according to forecasts, then in 2070 GAVI Alliance-funded vaccination could prevent 200,000 cases of cervical cancer and 100,000 deaths in some of the highest-burden countries.

INTERPRETATION:
Large between-country disparities exist for HPV vaccination, with countries with the most to gain yet to introduce national HPV vaccination. Support from the GAVI Alliance could help to reduce such disparities, but a substantial burden will remain even after presently projected vaccine introductions.


No abstract available.


BACKGROUND:
GlaxoSmithKline Biologicals and the PATH Malaria Vaccine Initiative are working in partnership to develop a malaria vaccine to protect infants and children living in malaria endemic regions of sub-Saharan Africa, which can be delivered through the Expanded Programme on Immunization. The RTS,S/AS candidate vaccine has been evaluated in multiple phase I/II studies and shown to have a favourable safety profile and to be well-tolerated in both adults and children. This paper details the design of the phase III multicentre efficacy trial of the RTS,S/AS01 malaria vaccine candidate, which is pivotal for licensure and policy decision-making.

METHODS:
The phase III trial is a randomized, controlled, multicentre, participant- and observer-blind study on-going in 11 centres associated with different malaria transmission settings in seven countries in sub-Saharan Africa. A minimum of 6,000 children in each of two age categories (6-12 weeks, 5-17 months) have been enrolled. Children were randomized 1:1:1 to one of three study groups: (1) primary vaccination with RTS,S/AS01 and booster dose of RTS,S/AS01; (2) primary vaccination with RTS,S/AS01 and a control vaccine at time of booster; (3) primary vaccination with control vaccine
and a control vaccine at time of booster. Primary vaccination comprises three doses at monthly intervals; the booster dose is administered at 18 months post-primary course. Subjects will be followed to study month 32. The co-primary objectives are the evaluation of efficacy over one year post-dose 3 against clinical malaria when primary immunization is delivered at: (1) 6-12 weeks of age, with co-administration of DTPwHepB/Hib antigens and OPV; (2) 5-17 months of age. Secondary objectives include evaluation of vaccine efficacy against severe malaria, anaemia, malaria hospitalization, fatal malaria, all-cause mortality and other serious illnesses including sepsis and pneumonia. Efficacy of the vaccine against clinical malaria under different transmission settings, the evolution of efficacy over time and the potential benefit of a booster will be evaluated. In addition, the effect of RTS,S/AS01 vaccination on growth, and the safety and immunogenicity in HIV-infected and malnourished children will be assessed. Safety of the primary course of immunization and the booster dose will be documented in both age categories.

CONCLUSIONS:
This pivotal phase III study of the RTS,S/AS01 candidate malaria vaccine in African children was designed and implemented by the Clinical Trials Partnership Committee. The study will provide efficacy and safety data to fulfil regulatory requirements, together with data on a broad range of endpoints that will facilitate the evaluation of the public health impact of the vaccine and will aid policy and implementation decisions.

Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2004(2):CD000363.

BACKGROUND:
Malaria is an important cause of illness and death in many parts of the world, especially in sub-Saharan Africa. There has been a renewed emphasis on preventive measures at community and individual levels. Insecticide-treated nets (ITNs) are the most prominent malaria preventive measure for large-scale deployment in highly endemic areas.

OBJECTIVES:
To assess the impact of insecticide-treated bed nets or curtains on mortality, malarial illness (life-threatening and mild), malaria parasitaemia, anaemia, and spleen rates.

SEARCH STRATEGY:
I searched the Cochrane Infectious Diseases Group trials register (January 2003), CENTRAL (The Cochrane Library, Issue 1, 2003), MEDLINE (1966 to October 2003), EMBASE (1974 to November 2002), LILACS (1982 to January 2003), and reference lists of reviews, books, and trials. I handsearched journals, contacted researchers, funding agencies, and net and insecticide manufacturers.

SELECTION CRITERIA:
Individual and cluster randomized controlled trials of insecticide-treated bed nets or curtains compared to nets without insecticide or no nets. Trials including only pregnant women were excluded.

DATA COLLECTION AND ANALYSIS:
The reviewer and two independent assessors reviewed trials for inclusion. The reviewer assessed trial methodological quality and extracted and analysed data.

MAIN RESULTS:
Fourteen cluster randomized and eight individually randomized controlled trials met the inclusion criteria. Five trials measured child mortality: ITNs provided 17% protective efficacy (PE) compared to no nets (relative rate 0.83, 95% confidence interval (CI) 0.76 to 0.90), and 23% PE compared to untreated nets (relative rate 0.77, 95% CI 0.63 to 0.95). About 5.5 lives (95% CI 3.39 to 7.67) can be saved each year for every 1000 children protected with ITNs. In areas with stable malaria, ITNs reduced the incidence of uncomplicated malarial episodes in areas of stable malaria by 50% compared to no nets, and 39% compared to untreated nets; and in areas of unstable malaria: by 62% for compared to no nets and 43% compared to untreated nets for Plasmodium falciparum
episodes, and by 52% compared to no nets and 11% compared to untreated nets for P. vivax episodes. When compared to no nets and in areas of stable malaria, ITNs also had an impact on severe malaria (45% PE, 95% CI 20 to 63), parasite prevalence (13% PE), high parasitaemia (29% PE), splenomegaly (30% PE), and their use improved the average haemoglobin level in children by 1.7% packed cell volume.

REVIEWERS’ CONCLUSIONS:
ITNs are highly effective in reducing childhood mortality and morbidity from malaria. Widespread access to ITNs is currently being advocated by Roll Back Malaria, but universal deployment will require major financial, technical, and operational inputs.


BACKGROUND:
In malaria endemic areas, pre-school children are at high risk of severe and repeated malaria illness. One possible public health strategy, known as Intermittent Preventive Treatment in children (IPTc), is to treat all children for malaria at regular intervals during the transmission season, regardless of whether they are infected or not.

OBJECTIVES:
To evaluate the effects of IPTc to prevent malaria in preschool children living in endemic areas with seasonal malaria transmission.

SEARCH METHODS:
We searched the Cochrane Infectious Diseases Group Specialized Register (July 2011), CENTRAL (The Cochrane Library 2011, Issue 6), MEDLINE (1966 to July 2011), EMBASE (1974 to July 2011), LILACS (1982 to July 2011), mRCT (July 2011), and reference lists of identified trials. We also contacted researchers working in the field for unpublished and ongoing trials.

SELECTION CRITERIA:
Individually randomized and cluster-randomized controlled trials of full therapeutic dose of antimalarial or antimalarial drug combinations given at regular intervals compared with placebo or no preventive treatment in children aged six years or less living in an area with seasonal malaria transmission.

DATA COLLECTION AND ANALYSIS:
Two authors independently assessed eligibility, extracted data and assessed the risk of bias in the trials. Data were meta-analysed and measures of effects (ie rate ratio, risk ratio and mean difference) are presented with 95% confidence intervals (CIs). The quality of evidence was assessed using the GRADE methods.

MAIN RESULTS:
Seven trials (12,589 participants), including one cluster-randomized trial, met the inclusion criteria. All were conducted in West Africa, and six of seven trials were restricted to children aged less than 5 years. IPTc prevents approximately three quarters of all clinical malaria episodes (rate ratio 0.26; 95% CI 0.17 to 0.38; 9321 participants, six trials, high quality evidence), and a similar proportion of severe malaria episodes (rate ratio 0.27, 95% CI 0.10 to 0.76; 5964 participants, two trials, high quality evidence). These effects remain present even where insecticide treated net (ITN) usage is high (two trials, 5964 participants, high quality evidence). IPTc probably produces a small reduction in all-cause mortality consistent with the effect on severe malaria, but the trials were underpowered to reach statistical significance (risk ratio 0.66, 95% CI 0.31 to 1.39, moderate quality evidence). The effect on anaemia varied between studies, but the risk of moderately severe anaemia is probably lower with IPTc (risk ratio 0.71, 95% CI 0.52 to 0.98; 8805 participants, five trials, moderate quality evidence). Serious drug-related adverse events, if they occur, are probably rare, with none reported in the six trials (9533 participants, six trials, moderate quality evidence).

Amodiaquine plus sulphadoxine-pyrimethamine is the most studied drug combination for seasonal chemoprevention. Although effective, it causes increased vomiting in this age-group (risk ratio
A priority measures. Research into possible interactions between malaria control measures was highlighted. The likely impact would have to be assessed in the context of multiple other potential control measures. In order to compare findings in trials, it was suggested that efficacy estimates not only first episodes, and on duration of efficacy. Further research is required on the analysis of such multiple episode data. It will also be important to examine endpoints such as severe malaria and death, though it may be difficult for the latter to be a primary endpoint in trials. In order to compare findings in trials, it was suggested that efficacy estimates are reported at different time intervals after vaccination and that data sharing should be enhanced for all malaria vaccine clinical trials. It was appreciated that the epidemiology of malaria is changing in many settings and this may affect the public health benefit of a newly available malaria vaccine, whose likely impact would have to be assessed in the context of multiple other potential control measures. Research into possible interactions between malaria control measures was highlighted as a priority.


The RTS,S/AS candidate malaria vaccine has demonstrated efficacy against a variety of endpoints in Phase IIa and Phase IIb trials over more than a decade. A multi-country phase III trial of RTS,S/AS01 is now underway with submission as early as 2012, if vaccine safety and efficacy are confirmed. The immunologic basis for how the vaccine protects against both infection and disease remains uncertain. It is, therefore, timely to review the information currently available about the vaccine with regard to how it impacts the human-Plasmodium falciparum host-pathogen relationship. In this article, what is known about mechanisms involved in partial protection against malaria induced by RTS,S is reviewed.


The WHO Initiative for Vaccine Research and Global Malaria Programme convened a joint scientific forum in June 2008 to discuss scientific, regulatory and public health perspectives on the measurement of efficacy in malaria vaccine field efficacy trials. Participants included clinical trialists, statisticians and epidemiologists from both developed and developing countries, vaccine researchers and developers from academia and industry, and representatives of regulatory agencies. The efficacy of a vaccine against a disease is a summary indication of the extent to which those vaccinated are protected. However, there are several ways of measuring this and for high incidence diseases, such as malaria, in which there is variation in exposure and susceptibility from person to person, the choice of the appropriate measure of efficacy is more complex than is the case for low incidence diseases. There was agreement amongst statisticians at the meeting that basing analyses on "time to event" is the most appropriate method to analyse both incident infection and clinical malaria data from trials. However, policymakers would need to understand that this measure is different from that based on the proportion event-free up to a defined time, which has been used in reporting clinical challenge trials of malaria vaccines. For the assessment of public health impact, data should be reported on all episodes of malaria that a trial subject experiences, not only first episodes, and on duration of efficacy. Further research is required on the analysis of such multiple episode data. It will also be important to examine endpoints such as severe malaria and death, though it may be difficult for the latter to be a primary endpoint in trials. In order to compare findings in trials, it was suggested that efficacy estimates are reported at different time intervals after vaccination and that data sharing should be enhanced for all malaria vaccine clinical trials. It was appreciated that the epidemiology of malaria is changing in many settings and this may affect the public health benefit of a newly available malaria vaccine, whose likely impact would have to be assessed in the context of multiple other potential control measures. Research into possible interactions between malaria control measures was highlighted as a priority.

BACKGROUND:
The RTS,S/AS01 vaccine targets the circumsporozoite protein of Plasmodium falciparum and has partial protective efficacy against clinical and severe malaria disease in infants and children. We investigated whether the vaccine efficacy was specific to certain parasite genotypes at the circumsporozoite protein locus.

METHODS:
We used polymerase chain reaction-based next-generation sequencing of DNA extracted from samples from 4985 participants to survey circumsporozoite protein polymorphisms. We evaluated the effect that polymorphic positions and haplotypic regions within the circumsporozoite protein had on vaccine efficacy against first episodes of clinical malaria within 1 year after vaccination.

RESULTS:
In the per-protocol group of 4577 RTS,S/AS01-vaccinated participants and 2335 control-vaccinated participants who were 5 to 17 months of age, the 1-year cumulative vaccine efficacy was 50.3% (95% confidence interval [CI], 34.6 to 62.3) against clinical malaria in which parasites matched the vaccine in the entire circumsporozoite protein C-terminal (139 infections), as compared with 33.4% (95% CI, 29.3 to 37.2) against mismatched malaria (1951 infections) (P=0.04 for differential vaccine efficacy). The vaccine efficacy based on the hazard ratio was 62.7% (95% CI, 51.6 to 71.3) against matched infections versus 54.2% (95% CI, 49.9 to 58.1) against mismatched infections (P=0.06). In the group of infants 6 to 12 weeks of age, there was no evidence of differential allele-specific vaccine efficacy.

CONCLUSIONS:
These results suggest that among children 5 to 17 months of age, the RTS,S vaccine has greater activity against malaria parasites with the matched circumsporozoite protein allele than against mismatched malaria. The overall vaccine efficacy in this age category will depend on the proportion of matched alleles in the local parasite population; in this trial, less than 10% of parasites had matched alleles. (Funded by the National Institutes of Health and others.).

The burden of malaria in countries in sub-Saharan Africa has declined with scaling up of prevention, diagnosis, and treatment. To assess the contribution of specific malaria interventions and other general factors in bringing about these changes, we reviewed studies that have reported recent changes in the incidence or prevalence of malaria in sub-Saharan Africa. Malaria control in southern Africa (South Africa, Mozambique, and Swaziland) began in the 1980s and has shown substantial, lasting declines linked to scale-up of specific interventions. In The Horn of Africa, Ethiopia and Eritrea have also experienced substantial decreases in the burden of malaria linked to the introduction of malaria control measures. Substantial increases in funding for malaria control and the procurement and distribution of effective means for prevention and treatment are associated with falls in malaria burden. In central Africa, little progress has been documented, possibly because of publication bias. In some countries a decline in malaria incidence began several years before scale-up of malaria control. In other countries, the change from a failing drug (chloroquine) to a more effective drug (sulphadoxine plus pyrimethamine or an artemisinin combination) led to immediate improvements; in others malaria reduction seemed to be associated with the scale-up of insecticide-treated bednets and indoor residual spraying.

BACKGROUND:
The phase 3 trial of the RTS,S/AS01 malaria vaccine candidate showed modest efficacy of the vaccine against Plasmodium falciparum malaria, but was not powered to assess mortality endpoints. Impact projections and cost-effectiveness estimates for longer timeframes than the trial follow-up and across a range of settings are needed to inform policy recommendations. We aimed to assess the public health impact and cost-effectiveness of routine use of the RTS,S/AS01 vaccine in African settings.

METHODS:
We compared four malaria transmission models and their predictions to assess vaccine cost-effectiveness and impact. We used trial data for follow-up of 32 months or longer to parameterise vaccine protection in the group aged 5-17 months. Estimates of cases, deaths, and disability-adjusted life-years (DALYs) averted were calculated over a 15 year time horizon for a range of levels of Plasmodium falciparum parasite prevalence in 2-10 year olds (PFPR2-10; range 3-65%). We considered two vaccine schedules: three doses at ages 6, 7-5, and 9 months (three-dose schedule, 90% coverage) and including a fourth dose at age 27 months (four-dose schedule, 72% coverage).

We estimated cost-effectiveness in the presence of existing malaria interventions for vaccine prices of US$2-10 per dose.

FINDINGS:
In regions with a PFPR2-10 of 10-65%, RTS,S/AS01 is predicted to avert a median of 93 940 (range 20 490-126 540) clinical cases and 394 (127-708) deaths for the three-dose schedule, or 116 480 (31 450-160 410) clinical cases and 484 (189-859) deaths for the four-dose schedule, per 100 000 fully vaccinated children. A positive impact is also predicted at a PFPR2-10 of 5-10%, but there is little impact at a prevalence of lower than 3%. At $5 per dose and a PFPR2-10 of 10-65%, we estimated a median incremental cost-effectiveness ratio compared with current interventions of $30 (range 18-211) per clinical case averted and $80 (44-279) per DALY averted for the three-dose schedule, and of $25 (16-222) and $87 (48-244), respectively, for the four-dose schedule. Higher ICERs were estimated at low PFPR2-10 levels.

INTERPRETATION:
We predict a significant public health impact and high cost-effectiveness of the RTS,S/AS01 vaccine across a wide range of settings. Decisions about implementation will need to consider levels of malaria burden, the cost-effectiveness and coverage of other malaria interventions, health priorities, financing, and the capacity of the health system to deliver the vaccine.


BACKGROUND:
Primary malaria prevention on a large scale depends on two vector control interventions: indoor residual spraying (IRS) and insecticide-treated mosquito nets (ITNs). Historically, IRS has reduced malaria transmission in many settings in the world, but the health effects of IRS have never been properly quantified. This is important, and will help compare IRS with other vector control interventions.

OBJECTIVES:
To quantify the impact of IRS alone, and to compare the relative impacts of IRS and ITNs, on key malariological parameters.

SEARCH STRATEGY:
We searched the Cochrane Infectious Diseases Group Specialized Register (September 2009), CENTRAL (The Cochrane Library 2009, Issue 3), MEDLINE (1966 to September 2009), EMBASE (1974
to September 2009), LILACS (1982 to September 2009), mRCT (September 2009), reference lists, and conference abstracts. We also contacted researchers in the field, organizations, and manufacturers of insecticides (June 2007).

**SELECTION CRITERIA:**
Cluster randomized controlled trials (RCTs), controlled before-and-after studies (CBA) and interrupted time series (ITS) of IRS compared to no IRS or ITNs. Studies examining the impact of IRS on special groups not representative of the general population, or using insecticides and dosages not recommended by the World Health Organization (WHO) were excluded.

**DATA COLLECTION AND ANALYSIS:**
Two authors independently reviewed trials for inclusion. Two authors extracted data, assessed risk of bias and analysed the data. Where possible, we adjusted confidence intervals (CIs) for clustering. Studies were grouped into those comparing IRS with no IRS, and IRS compared with ITNs, and then stratified by malaria endemicity.

**MAIN RESULTS:**
IRS versus no IRS
Stable malaria (entomological inoculation rate (EIR) > 1): In one RCT in Tanzania IRS reduced re-infection with malaria parasites detected by active surveillance in children following treatment; protective efficacy (PE) 54%. In the same setting, malaria case incidence assessed by passive surveillance was marginally reduced in children aged one to five years; PE 14%, but not in children older than five years (PE -2%). In the IRS group, malaria prevalence was slightly lower but this was not significant (PE 6%), but mean haemoglobin was higher (mean difference 0.85 g/dl). In one CBA trial in Nigeria, IRS showed protection against malaria prevalence during the wet season (PE 26%; 95% CI 20 to 32%) but not in the dry season (PE 6%; 95% CI -4 to 15%). In one ITS in Mozambique, the prevalence was reduced substantially over a period of 7 years (from 60 to 65% prevalence to 4 to 8% prevalence; the weighted PE before-after was 74% (95% CI 72 to 76%).

Unstable malaria (EIR < 1): In two RCTs, IRS reduced the incidence rate of all malaria infections; PE 31% in India, and 88% (95% CI 69 to 96%) in Pakistan. By malaria species, IRS also reduced the incidence of P. falciparum (PE 93%, 95% CI 61 to 98% in Pakistan) and P. vivax (PE 79%, 95% CI 45 to 90% in Pakistan); There were similar impacts on malaria prevalence for any infection: PE 76% in Pakistan; PE 28% in India. When looking separately by parasite species, for P. falciparum there was a PE of 92% in Pakistan and 34% in India; for P. vivax there was a PE of 68% in Pakistan and no impact demonstrated in India (PE of -2%).

IRS versus Insecticide Treated Nets (ITNs)
Stable malaria (EIR > 1): Only one RCT was done in an area of stable transmission (in Tanzania). When comparing parasitological re-infection by active surveillance after treatment in short-term cohorts, ITNs appeared better, but it was likely not to be significant as the unadjusted CIs approached 1 (risk ratio IRS:ITN = 1.22). When the incidence of malaria episodes was measured by passive case detection, no difference was found in children aged one to five years (risk ratio = 0.88, direction in favour of IRS). No difference was found for malaria prevalence or haemoglobin.

Unstable malaria (EIR < 1): Two studies; for incidence and prevalence, the malaria rates were higher in the IRS group compared to the ITN group in one study. Malaria incidence was higher in the IRS arm in India (risk ratio IRS:ITN = 1.48) and in South Africa (risk ratio 1.34 but the cluster unadjusted CIs included 1). For malaria prevalence, ITNs appeared to give better protection against any infection compared to IRS in India (risk ratio IRS:ITN = 1.70) and also for both P. falciparum (risk ratio IRS:ITN = 1.78) and P. vivax (risk ratio IRS:ITN = 1.37).

**AUTHORS’ CONCLUSIONS:**
Historical and programme documentation has clearly established the impact of IRS. However, the number of high-quality trials are too few to quantify the size of effect in different transmission settings. The evidence from randomized comparisons of IRS versus no IRS confirms that IRS reduces malaria incidence in unstable malaria settings, but randomized trial data from stable malaria settings is very limited. Some limited data suggest that ITN give better protection than IRS in unstable areas, but more trials are needed to compare the effects of ITNs with IRS, as well as to quantify their combined effects.

BACKGROUND:
The efficacy and safety of the RTS,S/AS01 candidate malaria vaccine during 18 months of follow-up have been published previously. Herein, we report the final results from the same trial, including the efficacy of a booster dose.

METHODS:
From March 27, 2009, until Jan 31, 2011, children (age 5-17 months) and young infants (age 6-12 weeks) were enrolled at 11 centres in seven countries in sub-Saharan Africa. Participants were randomly assigned (1:1:1) at first vaccination by block randomisation with minimisation by centre to receive three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20 (R3R group); three doses of RTS,S/AS01 and a dose of comparator vaccine at month 20 (R3C group); or a comparator vaccine at months 0, 1, 2, and 20 (C3C [control group]). Participants were followed up until Jan 31, 2014. Cases of clinical and severe malaria were captured through passive case detection. Serious adverse events (SAEs) were recorded. Analyses were by modified intention to treat and per protocol. The coprimary endpoints were the occurrence of malaria over 12 months after dose 3 in each age category. In this final analysis, we present data for the efficacy of the booster on the occurrence of malaria. Vaccine efficacy (VE) against clinical malaria was analysed by negative binomial regression and against severe malaria by relative risk reduction. This trial is registered with ClinicalTrials.gov, number NCT00866619.

FINDINGS:
8922 children and 6537 young infants were included in the modified intention-to-treat analyses. Children were followed up for a median of 48 months (IQR 39-50) and young infants for 38 months (34-41) after dose 1. From month 0 until study end, compared with 9585 episodes of clinical malaria that met the primary case definition in children in the C3C group, 6616 episodes occurred in the R3R group (VE 36-3%, 95% CI 31-8-40-5) and 7396 occurred in the R3C group (28-3%, 23-3-32-9); compared with 171 children who experienced at least one episode of severe malaria in the C3C group, 116 children experienced at least one episode of severe malaria in the R3R group (32-2%, 13-7 to 46-9) and 169 in the R3C group (1-1%, -23-0 to 20-5). In young infants, compared with 6170 episodes of clinical malaria that met the primary case definition in the C3C group, 4993 episodes occurred in the R3R group (VE 25-9%, 95% CI 19-9-31-5) and 5444 occurred in the R3C group (18-3%, 11-7-24-4); and compared with 116 infants who experienced at least one episode of severe malaria in the C3C group, 96 infants experienced at least one episode of severe malaria in the R3R group (17-3%, 95% CI 9-4 to 37-5) and 104 in the R3C group (10-3%, -17-9 to 31-8). In children, 1774 cases of clinical malaria were averted per 1000 children (95% CI 1387-2186) in the R3R group and 1363 per 1000 children (995-1797) in the R3C group. The numbers of cases averted per 1000 young infants were 983 (95% CI 592-1337) in the R3R group and 558 (158-926) in the R3C group. The frequency of SAEs overall was balanced between groups. However, meningitis was reported as a SAE in 22 children: 11 in the R3R group, ten in the R3C group, and one in the C3C group. The incidence of generalised convulsive seizures within 7 days of RTS,S/AS01 booster was 2.2 per 1000 doses in young infants and 2.5 per 1000 doses in children.

INTERPRETATION:
RTS,S/AS01 prevented a substantial number of cases of clinical malaria over a 3-4 year period in young infants and children when administered with or without a booster dose. Efficacy was enhanced by the administration of a booster dose in both age categories. Thus, the vaccine has the potential to make a substantial contribution to malaria control when used in combination with other effective control measures, especially in areas of high transmission.

BACKGROUND:
A malaria vaccine could be an important addition to current control strategies. We report the safety and vaccine efficacy (VE) of the RTS,S/AS01 vaccine during 18 mo following vaccination at 11 African sites with varying malaria transmission.

METHODS AND FINDINGS:
6,537 infants aged 6-12 wk and 8,923 children aged 5-17 mo were randomized to receive three doses of RTS,S/AS01 or comparator vaccine. VE against clinical malaria in children during the 18 mo after vaccine dose 3 (per protocol) was 46% (95% CI 42% to 50%) (range 40% to 77%; VE, p<0.01 across all sites). VE during the 20 mo after vaccine dose 1 (intention to treat [ITT]) was 45% (95% CI 41% to 49%). VE against severe malaria, malaria hospitalization, and all-cause hospitalization was 34% (95% CI 15% to 48%), 41% (95% CI 30% to 50%), and 19% (95% CI 11% to 27%), respectively (ITT). VE against clinical malaria in infants was 27% (95% CI 20% to 32%, per protocol; 27% [95% CI 21% to 33%], ITT), with no significant protection against severe malaria, malaria hospitalization, or all-cause hospitalization. Post-vaccination anti-circumsporozoite antibody geometric mean titer varied from 348 to 787 EU/ml across sites in children and from 117 to 335 EU/ml in infants (per protocol). VE waned over time in both age categories (Schoenfeld residuals p<0.001). The number of clinical and severe malaria cases averted per 1,000 children vaccinated ranged across sites from 37 to 2,365 and from -1 to 49, respectively; corresponding ranges among infants were -10 to 1,402 and -13 to 37, respectively (ITT). Meningitis was reported as a serious adverse event in 16/5,949 and 1/2,974 children and in 9/4,358 and 3/2,179 infants in the RTS,S/AS01 and control groups, respectively.

CONCLUSIONS:
RTS,S/AS01 prevented many cases of clinical and severe malaria over the 18 mo after vaccine dose 3, with the highest impact in areas with the greatest malaria incidence. VE was higher in children than in infants, but even at modest levels of VE, the number of malaria cases averted was substantial. RTS,S/AS01 could be an important addition to current malaria control in Africa.

Where malaria prospers most, human societies have prospered least. The global distribution of per-capita gross domestic product shows a striking correlation between malaria and poverty, and malaria-endemic countries also have lower rates of economic growth. There are multiple channels by which malaria impedes development, including effects on fertility, population growth, saving and investment, worker productivity, absenteeism, premature mortality and medical costs.

BACKGROUND:
Routine vaccination of infants against Streptococcus pneumoniae (pneumococcus) needs substantial investment by governments and charitable organisations. Policymakers need information about the projected health benefits, costs, and cost-effectiveness of vaccination when considering these investments. Our aim was to incorporate these data into an economic analysis of pneumococcal vaccination of infants in countries eligible for financial support from the Global Alliance for Vaccines & Immunization (GAVI).

METHODS:
We constructed a decision analysis model to compare pneumococcal vaccination of infants aged 6, 10, and 14 weeks with no vaccination in the 72 countries that were eligible as of 2005. We used published and unpublished data to estimate child mortality, effectiveness of pneumococcal conjugate vaccine, and immunisation rates.
FINDINGS:
Pneumococcal vaccination at the rate of diptheria-tetanus-pertussis vaccine coverage was projected to prevent 262,000 deaths per year (7%) in children aged 3-29 months in the 72 developing countries studied, thus averting 8.34 million disability-adjusted life years (DALYs) yearly. If every child could be reached, up to 407,000 deaths per year would be prevented. At a vaccine cost of International 5 dollars per dose, vaccination would have a net cost of 838 million dollars, a cost of 100 dollars per DALY averted. Vaccination at this price was projected to be highly cost-effective in 68 of 72 countries when each country’s per head gross domestic product per DALY averted was used as a benchmark.

INTERPRETATION:
At a vaccine cost of between 1 dollar and 5 dollars per dose, purchase and accelerated uptake of pneumococcal vaccine in the world's poorest countries is projected to substantially reduce childhood mortality and to be highly cost-effective.


BACKGROUND:
An effective malaria vaccine, deployed in conjunction with other malaria interventions, is likely to substantially reduce the malaria burden. Efficacy against severe malaria will be a key driver for decisions on implementation. An initial study of an RTS, S vaccine candidate showed promising efficacy against severe malaria in children in Mozambique. Further evidence of its protective efficacy will be gained in a pivotal, multi-centre, phase III study. This paper describes the case definitions of severe malaria used in this study and the programme for standardized assessment of severe malaria according to the case definition.

METHODS:
Case definitions of severe malaria were developed from a literature review and a consensus meeting of expert consultants and the RTS, S Clinical Trial Partnership Committee, in collaboration with the World Health Organization and the Malaria Clinical Trials Alliance. The same groups, with input from an Independent Data Monitoring Committee, developed and implemented a programme for standardized data collection. The case definitions developed reflect the typical presentations of severe malaria in African hospitals. Markers of disease severity were chosen on the basis of their association with poor outcome, occurrence in a significant proportion of cases and on an ability to standardize their measurement across research centres. For the primary case definition, one or more clinical and/or laboratory markers of disease severity have to be present, four major co-morbidities (pneumonia, meningitis, bacteraemia or gastroenteritis with severe dehydration) are excluded, and a Plasmodium falciparum parasite density threshold is introduced, in order to maximize the specificity of the case definition. Secondary case definitions allow inclusion of co-morbidities and/or allow for the presence of parasitaemia at any density. The programmatic implementation of standardized case assessment included a clinical algorithm for evaluating seriously sick children, improvements to care delivery and a robust training and evaluation programme for clinicians.

CONCLUSIONS:
The case definition developed for the pivotal phase III RTS, S vaccine study is consistent with WHO recommendations, is locally applicable and appropriately balances sensitivity and specificity in the diagnosis of severe malaria. Processes set up to standardize severe malaria data collection will allow robust assessment of the efficacy of the RTS, S vaccine against severe malaria, strengthen local capacity and benefit patient care for subjects in the trial.

**BACKGROUND:**
The RTS,S malaria vaccine is currently undergoing phase 3 trials. High vaccine-induced antibody titres to the circumsporozoite protein (CSP) antigen have been associated with protection from infection and episodes of clinical malaria.

**METHODS:**
Using data from 5,144 participants in nine phase 2 trials, we explore predictors of vaccine immunogenicity (anti-CSP antibody titres), decay in antibody titres, and the association between antibody titres and clinical outcomes. We use empirically-observed relationships between these factors to predict vaccine efficacy in a range of scenarios.

**RESULTS:**
Vaccine-induced anti-CSP antibody titres were significantly associated with age (P = 0.04), adjuvant (P <0.001), pre-vaccination anti-hepatitis B surface antigen titres (P = 0.005) and pre-vaccination anti-CSP titres (P <0.001). Co-administration with other vaccines reduced anti-CSP antibody titres although not significantly (P = 0.095). Antibody titres showed a bi-phasic decay over time with an initial rapid decay in the first three months and a second slower decay over the next three to four years. Antibody titres were significantly associated with protection, with a titre of 51 (95% Credible Interval (Crl): 29 to 85) ELISA units/ml (EU/mL) predicted to prevent 50% of infections in children. Vaccine efficacy was predicted to decline to zero over four years in a setting with entomological inoculation rate (EIR) = 20 infectious bites per year (ibpy). Over a five-year follow-up period at an EIR = 20 ibpy, we predict RTS,S will avert 1,782 cases per 1,000 vaccinated children, 1,452 cases per 1,000 vaccinated infants, and 887 cases per 1,000 infants when co-administered with expanded programme on immunisation (EPI) vaccines. Our main study limitations include an absence of vaccine-induced cellular immune responses and short duration of follow-up in some individuals.

**CONCLUSIONS:**
Vaccine-induced anti-CSP antibody titres and transmission intensity can explain variations in observed vaccine efficacy.


**BACKGROUND:**
The control and elimination of malaria requires expanded coverage of and access to effective malaria control interventions such as insecticide-treated nets (ITNs), indoor residual spraying (IRS), intermittent preventive treatment (IPT), diagnostic testing and appropriate treatment. Decisions on how to scale up the coverage of these interventions need to be based on evidence of programme effectiveness, equity and cost-effectiveness.

**METHODS:**
A systematic review of the published literature on the costs and cost-effectiveness of malaria interventions was undertaken. All costs and cost-effectiveness ratios were inflated to 2009 USD to allow comparison of the costs and benefits of several different interventions through various delivery channels, across different geographical regions and from varying costing perspectives.

**RESULTS:**
Fifty-five studies of the costs and forty three studies of the cost-effectiveness of malaria interventions were identified, 78% of which were undertaken in sub-Saharan Africa, 18% in Asia and 4% in South America. The median financial cost of protecting one person for one year was $2.20 (range $0.88-$9.54) for ITNs, $6.70 (range $2.22-$12.85) for IRS, $0.60 (range $0.48-$1.08) for IPT in infants, $4.03 (range $1.25-$11.80) for IPT in children, and $2.06 (range $0.47-$3.36) for IPT in pregnant women. The median financial cost of diagnosing a case of malaria was $4.32 (range $0.34-$9.34). The median financial cost of treating an episode of uncomplicated malaria was $5.84 (range $2.36-$23.65) and the median financial cost of treating an episode of severe malaria was
$30.26 (range $15.64-$137.87). Economies of scale were observed in the implementation of ITNs, IRS and IPT, with lower unit costs reported in studies with larger numbers of beneficiaries. From a provider perspective, the median incremental cost effectiveness ratio per disability adjusted life year averted was $27 (range $8.15-$110) for ITNs, $143 (range $135-$150) for IRS, and $24 (range $1.08-$44.24) for IPT.

CONCLUSIONS:
A transparent evidence base on the costs and cost-effectiveness of malaria control interventions is provided to inform rational resource allocation by donors and domestic health budgets and the selection of optimal packages of interventions by malaria control programmes.


BACKGROUND:
The RTS,S/AS01 malaria vaccine targets the circumsporozoite protein, inducing antibodies associated with the prevention of Plasmodium falciparum infection. We assessed the association between anti-circumsporozoite antibody titres and the magnitude and duration of vaccine efficacy using data from a phase 3 trial done between 2009 and 2014.

METHODS:
Using data from 8922 African children aged 5-17 months and 6537 African infants aged 6-12 weeks at first vaccination, we analysed the determinants of immunogenicity after RTS,S/AS01 vaccination with or without a booster dose. We assessed the association between the incidence of clinical malaria and anti-circumsporozoite antibody titres using a model of anti-circumsporozoite antibody dynamics and the natural acquisition of protective immunity over time.

FINDINGS:
RTS,S/AS01-induced anti-circumsporozoite antibody titres were greater in children aged 5-17 months than in those aged 6-12 weeks. Pre-vaccination anti-circumsporozoite titres were associated with lower immunogenicity in children aged 6-12 weeks and higher immunogenicity in those aged 5-17 months. The immunogenicity of the booster dose was strongly associated with immunogenicity after primary vaccination. Anti-circumsporozoite titres wane according to a biphasic exponential distribution. In participants aged 5-17 months, the half-life of the short-lived component of the antibody response was 45 days (95% credible interval 42-48) and that of the long-lived component was 591 days (557-632). After primary vaccination 12% (11-13) of the response was estimated to be long-lived, rising to 30% (28-32%) after a booster dose. An anti-circumsporozoite antibody titre of 121 EU/ml (98-153) was estimated to prevent 50% of infections. Waning anti-circumsporozoite antibody titres predict the duration of efficacy against clinical malaria across different age categories and transmission intensities, and efficacy wanes more rapidly at higher transmission intensity.

INTERPRETATION:
Anti-circumsporozoite antibody titres are a surrogate of protection for the magnitude and duration of RTS,S/AS01 efficacy, with or without a booster dose, providing a valuable surrogate of effectiveness for new RTS,S formulations in the age groups considered.


BACKGROUND:
Intermittent preventive treatment of malaria in children less than five years of age (IPTc) has been investigated as a measure to control the burden of malaria in the Sahel and sub-Saharan areas of Africa where malaria transmission is markedly seasonal.

METHODS AND FINDINGS:
IPTc studies were identified using a systematic literature search. Meta-analysis was used to assess
the protective efficacy of IPTc against clinical episodes of falciparum malaria. The impact of IPTc on all-cause mortality, hospital admissions, severe malaria and the prevalence of parasitaemia and anaemia was investigated. Three aspects of safety were also assessed: adverse reactions to study drugs, development of drug resistance and loss of immunity to malaria. Twelve IPTc studies were identified: seven controlled and five non-controlled trials. Controlled studies demonstrated protective efficacies against clinical malaria of between 31% and 93% and meta-analysis gave an overall protective efficacy of monthly administered IPTc of 82% (95%CI 75%-87%) during the malaria transmission season. Pooling results from twelve studies demonstrated a protective effect of IPTc against all-cause mortality of 57% (95%CI 24%-76%) during the malaria transmission season. No serious adverse events attributable to the drugs used for IPTc were observed in any of the studies. Data from three studies that followed children during the malaria transmission season in the year following IPTc administration showed evidence of a slight increase in the incidence of clinical malaria compared to children who had not received IPTc.

CONCLUSIONS:
IPTc is a safe method of malaria control that has the potential to avert a significant proportion of clinical malaria episodes in areas with markedly seasonal malaria transmission and also appears to have a substantial protective effect against all-cause mortality. These findings indicate that IPTc is a potentially valuable tool that can contribute to the control of malaria in areas with markedly seasonal transmission.
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