

Progress with new malaria vaccines

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Abstract Malaria is a parasitic disease of major global health significance that causes an estimated 2.7 million deaths each year. In this review we describe the burden of malaria and discuss the complicated life cycle of *Plasmodium falciparum*, the parasite responsible for most of the deaths from the disease, before reviewing the evidence that suggests that a malaria vaccine is an attainable goal. Significant advances have recently been made in vaccine science, and we review new vaccine technologies and the evaluation of candidate malaria vaccines in human and animal studies worldwide. Finally, we discuss the prospects for a malaria vaccine and the need for iterative vaccine development as well as potential hurdles to be overcome.

Keywords Malaria vaccines/pharmacology; Vaccines, Synthetic/pharmacology; Vaccines, DNA/pharmacology; Malaria, Falciparum/immunology; Plasmodium falciparum/growth and development/immunology; Antigens, Protozoan/immunology; Models, Animal; Human; Clinical trials, Phase I; Clinical trials, Phase II (source: MeSH, NLM).

Mots clés Vaccin antipaludéen/pharmacologie; Vaccin synthèse/pharmacologie; Vaccins AND/pharmacologie; Paludisme plasmodium falciparum/immunologie; Plasmodium falciparum/croissance et développement/immunologie; Antigène protozoaire/immunologie; Modèle animal; Humain; Essai clinique phase I; Essai clinique phase II (source: MeSH, INSERM).

Palabras clave Vacunas contra la malaria/farmacología; Vacunas sintéticas/farmacología; Vacunas de ADN/farmacología; Paludismo falciparum/inmunología; Plasmodium falciparum/crecimiento y desarrollo/inmunología; Antígenos de protozoarios/inmunología; Modelos animales; Humano; Ensayos clínicos fase I; Ensayos (fuente: DeCS, BIREME).

الكلمات المفتاحية: لقاحات الملاريا، فارماكولوجيا لقاحات الملاريا، اللقاحات، اللقاحات التخليقية، فارماكولوجيا اللقاحات التخليقية، الدنا، فارماكولوجيا الدنا، الملاريا، الملاريا المنجلية، مناعيات الملاريا المنجلية، المتصورات المنجلية، نمو وتطور المتصورات المنجلية، مناعيات المتصورات المنجلية، المستضدات، مستضدات الأوالي، مناعيات مستضدات الأوالي، نماذج حيوانية، نماذج بشرية، تجارب سريرية (إكلينيكية)، التطور الأول من التجارب السريرية (الإكلينيكية)، التطور الثاني من التجارب السريرية (الإكلينيكية). (المصدر: رؤوس الموضوعات الطبية المكتب الإقليمي لشرق المتوسط).

Bulletin of the World Health Organization 2003;81:902-909

Voir page 906 le résumé en français. En la página 906 figura un resumen en español.

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Introduction

Malaria is a parasitic disease of major global health significance caused by one of four species of the *Plasmodium* genus, i.e. *P. falciparum*, *P. vivax*, *P. ovale* or *P. malariae*. This review focuses on the development of vaccines against *P. falciparum* because it is the cause of most of the deaths from malaria. It is estimated that up to 2.7 million people, mainly children, die each year from malaria and more than 2 billion people live in regions where inhabitants are exposed to infection with *P. falciparum* (1). Infection with *P. falciparum* leads to a wide spectrum of clinical disease including life-threatening anaemia and coma in children, and a severe disease syndrome during pregnancy in primigravida women (2). However, malaria is more than just a health problem — in regions where the disease flourishes, societies have prospered least. The global distribution of per-capita gross domestic product shows a striking correlation between malaria and poverty. Countries in which malaria is endemic also have lower rates of economic growth as a consequence of numerous factors including effects of the disease on fertility, population

growth, saving and investment, worker productivity, absenteeism, premature mortality and medical costs (3).

The burden of malarial disease continues to increase as the countries in which it is endemic face increasing and ever more widespread drug-resistance in the parasite and increasing resistance of the vector to insecticide, together with a lack of the necessary infrastructure to tackle the problems. This increase is occurring despite evidence that certain mechanisms for controlling malaria are proving successful; these include the use of insecticide-treated bednets (4, 5) and the development and availability of new anti-malarial drugs such as dapsone-proguanil (6, 7) and artemisinin derivatives (8). An effective vaccine against this parasitic disease is urgently needed. We outline below the complex life cycle of the malaria parasite before reviewing the evidence that supports the view that a malaria vaccine is feasible. We then review recent developments in vaccinology that may speed up the process of developing a successful vaccine, and finally discuss those vaccines that are currently being tested in clinical trials or are close to being tested.

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Ref. No. 03-002519

Life cycle of the *Plasmodium falciparum* parasite

P. falciparum has a complicated life cycle involving several stages, with different antigens being expressed at each stage. Thus, unlike most currently licensed vaccines, a live attenuated or killed whole organism vaccine is unlikely to be practical because an attenuated parasite from one stage of the life cycle may well confer immunity only to that stage. A vaccine that works at one stage in the life cycle of the parasite was thought until recently to be unlikely to have any effect on any other stage. However, data from the malaria genome project call into question some of the previously held ideas about the stage-specific expression of antigens and several antigens formerly believed to be specific to one stage have been found also at other stages of the life cycle (9). The main stages of the parasite's life cycle can be summarized as follows:

- **Pre-erythrocytic stage:** *P. falciparum* is spread by the bite of an infected female anopheline mosquito that ejects an estimated 15 sporozoites (10) into the circulation of the host. These sporozoites migrate to liver cells, which become infected within minutes of biting. Once inside the liver cells these sporozoites mature over 6–7 days into liver-stage trophozoites and then into schizonts before rupturing the infected liver cell and releasing an estimated 20 000–40 000 merozoites into the circulation.
- **Blood stage:** Once in the systemic circulation, the merozoites follow a cycle of invasion of the erythrocytes and multiplication takes place until either the infection is brought under control by the immune system or death of the host results.
- **Sexual stage:** Some of the blood stage merozoites differentiate into male and female gametocytes that are subsequently taken up by a feeding mosquito to complete the life cycle. The male gametocyte responds to signals within the mosquito to exflagellate and a zygote is formed. After migration through the mosquito midgut, differentiation into an adherent oocyst occurs. Ultimately this oocyst lyses and releases sporozoites that are transferred to the salivary glands.

The choice of which stage to target is one problem in malaria vaccine development, but the question of which antigen or antigens from that stage to incorporate into a subunit vaccine is even more difficult to answer. The genomic sequence of the parasite has now been sequenced offering vaccinologists a choice of about 5300 gene products to target (11).

Is a malaria vaccine feasible?

Despite decades of research, an effective vaccine against malaria has remained elusive. There are, however, several lines of evidence to suggest that protective immunity to malaria is possible. These are summarized below.

- Immunization with irradiated sporozoites has been shown to result in partial or complete protection in mice (12), monkeys (13) and humans (14) from experimental malaria challenge with viable sporozoites.
- Repeated infection of an individual with malaria leads to the gradual acquisition of what is termed “naturally acquired immunity” (15). This is short-lived, partially strain-specific immunity that leads at first to a reduction in death rate and incidence of complications, then to a decreased incidence of clinical malaria and ultimately results in the suppression of parasitaemia to low or undetectable levels.

- Passive transfer of purified immunoglobulins from “immune” individuals can protect children as demonstrated by transfer of sera obtained from “immune” African individuals to Thai children experiencing recrudescence of malaria infection (16).
- Many studies in animal models that have been completed, and some of the clinical studies that are currently in progress, have shown protective efficacy in both small phase I/IIa studies and in larger phase IIb field studies. These are discussed in more detail below.

Vaccine strategies

The view has been expressed for some time that a malaria vaccine is “just around the corner”, but recent advances in molecular biology have given rise to some new hopes. The use of recombinant DNA technology as a means of generating subunit protein vaccines in a variety of expression systems represents a significant advance. Now that the genomic sequence of *P. falciparum* has been elucidated (11), analyses of genome sequence, DNA polymorphisms, and messenger RNA and protein expression profiles are likely to lead to a better understanding of the molecular basis of the vector–human and host–parasite interactions and to suggest strategies for designing new vaccines (17). However, many of these subunit proteins are only slightly immunogenic and require potent adjuvants.

Advances in vaccinology will also speed up the process of vaccine development. DNA vaccines and recombinant viral vector vaccines are now at the pre-clinical and clinical testing stages at various centres. DNA vaccines use plasmids of double-stranded DNA in which the DNA sequence for a protein or series of epitopes has been inserted under the control of a mammalian promoter. These vaccines can be injected intramuscularly, subcutaneously or intradermally and are taken up by muscle cells and dendritic cells, where the genetic information for the malaria protein is translated. Encouraging results have been seen in animal test systems, but the current generation of DNA vaccines is insufficiently immunogenic in humans to offer protective efficacy. These vaccines, however, do have the potential to be modified to enhance protein expression and immunogenicity. This may be done, for example, by optimizing gene codons for mammalian expression (18), administration with plasmids expressing cytokines such as GM-CSF (19, 20) and interleukin-12 (21) or other immunostimulatory molecules such as CpG motifs (21–23). Alternative methods of administration may also enhance immunogenicity e.g. administration by use of an intradermal “gene gun” (24).

DNA vaccines are effective at priming cellular immune responses including those of Th1-type CD4 T cells and CD8+ cytotoxic T cells (CTL), which are likely to be important in liver-stage malaria (see below). Researchers at the University of Oxford, England, found that high levels of specific CTL were produced by priming the immune response with a DNA vaccine and heterologous boosting of the response with a recombinant modified vaccinia virus Ankara (MVA) expressing the same antigen as the DNA (25–27). Strong CTL responses against several infectious diseases including malaria (25–27), tuberculosis (28, 29) and human immunodeficiency virus (HIV) (30–32) have been generated by this prime–boost approach. Indeed, in mouse models of malaria, use of these prime–boost regimes has led to complete protection against experimental malaria challenge (25) and in cases of murine tuberculosis, protection equivalent to that conferred by BCG was reported (28). In addition to MVA, recombinant avipox vectors have been developed, for example,

fowlpox strain 9. When used in prime–boost combinations with MVA, fowlpox strain 9 can substitute for DNA as a priming vaccine; it has been found to be immunogenic and to have protective efficacy in a mouse model of malaria (33). Like DNA vaccines, recombinant viral vectors are amenable to modification and the development of recombinant virus vectors that co-express a vaccine candidate antigen and an immune modulator may serve to amplify protective immune effectors or to down-regulate immune responses that correlate with adverse disease profiles (i.e. if a Th1-type response is required for protection, then the addition of cytokines may polarize the response in this direction, namely, away from a Th2 response) (34, 35).

Pre-erythrocytic vaccines

Pre-erythrocytic vaccines are an attractive prospect as they would prevent the invasion of hepatocytes by sporozoites or destroy parasites in infected hepatocytes and would thus prevent both clinical disease and the transmission of malaria. The efficacy of these vaccines can be quickly assessed using the safe, well-established malaria challenge models available for rodents, primates and humans. There is evidence that vaccination with irradiated sporozoites, which abort their development at the liver stage, can lead to protection of up to 90% of immunized human volunteers following a regime involving the bites of more than 1000 irradiated infected mosquitoes over a period of time (36). Although these results are impressive, this is currently not a viable vaccination strategy. However, the results do provide evidence that the sporozoite stage could be a key target. Although the immune mechanism underlying this protection is not clearly understood, there is evidence for a role of T lymphocytes that lyse infected hepatocytes or have a cytokine-mediated (γ -interferon effect) (37). Indeed, in the animal experimental system, gene knock-out mice deficient in CD8 T-cell function are not protected by this form of immunization and protection can be adoptively transferred by T cells cloned from protected mice. Antibodies directed against the sporozoite that prevent its entry into hepatocytes may also play a role.

Probably the best characterized pre-erythrocytic antigen is the circumsporozoite protein (CSP) which is expressed on the extracellular sporozoite and the intracellular hepatic stages of the parasite (38). A considerable body of work has been directed at generating protective antibody responses to the NANP repeat region of CSP. The results of preliminary studies of recombinant (39) and synthetic (40) CSP vaccines in humans showed that such vaccines were safe and immunogenic but had only limited efficacy. A collaboration between GlaxoSmithKline Biologicals and the US Walter Reed Army Institute of Research has led to the development of the candidate vaccine RTS,S. The antigen in this vaccine consists of a hybrid in which the carboxy terminus of the circumsporozoite protein is fused to hepatitis B surface antigen (HBsAg), and is expressed together with unfused HBsAg in yeast (41). When administered with the potent adjuvant AS02 (which includes monophosphoryl lipid A, QS-21 and a proprietary oil-in-water emulsion) RTS,S provided significant, albeit short-lived, protection (41%) against laboratory challenge with a homologous strain and is the most successful candidate vaccine to be developed to date (42). RTS,S/AS02 is a potent inducer of Th1-type cellular and humoral immunity that generates high concentrations of IgG to the CSP repeat region and provokes strong proliferative T-lymphocyte responses to RTS,S but there are no detectable CSP peptide-specific CD8 T-cells (43). The efficacy of RTS,S/AS02 has also been evaluated

in a field study in semi-immune adult men in collaboration with the MRC Laboratories in the Gambia. The efficacy during the first 9 weeks of follow-up was estimated to be 71% but decreased to 0% over the next 6 weeks (44). It is not yet clear which immune mechanism is responsible for the efficacy of this vaccine, but the high levels of antibodies induced are likely to contribute. Further phase I and IIa studies of RTS,S/AS02 are being carried out at University of Oxford, England, to establish whether the addition of MVA encoding CSP to the RTS,S vaccine regime can improve its efficacy and/or the longevity of the response.

An alternative approach to generating potent anti-CSP antibody responses has been developed by Apovia Inc. in collaboration with New York University, USA. This approach uses a modified hepatitis B virus core particle containing T- and B-cell epitopes from the repeat region and a universal T-cell epitope from the C terminus of CSP called ICC-1132. This vaccine has been found to be highly immunogenic in mice and in cynomolgus monkeys. In addition to generating strong malaria-specific immune responses in malaria-naïve hosts, ICC-1132 elicits potent anamnestic antibody responses in mice primed with *P. falciparum* sporozoites. This suggests a potential advantage of enhancing the sporozoite-primed responses of semi-immune individuals in endemic areas (45). Phase I clinical trials are now under way.

Immunization with plasmid DNA encoding CSP from *P. yoelii* has been shown to elicit protection against sporozoite challenge in BALB/c mice (46). Use of the same model, but employing a two-plasmid vaccine improved the immunogenicity (47). Further improvement in murine immunogenicity in the same mouse model can be achieved by co-administration of a plasmid expressing murine GM-CSF (20). Plasmid DNA encoding *P. falciparum* CSP has been shown to be safe and immunogenic in humans (in whom it induced CD4- and CD8-expressing T-cell-dependent γ -interferon responses as measured in an enzyme-linked immunospot assay) (48, 49). This work paved the way for the US Navy's multi-gene, multi-stage DNA vaccine programme. One of these DNA vaccine formulations, MuStDO9, consists of five plasmids (CSP, SSP2, EXP1, LSA1 and LSA3) encoding proteins from the sporozoite and liver-stages of *P. falciparum* and four encoding proteins (AMA1 and EBA175 and two alleles of MSP1) from the blood stage. To date no DNA vaccine used alone has been reported to be efficacious in humans although human challenge studies have been undertaken in both the United Kingdom and the USA (50–52).

After it was established that DNA-MVA and FP9-MVA prime–boost immunization regimes could lead to complete protection against malaria in a mouse model (25, 33), clinical trials of this approach in humans were initiated at the University of Oxford, England, in 1999. The DNA, MVA and FP9 vaccines used initially encoded an identical DNA sequence consisting of a string of T- and B-cell epitopes from pre-erythrocytic antigens (the multi-epitope or ME string) fused to the entire sequence of thrombospondin-related adhesion protein (TRAP). TRAP is a pre-erythrocytic antigen that has been shown to be important for gliding motility and infectivity of liver cells (53) and naturally exposed Gambians have T-cell responses to several conserved regions (54). Several sequential clinical trials of DNA ME-TRAP, MVA ME-TRAP and FP9 ME-TRAP vaccines have been conducted to evaluate their safety, immunogenicity and protective efficacy in human volunteers. These vaccines are safe (55), highly immunogenic for CD4+ and CD8+ T lymphocytes and have shown encouraging and statistically significant results in studies

of efficacy against a stringent, heterologous strain sporozoite challenge (56). These vaccines have also been administered to semi-immune Gambians and a phase IIb study of DNA-MVA prime–boost immunization is currently under way in the Gambia. MVA and FP9 vaccines that encode codon-optimized CSP have also been developed; these will be entering phase I and IIa studies in 2003.

Two other pre-erythrocytic antigens are also being investigated, namely, liver-stage antigens (LSAs) 1 and 3. LSA1 is known to be expressed by liver-stage parasites and studies of naturally exposed populations have related immune responses against this antigen to protection (57). LSA3 which is expressed by both pre-erythrocytic and blood-stage parasites appears to be highly conserved and shows promising antigenic and immunogenic properties. In chimpanzees (*Pan troglodytes*), the primates most closely related to humans, immunization with various LSA3 constructs induced protection against successive challenges with large numbers of *P. falciparum* sporozoites (58), but the study did not determine whether this was pre-erythrocytic or blood-stage protection.

Blood-stage vaccines

The success of an effective blood-stage vaccine is generally considered as being likely to rely on generating high titres of antibody that would either prevent the invasion of erythrocytes by merozoites, enhance clearance of parasitized erythrocytes or prevent sequestration of erythrocytes and thus the complications of malaria (e.g. malarial anaemia, cerebral malaria and the severe malaria of pregnancy). The clinical testing of a blood-stage vaccine poses problems although a blood-stage challenge model has been developed in which parasite growth rate is the marker of efficacy (59). Most of the development of blood-stage vaccines has been focused on targeting the antigens responsible for parasite entry into cells. The best-characterized antigen is MSP1, a major surface merozoite protein. Antibodies to the C-terminus, a 19-kDa fragment of MSP1, PfMSP1(19), have been associated with resistance to clinical malaria in two populations of children in West Africa (60). These antibodies have been purified from sera obtained from humans immune to malaria and can:

- compete with invasion-inhibiting monoclonal antibodies for binding to PfMSP1(19); and
- mediate inhibition of parasite growth in vitro, in the absence of complement and mononuclear cells, at physiological concentrations of antibody (61).

These studies suggest that vaccines designed to induce antibodies to PfMSP1(19) may protect against the high levels of malaria parasitaemia associated with clinical disease. The protective efficacy of an MSP1 vaccine against lethal *P. falciparum* challenge has been demonstrated in *Aotus nancymai* monkeys (62). The safety and immunogenicity of two yeast-derived, PfMSP1(19) vaccines have been evaluated in a phase I trial. Healthy adults were given two or three doses of alum-adsorbed vaccine. The first two doses were well-tolerated, but some subjects suffered hypersensitivity reactions after the third dose. These vaccines were immunogenic in humans, but changes to the formulation will be necessary (63).

Two phase I trials of the safety and immunogenicity of a three-component blood-stage vaccine have been conducted in volunteers from Brisbane, Australia, and Papua New Guinea where malaria is endemic. The preparations tested were recombinant

proteins that corresponded to parts of the two merozoite surface proteins (MSPs) of *P. falciparum* (MSP1 and 2), and of the ring-infected erythrocyte surface antigen (RESA) that were emulsified with the adjuvant Montanide ISA720. The vaccine was immunogenic and no antigenic competition was observed: volunteers who received a mixture of antigens showed similar responses to those who received the three antigens at separate sites (64). Although no evidence of the efficacy of this vaccine was seen in a human blood-stage challenge study (65), a significant reduction in parasite densities was observed in one group of vaccinees in an efficacy study of Papua New Guinean children (66). Apical membrane antigen 1 (AMA1) is also considered to be one of the leading candidates for inclusion in a vaccine against blood stages of *P. falciparum* and the AMA1 gene is relatively well conserved compared to those of some other potential vaccine components. Monoclonal antibodies raised in rabbits and those purified from human sera can inhibit invasion of erythrocytes by merozoites (67).

Human antibodies that can be shown to inhibit the growth of parasites in assays of antibody-dependent cellular inhibition may be implicated in defence against malaria. Merozoite surface protein 3 (MSP3) and *P. falciparum* glutamine-rich protein (GLURP) induce such antibodies and therefore may be good targets for the induction of blood-stage immunity (68, 69). Support comes from a study in which protective efficacy has been demonstrated in *A. nancymai* monkeys using an MSP3 vaccine formulation (70).

Perhaps the ideal candidate for a vaccine that would protect against the complications of *P. falciparum* infection would be the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) because many of the complications of severe malaria are likely to be caused by the expression of this protein on erythrocytes and their subsequent cyto-adherence to endothelial cells in the micro-vasculature or by glycosaminoglycans in the placenta. However, PfEMP1 is highly polymorphic and each parasite clone contains approximately 50 different copies of the gene (51). During a chronic infection, each new wave of parasites expresses a new variant of this antigen thus allowing parasite development to continue despite the presence of antibodies directed against the preceding wave (71).

Transmission-blocking vaccines

Transmission-blocking vaccines (TBVs) against malaria are intended to induce immunity against the stages of the parasite that infect mosquitoes so that individuals immunized with TBVs cannot transmit malaria. These vaccines target the sexual stage of the malaria parasite with the aim of generating antibody responses that inhibit exflagellation and fertilization of the parasites in the mosquito vector. Because malarial infections are transmitted mainly within a few hundred metres of an infectious human source, TBVs used within a community could protect the immediate neighbourhood of the vaccinated individuals if high population coverage were achieved. But because these vaccines do not prevent infection in vaccinated individuals or moderate the course of the disease they are an unattractive financial venture for vaccine companies in developed countries and in developed country markets. However, TBVs against the two major species of human malaria parasite, *P. falciparum* and *P. vivax*, are under development (72). The antigens Pfs28 and Pfs25 are the furthest along in development and testing. Antibodies to Pfs28 block *P. falciparum* transmission, and when combined with antibodies to Pfs25 there is a synergistic effect. Pfs28 and Pfs25

are immunogenic, are structurally similar and have limited antigenic diversity (73). A recombinant fusion protein of these antigens called TBV25-28 has been found to be immunogenic in animal models (74) and phase I clinical studies of the *P. vivax* 25KD homologue in humans have now begun at the Malaria Vaccine Development Unit, NIH, USA.

In theory, candidate transmission-blocking vaccines should be the easiest to test for efficacy without the need for the infection of humans. Mosquitoes can be fed gametocyte-infected blood with or without serum from vaccinated volunteers to see if infection occurs (72).

Conclusion

Tremendous progress has been made in malaria vaccine research over the last decade as illustrated by some of the examples above. Advances in genomics have allowed a continuing proteomics programme that has identified many new potential vaccine candidates such as products of the *rifin*, *stevor* and *clag* genes (17). The question of which antigen or combinations of antigens to use will need to be answered. A multivalent approach (using several antigens from the same stage) is likely to be more successful than the single antigen approaches used so far because of the marked heterogeneity of host responses to malaria. However, the initial challenge is to identify protective components of the final vaccine individually to establish the best antigens to put into a multivalent formulation. As with combination drug therapy, the hope is that this approach would also reduce the rate at which parasites develop resistance to the vaccine. There is also the question of what type of immune response should be generated. Intuitively, both B- and T-cell responses are necessary as both are required in protection at different stages. For example, T-cell inducing vaccines have been shown to reduce the number

of parasites emerging from the liver (56), but if potent antibody responses against the sporozoite could also be induced then the number of liver cells initially infected should be smaller. This raises the question of which stage of the parasite's life cycle to target. A multi-stage approach may well be the answer. For example, if liver-stage antigens and blood-stage antigens were combined into a single formulation, any parasites that escape control at the liver stage could be "mopped up" by blood-stage immunity. This could be combined with the use of a transmission-blocking vaccine to prevent the spread of parasites that develop resistance within a community.

The task of the immunologist will be to identify correlates of protection so that a more iterative approach to vaccine design and to the planning of field trials can be taken. It is not yet clear how well the results of small efficacy trials in malaria-naïve populations will translate to efficacy in the field.

Perhaps, the biggest hurdle to the development of a successful malaria vaccine in the past has been chronic underfunding and a lack of political will. The question of funding is now being addressed and generous initiatives from source such as the Malaria Vaccine Initiative at PATH (Program for Appropriate Technology in Health), the Wellcome Trust, the National Institutes of Health, The European Malaria Vaccine Initiative and WHO have helped considerably. Clearly, a larger global health fund is required to stimulate a market for malaria vaccines because an anti-morbidity vaccine for African children that will not be used by travellers is not a commercially attractive prospect for large companies.

Despite the difficulties that have been encountered to date in efforts towards the development of a malaria vaccine, recent progress gives rise to much hope. Although, a deployable vaccine may not be "just around the corner", it is an achievable goal. ■

Conflicts of interest: none declared.

Résumé

Progrès dans la mise au point des vaccins antipaludiques

Le paludisme est une maladie parasitaire d'importance majeure dans le monde entier, qui provoquerait, selon les estimations, 2,7 millions de décès chaque année. Dans le présent article, les auteurs décrivent la charge du paludisme et expliquent le cycle de vie complexe de *Plasmodium falciparum*, le parasite responsable de la plupart des décès dus à cette maladie. Ils passent ensuite en revue les données permettant de penser que

le vaccin antipaludique est un objectif réalisable. La vaccinologie a fait récemment de grands progrès et les auteurs font le point, à partir d'études publiées dans le monde entier, des nouvelles technologies et évaluent les vaccins candidats chez l'homme et l'animal. Ils concluent en examinant les perspectives dans ce domaine, la nécessité d'un développement itératif pour ce type de vaccins ainsi que les obstacles potentiels à surmonter.

Resumen

Progresos en el desarrollo de nuevas vacunas contra la malaria

La malaria es una enfermedad parasitaria de enorme trascendencia para la salud mundial, que según se estima causa unos 2,7 millones de defunciones cada año. En esta revisión describimos la carga de malaria y analizamos el complejo ciclo de vida de *Plasmodium falciparum*, el parásito responsable de la mayoría de las defunciones debidas a esa enfermedad, para pasar a continuación a examinar la evidencia indicativa de que la obtención de una vacuna antimalárica es una meta alcanzable.

A la vista de los importantes progresos realizados últimamente en el campo de la vacunología, examinamos las nuevas tecnologías surgidas en ese terreno y hacemos una evaluación de las protovacunas antimaláricas empleadas en estudios realizados en el hombre y en animales en todo el mundo. Por último, nos referimos a las perspectivas de obtener una vacuna contra la malaria y a la necesidad de desarrollarla de forma iterativa, así como a las dificultades que podrían aparecer.

ملخص

التقدم المحرز لإنتاج لقاح جديد للملاريا

ملحوظ في علم اللقاحات، وسنستعرض التكنولوجيات التي تستخدم في إنتاج اللقاحات، وتقييم اللقاحات المرشحة للاستخدام في العالم لدى الإنسان ولدى الحيوانات. وفي الختام سنناقش قضايا تتعلق بلقاح الملاريا والحاجة إلى تطوير لقاحات متعددة، إلى جانب المضاعف التي ينبغي التغلب عليها.

الملخص: الملاريا من الأمراض الطفيلية الشديدة الأهمية في العالم، إذ تسبب ما يقرب من مليوني وسبعمئة وفاة بالعالم سنوياً. وفي هذه الورقة سنستعرض عبء الملاريا، ونصف الدورة المعقدة لحياة الطفيليات التي تسبب أكثر الوفيات بالملاريا، وهي المتصورات المنجلية، ثم نستعرض البيانات التي تثبت أن لقاح الملاريا هدف يمكن تحقيقه، فقد تم إحراز تقدم

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