Conference report

Meeting report: WHO consultation on Malaria vaccine development, Geneva, 15-16 July 2019

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ABSTRACT

Considerable progress has been made in malaria control in the last two decades, but progress has stalled in the last few years. New tools are needed to achieve public health goals in malaria control and elimination. A first generation vaccine, RTS,S/AS01, is currently being evaluated as it undergoes pilot implementation through routine health systems in parts of three African countries. The development of this vaccine took over 30 years and has been full of uncertainties. Even now, important unknowns remain as to its future role in public health. Lessons need to be learnt for second generation and future vaccines, including how to facilitate early planning of investments, streamlining of development, regulatory and policy pathways.

A number of candidate vaccines populate the current development pipeline, some of which have the potential to contribute to burden reduction if efficacy is confirmed in conditions of natural exposure, and if they are amenable to affordable supply and programmatic implementation. New, innovative technologies will be needed if future malaria vaccines are to overcome important scientific hurdles and induce durable, high level protection.

WHO convened a stakeholder consultation on the status of malaria vaccine research and development to inform the recently reconstituted Malaria Vaccine Advisory Committee (MALVAC) which will assist WHO in updating its current guidance and recommendations about priorities and product preferences for malaria vaccines.

Keywords: Malaria, vaccines, World Health Organization, Africa, Plasmodium falciparum, Plasmodium vivax

1. Introduction and objectives

In 2018, malaria caused an estimated 228 million cases and 405,000 deaths (1). Although dramatic progress has been made in malaria control and elimination since 2000, progress has stalled in the last few years. Now more than ever, new tools will be needed to achieve global control and elimination targets (2). The malaria vaccine RTS,S/AS01 received a favourable European Medicines Agency (EMA) scientific opinion (3) and, in April 2019, started pilot implementation, as called for by the World Health Organisation (WHO) (4). While the potential impact in children from this partially effective vaccine is important (5), second generation and future malaria vaccines able to provide a higher level of protection and reduce transmission are highly desirable.

The Malaria Vaccine Advisory Committee (MALVAC) was established to help WHO articulate its vision, product preferences and recommendations on malaria vaccine research and development (R&D) priorities. In 2013 and 2014, respectively, WHO issued a Malaria Vaccine Technical Roadmap (2), and expressed Preferred Product Characteristics (6). In 2019, MALVAC reconvened with the aim of updating this technical guidance and in July held a malaria vaccine stakeholder meeting with participants from academia, industry, public health agencies, funding bodies and regulatory authorities, to review the state-of-the-art in malaria vaccine development, and to inform MALVAC's subsequent considerations (Figure 1).

2. Articulating global needs and programmatic suitability

2.1. Immunisation programmes: present challenges and a life course vision of the future

The last two decades saw substantial progress in worldwide vaccine access, with 12 vaccines included in the expanded programme of immunisation (EPI), and an estimated global coverage with DTP3 of 86% in 2018 (7). However, recent years have showed stagnation in coverage rates, with 19.4 million children not receiving DTP3 in 2018. Coverage is geographically heterogeneous, with the African region having the lowest rate among the WHO regions, and almost half of the world's un- and under-vaccinated children.

To maximize global health impact of vaccination, a renewed approach is needed. Strategic drivers of vaccine development have traditionally relied on burden estimates and trial testing of efficacy and safety. Public-private partnerships were created to 'push' pre-licensure clinical research for vaccines targeting poverty-related diseases. A long-term vision for sustainable access has often been missing from early vaccine R&D efforts. To achieve greater impact, an early articulated end-to-end vision for product development and implementation is required, taking into account programmatic feasibility, barriers to access and societal value. Requirements for effectiveness evaluation, pilot introduction and financing mechanisms need to be defined early, as expressed in the Immunization Agenda 2030: A Global Strategy to Leave No One Behind (8).

2.2. Recent changes in malaria epidemiology

Major reductions in malaria morbidity and mortality occurred between 2000-2015. Building on encouraging trends, the Global Technical Strategy (GTS) for Malaria 2016-2030, adopted by the World Health Assembly in May 2015, set ambitious goals to reduce global malaria incidence and mortality rates by at least 90% by 2030 (9). Recent data, however, showed stalling in progress (1), placing the 2020 GTS milestones for reduction of malaria disease and death beyond reach. A targeted response in high burden countries was launched in 2018, to address the 3.5 million more cases recorded in the 10 most highly burdened countries in Africa in 2017 as compared to 2016 (10).

A number of countries continue their march to towards malaria elimination. In 2017, a WHO initiative started to support 21 malaria-eliminating countries in "getting to zero" by 2020 (11). The Strategic Advisory Group on Malaria Eradication (SAGme) was formed to advise WHO on the feasibility, potential strategies and cost of eradicating malaria. The SAGme concluded that, although non-specific global changes in society and the environment tend to support progress in malaria control, malaria eradication will not be possible by 2050 even with full scale-up of current interventions (12).

Insecticides for vector control and medicines for infection cure and prevention are the current pillars of malaria control strategies. Both are susceptible to biological resistance. The stagnation of progress with malaria control, the development and spread of biological resistance to key malaria control tools and the forecasted difficulty in eradicating malaria from the globe with the available tools, all point to the urgent need for new tools, including vaccines with efficacy against *Plasmodium (P.) falciparum*, *P. vivax* and potentially other malaria species.

3. Potential use of vaccines and key product attributes

3.1. Articulation of use cases in various epidemiologic settings

The epidemiological heterogeneity of malaria draws attention to the need for specific vaccine attributes. A vaccine intended to reduce malaria hospitalisation, severe disease and death in stable transmission settings will need to be effective in young children – especially children <3 years of age (13). Highly efficacious vaccines providing persistent protection are preferable, but vaccines with moderate efficacy and limited duration of protection may have significant impact if they can be practically delivered at an affordable cost to protect young children at high risk of severe malaria and death.

Malaria transmission is highly dependent on climate and subject to varying degrees of seasonality (Figure 2). Of the most highly burdened countries in Africa, 80% are at least partly in intensely seasonal transmission settings (13–15). In such settings, a vaccine that can be affordably delivered on a seasonal basis may be useful, even if protection is of limited duration.

Specific population groups need to be considered for vaccine strategies. A substantial number of people are at risk of infection in Asia (1.69 billion Asians compared to 0.80 billion in Africa) (16). South America accounts for 0.3% of global malaria (~776 000 cases). Mobile and migrant populations represent hundreds of millions of people, providing an important reservoir of infection (17). Sub-patent asymptomatic infections contribute to transmission (18), and frequently escape conventional control methods (19). Both Asia and South America have a predominance of *P. vivax*. In settings

where both *P. falciparum* and *P. vivax* are prevalent, vaccines able to target both species are highly desirable. In elimination and low-endemicity settings, where the infection risk is spread across the population age spectrum, vaccines preventing infection over a long duration will be key for impact.

3.2. Pregnancy

Malaria in pregnancy (MIP) exerts profound negative consequences on the health of the mother and foetus and can increase the risk of malaria during infancy. Available preventative measures include insecticide-treated mosquito nets and the use of intermittent preventive treatment in pregnancy with sulphadoxine-pyrimethamine (IPTp-SP). However, coverage of both interventions remains patchy (1), neither is highly effective, and both are susceptible to biological resistance (20).

MIP is associated with sequestration of *P. falciparum* infected erythrocytes in the placenta through binding to the glycosaminoglycan, chondroitin sulfate A (CSA), via the highly polymorphic protein VAR2CSA. Exposure in areas of relatively intense malaria transmission induces some anti-VAR2CSA immunity after one or two pregnancies, conferring partial protection against subsequent MIP. There are two VAR2CSA antigen-based candidate vaccines currently in phase 1 trials. PrimVac (21) is derived from VAR2CSA of parasite line 3D7, and PAMVAC (22) from the genetically distinct parasite line FCR3. In addition, any vaccine able to prevent *P. falciparum* infection that can be delivered safely to women of childbearing age or early in pregnancy, should have the potential to reduce the burden of MIP.

3.3. Modelling potential impact

The phase 3 trial of the RTS,S/AS01 malaria vaccine showed partial efficacy against a variety of *P. falciparum* malaria syndromes (Table 1) (23–25), but was not designed to assess mortality. The WHO recommended pilot implementation studies, now underway in three African countries, include the assessment of impact on mortality (see below).

Impact projections and cost-effectiveness estimates for long timeframes were conducted to support WHO and GAVI decisions and investment planning (26). Four mathematical models provided health-economic impact estimates, using assumptions informed by phase 3 trial data (27). In children aged 2-10 years in regions with a parasite prevalence of 10-65%, RTS,S/AS01 was 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. The four models provided consistent estimates. It was concluded that the RTS,S/AS01 vaccine would generate significant public health impact and be highly cost-effective across a wide range of settings.

Modelling can inform preferred product characteristics for future vaccines, such as efficacy, duration of protection, timing of immunisation and target population (25), and can support decision making, informed by country estimates of health and/or budget impact (28).

4. Recent progress in malaria vaccine R&D

4.1. Controlled human malaria infection (CHMI) models

Sporozoite challenge

Experimental challenge trials can inform vaccine formulation, dose, route, schedule and development programmes, thereby de-risking investments through early indication of efficacy (29–31).

The most established controlled human malaria infection (CHMI) model involves bites of *Plasmodium*-infected insectary-raised mosquitoes to study participants (32). The exact *P. falciparum* sporozoite dosage is variable, but likely exceeds that delivered by infectious bites in the field. More recently, CHMI has included direct venous injection (DVI) of *P. falciparum* sporozoites (33). DVI has the potential for improved standardisation and more precise dosing of the infectious load but bypasses the skin which is a potentially important anatomic compartment of immunity. Intradermal (34) and intramuscular (35) injection of *P. falciparum* sporozoites can lead to infection but is

complicated by heterogeneity in the number of sporozoites required, infection rates and time to patent infection.

Assessment of infection in CHMI studies is most commonly by polymerase chain reaction detection of *Plasmodium* 18S rRNA/rDNA, an approach approved by FDA in 2018 as a replacement for blood smears in trials of anti-malarial drugs and vaccines in non-endemic sites (36).

CHMI with *P. vivax* sporozoites through bites of infected *Anopheles (An.) albimanus* (37,38) and *An. dirus* (39) have additional complexities, including the lack of complete *in vitro* culture systems for *P. vivax*, requirement for fresh gametocytes from naturally infected donors and use of different *P. vivax* isolates for each study compromising comparison of results (40). *P. vivax* vaccine development is also complicated by the fact that sporozoites can induce dormant liver-stage hypnozoites, able to cause long-term repeated blood-stage infections, despite therapy (39).

Blood-stage malaria vaccine development

The blood-stage CHMI does not require entomology facilities, is applicable for blood- or sexual- (but not pre-erythrocytic-) stage candidates, and is more specific than sporozoite challenge to assess parasite multiplication rate for proof-of-concept (41,42). There is no risk of relapse following blood-stage *P. vivax* CHMI.

Blood-stage CHMI has been used for phase 2 evaluation of *P. falciparum* candidates (42–44). To date, two *P. vivax* blood-stage CHMI studies are published (40,45,46). In absence of a long-term *in vitro P. vivax* culture system, cryopreserved blood from returning travellers is used (45,46).

Sexual stage candidate vaccine development

Adapted CHMI models for evaluation of sexual stage candidates are in development, with the aim of inducing gametocytaemia and evaluating the transmissibility of gametocytes to mosquitoes.

Initial *P. falciparum* (47,48) and *P. vivax* (49) transmission models have demonstrated that gametocytes can be safely and reproducibly induced and transmitted by feeding to *An. stephensi* mosquitoes, inducing infections in 60-75% of mosquitoes.

These models could form a bridge between standard membrane feeding assays and field studies, reducing failure in the field and increasing the efficiency of sexual stage vaccine development.

4.2. Trial design in conditions of natural exposure

While CHMI studies can inform decision making in malaria vaccine development, candidates need evaluation in the target population subjected to natural exposure with diverse parasite populations. Trial design should be informed by data package requirements for regulatory and policy decision making.

Age is a crucial consideration. To impact severe malaria outcomes in stable transmission settings, vaccination is required in the first few months of life, with other EPI vaccines. Protection should last, with or without boosting, until at least three years of age (13). In settings with very low or unstable transmission, all age groups are at risk of severe disease.

Transmission intensity also influences the clinical manifestations (e.g. anaemia, cerebral malaria, respiratory distress, renal failure) and should be considered in the selection of trial endpoints. Results from the RTS,S/AS01 phase 3 trial (5) highlighted the value of malaria vaccine trials considering a range of transmission intensities, in seasonal and non-seasonal settings.

Trials should assess the superiority or non-inferiority of a candidate compared with standard prevention approaches. In the absence of an established standard comparator, a placebo control could be justified (50). The minimum follow-up for initial licensure may be shorter than that needed for assessment of the long-term effects of the vaccine, need for booster dose(s) or the possibility of a rebound effect. A malaria 'rebound' may result from a preventive intervention impairing the

development or maintenance of naturally acquired immunity, causing a subsequent period of increased risk of infection/disease compared with individuals not receiving the intervention.

Different analytical approaches should be considered depending on the stage of vaccine development and target group (Figure 3). Assessment of time-to-first event can be appropriate for proof-of-concept demonstration, but has limited value later in development, especially for common endpoints for which multiple episode analyses are more appropriate. For rare – including severe - events, vaccine efficacy can be measured as the reduction in the proportion of affected subjects at the end of follow-up. Prevention of any infection may be an indicator of a vaccine's potential to reduce transmission.

Transmission reduction is, however, difficult to evaluate. A vaccine could reduce transmission through (i) direct effects in individuals who are protected from infection and/or rendered unable to transmit to mosquitoes, and (ii) indirect effects resulting from herd immunity, whereby unvaccinated individuals are less likely to get infected due to reduced prevalence of infection among vaccine recipients. Metrics relevant to the mechanism of action are needed. Early potential for transmission reduction may be indicated by a reduction in the proportion of infected individuals for pre-erythrocytic vaccines, prevention of gametocytaemia for blood-stage vaccines and a reduction in mosquito infection for sexual-stage vaccines. Large-scale, ideally cluster-randomised, studies could provide insight into a vaccine's impact on transmission. In this context, molecular tools can be used to monitor genetic diversity and assess gametocytaemia in a population (51,52). Serology can contribute to document exposure (53).

5. Clinical development landscape analysis

Understanding vaccine elicited protective immunity

The National Institute of Allergy and Infectious Diseases (NIAID) organised a workshop in 2019 to review vaccine-elicited protective immunity to malaria, with experts in malaria and immunology, data science, bio-informatics and computational modelling.

Since 2010, approximately 100 malaria vaccine trials had been conducted, of which >90% targeted *P. falciparum*. Many variables were associated with vaccine efficacy and protective immunity, including host (e.g. genetic, age, gender, coinfection), parasite and mosquito factors (e.g. strain multiplicity, transmission intensity), target antigens, platforms (e.g. recombinant proteins, whole organisms, viral-vectored), regimen (e.g. prime/boost, delayed or fractional doses), and experimental conditions.

CHMI studies provide a good opportunity to study immune determinants of protection. Responses can be heterogeneous, providing opportunities for detailed evaluation of, for instance, determinants of time-to-infection. Investigations of mechanisms of protection can be conducted when people develop naturally acquired immunity in field conditions; their immune systems differ compared to malaria-naive individuals with profound immune disruptions induced by frequent exposure to malaria (54,55).

Numerous correlates of protection studies have identified various antibody, cell-mediated immunity and functional correlates. However, these appear to differ according to vaccine type (56–60). A systematic, systems vaccinology approach could take advantage of innovations in open data science. Technology is now available to collate multi-dimensional data and identify complex molecular risk signatures to inform mechanisms of protection. Novel bio-informatics tools use publicly available data to identify molecular signatures prior to vaccination and predict influenza vaccination outcomes (61). Computational models could replace animal models, bench models and clinical trials to support regulatory evaluation, as for small molecule research (62).

RTS,S/AS01 pre-erythrocytic vaccine

GlaxoSmithKline's (GSK's) RTS,S/AS01 vaccine received a positive scientific opinion from the EMA in July 2015 (3). WHO's Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) subsequently recommended pilot implementation in sub-Saharan Africa, covering moderate-to-high malaria transmission settings (4), in order to inform policy on the wider use of RTS,S/AS01. Vaccine implementation was only recommended for children aged 5–17 months as vaccine efficacy was lower in children aged 6–12 weeks at the time of dose 1 in the phase 3 trial (23,24). Subsequently, long-term (7-year) follow-up of the phase 3 trial confirmed a consistent benefit/risk balance for RTS,S/AS01 (63).

The WHO-coordinated Malaria Vaccine Implementation Programme (MVIP) involves evaluation of phased introduction of RTS,S/AS01 through EPI; vaccinations started in April 2019 in Malawi and Ghana, and September 2019 in Kenya (64,65).

Additionally, ongoing phase 4 studies comprise GSK's EMA-approved risk management plan (RMP) and post-authorisation evaluation programme (66). RTS,S/AS01 administered as a fractional dose has also shown the potential for improved efficacy (67,68) and is being trialled in children in endemic settings (NCT03276962). A further comparative field trial (NCT03143218) is ongoing of seasonal vaccination with RTS,S/AS01 combined with seasonal malaria chemoprevention.

PfSPZ pre-erythrocytic radiation attenuated vaccine

Sanaria's platform technology is aseptic, purified, vialed, cryopreserved *P. falciparum* sporozoites (PfSPZ). Several products are either available (fully infectious sporozoites for intravenous CHMI) or in development (radiation- and genetically-attenuated sporozoites for immunisation) (34). PfSPZ is produced through mosquito salivary gland dissection. The vaccine's mechanism of action is thought to be primarily through cell mediated responses, though the key target parasite proteins are currently unknown. Sporozoites express over 5,000 proteins, representing a large number of potential immune system targets.

CHMI investigations showed that three doses of $9x10^5$ PfSPZ administered through DVI can induce high (>90%) protection against CHMI after three weeks, using a strain homologous to that used for immunisation. However, efficacy was reduced for a heterologous strain, on delayed challenge, and in field conditions (56,57,60,69,70). Impact modelling and health-economic data need to further inform the potential role of this platform which incurs particular programmatic feasibility challenges (71). Whether the available results justify progression to advanced clinical development, including phase 3 plans in Equatorial Guinea with a Bioko island malaria elimination objective, is controversial. Other potential applications of this approach include prevention of malaria in travellers and the military.

R21 anti-sporozoite subunit vaccine

The R21 anti-sporozoite subunit candidate vaccine, developed at Oxford University, aims to produce an RTS,S-like vaccine targeting the same circumsporozoite protein antigen (CS), but with enhanced efficacy related to different immunogenic properties (72). The R21 particle is formed from a single CS-hepatitis B surface antigen (HBsAg) fusion protein, hence 100% of the molecules in each particle include the CS antigen, compared with 20% in RTS,S/AS01 which also includes free HBsAg. This difference could mean that R21 exposes more CS protein (CSP) epitopes to the immune system than RTS,S/AS01.

The matrix-M adjuvant was selected over AS01 due to ease of access and demonstrated potent immunogenicity (73). Unpublished phase 1 trials showed that a low dose formulation (10µg R21/Matrix-M) had similar immunogenicity to 50µg of RTS,S/AS01, and favourable safety. A 3-dose schedule of 10µg R21/Matrix-M induced 82% sterile protection against CHMI after 3 weeks (NCT02572388, NCT02925403, unpublished). Phase 1b and 2b studies are ongoing in African adults and children (NCT03896724, NCT03947190). The Serum Institute India has been identified as a manufacturing partner.

Blood-stage vaccines

Blood-stage vaccines target either the infected red blood cell (RBC) or the merozoite. The fast blood-stage merozoite multiplication rate is associated with a high degree of antigen polymorphism, protein functional redundancy and intracellular immune escape - important impediments to blood-stage malaria vaccine development. The recent identification of relatively conserved antigens with unique functional properties opens new prospects.

P. falciparum reticulocyte-binding protein homologue 5 (RH5) is currently the only protein demonstrated to bind basigin on the RBC surface, forming the basis for an interaction essential for invasion (74). The *P. falciparum* RH5 blood-stage candidate has exhibited significant *in vivo* protection against a stringent heterologous blood-stage challenge in Aotus monkeys (75) and shown promising results in the CHMI model (unpublished). In the first phase 1 trial of a viral vectored full-length RH5 candidate vaccine, substantial functional RH5-specific antibody responses were induced, exceeding those observed in African adults following years of natural malaria exposure (76). The full-length RH5 adjuvanted with AS01 is currently in phase 1/2a development (unpublished). Other promising antigens are in the discovery and pre-clinical stage.

SE36 (formerly BK-SE36) is a single recombinant protein blood-stage vaccine candidate construct targeting *P. falciparum* serine repeat antigen 5 (SERA5) (77). The SERA5 blood-stage antigen is highly expressed at the late trophozoite and schizont stages. In a phase 1a trial, all malaria-naïve healthy Japanese adults seroconverted after SE36 immunisation (78). Subsequent assessment in an endemic population in Uganda showed that pre-existing naturally acquired anti-SE36 antibodies influenced seroconversion, with higher vaccine immunogenicity seen in the youngest cohort (aged 6-10 years) (79). In a follow-up study, an association between vaccine-induced anti-SE36 antibody titres and protection was reported (80). Options for next steps in clinical development are being considered.

Sexual stage vaccines

Sexual stage candidate vaccines (sometime called transmission blocking vaccines (TBV)) aim to induce antibodies that prevent progression of the parasite life-cycle in the mosquito, and hence

transmission to another host (81). The lead antigen candidate targets are Pfs230 and Pfs48/45 (pre-fertilisation) and P25 and P28 (post-fertilisation). In the first TBV field trial in a malaria-exposed target population, Pfs25H-EPA, a protein-protein conjugate vaccine adjuvanted with Alhydrogel®, induced functional antibodies that reduced parasite transmission to *An. stephensi* mosquitoes in a laboratory assay. However, four doses were required to achieve activity, and titres decreased rapidly (82). There are early indications suggesting that Pfs230 has superior transmission-reducing activity compared to Pfs25 (83). A phase 2 age de-escalation trial of Pfs230-EPA/AS01 in Mali in 5-18 year olds is ongoing (84).

Monoclonal antibodies for malaria control and elimination

Monoclonal antibodies (mAbs) can be used as tools to assist a molecular-level characterisation of the human antibody response to vaccines and parasite infection, identify the most potent epitopes, and thereby have the potential to improve vaccine design. If a potent mAb is identified together with its binding target, the epitope could be isolated onto the surface of a vaccine construct and used to induce an antibody response in humans. mAbs also have the potential to establish themselves as preventive interventions. Key considerations for deploying mAbs as interventions include safety, extension of half-life to achieve durable protection, manufacturing capacity, formulation, cost of goods, route of administration, and programmatic suitability.

Functional potency is a key parameter for all applications of mAbs. Currently, mAbs are available to prevent severe RSV in some susceptible neonates, and the focus of considerable R&D activities for other infectious diseases including HIV, influenza, HPV and HBV; potent human mAbs have been developed for HIV (85). In the case of CSP, variations in the central repeat sequence hinder their structural and functional characterisation (86). Efforts to develop mAbs targeting sexual stage antigens are also underway (87).

mAbs could help explore how standard membrane feeding assays (SMFA), direct membrane feeding assays (DMFA) and direct skin feeding compare in the same gametocyte carrier passively immunized

with quantified doses of mAbs. This could provide a bridge between laboratory and field functional assays.

P. vivax vaccines

Although rates of *P. vivax* malaria have declined in the past five years for many countries, this trend has stalled, with the global burden recorded as 14.3 million cases in 2016 (88,89). Standard control measures are less effective against *P. vivax* due to the unique aspects of the parasite's biology, especially the hypnozoite stage in the liver (90). Modelling the effect of a vaccine on *P. vivax* transmission and elimination (91) indicates a pre-erythrocytic vaccine, which would prevent dormancy, would have potential (92). Blood-stage vaccines and TBVs could lower transmission (93). A multi-stage vaccine, targeting the liver-stage, blood-stage and sexual stages, administered through repeated mass vaccination campaigns, could potentially achieve elimination.

A few candidate *P. vivax* vaccines have been in clinical trials. VMP001/AS01, a subunit vaccine targeting CSP, was immunogenic in healthy volunteers, but failed to induce sterile protection in CHMI (39). A radiation-attenuated sporozoite candidate suggested protection is only achieved at very high doses (38). Initial published data for a blood-stage vaccine – *P. vivax* duffy-binding protein (PvDBP) - indicate promising immunogenicity in phase 1 (94). The sole current sexual-stage candidate - Pvs25H/Alhydrogel protein vaccine - elicited antibodies that showed activity in DMFA. A second trial with Montanide ISA51 adjuvant showed unexpected reactogenicity leading to interruption of the programme (95). Blood-stage CHMI provides a promising approach for testing blood-stage *P. vivax* candidate vaccines.

6. Malaria vaccine development coordination and funding

Significant advances have been made in understanding the biology of malaria in the last decades, leading to major progress and a first-generation malaria vaccine. However, the transformational strategies and products required to accelerate progress towards eradication remain elusive. Most

progress has been accomplished through public-private partnership and multi-institutional collaborations. Malaria vaccine development currently focuses on strengthening the candidate vaccine pipeline, with grants supporting research into novel delivery systems, adjuvants and antigens to improve efficacy and durability, and monoclonal antibodies. Building stringent stage-gates early in development could potentially focus resources on the most promising candidates.

The public-private partnership scene is changing, with the Bill and Melinda Gates Foundation focusing on the Gates Medical Research Institute as its operational partner, dedicated to upstream, translational research. Funders of malaria vaccine R&D predominantly support discovery and early-stage research, resulting in insufficient financial support for late-stage, post-proof-of-concept research and introduction. Early identification of the value-drivers for upcoming vaccines should help prioritise strategic investments. A new initiative from the European Union aims to make infectious tropical diseases investible, including malaria (96), through private capital, risk-sharing with public investment, provision of loans to product developers - repaid in case of business success, or otherwise converted into a grant.

7. Industry involvement in malaria development: GSK perspectives

GSK conducted an after-action review of the regulatory submission and post-approval process for RTS,S/AS01. Through the Article 58 procedure, the RTS,S/AS01 submission dossier was reviewed by several bodies at the EMA. Multiple high-level advisory committees at WHO (JTEG, SAGE, MPAC) played an important role in the regulatory and policy decision process. Coordination and alignment of the processes was inadequate with different requirements for post-approval studies expressed by different committees, requiring revision of the legally-binding RMP agreed between EMA and GSK to accommodate the additional expectations from WHO. Some of the most significant difficulties may have been prevented if WHO had been included as a co-rapporteur when EMA assigned rapporteur and co-rapporteur roles for files review.

At the start of the pilot implementation, important uncertainties remained about future vaccine demand and the manufacturing capacity that would be needed. Difficulty in identifying co-funding from external sources led to a company decision to focus its malaria vaccine programme entirely on late-stage activities for RTS,S/AS01 with no further investment in other malaria vaccine projects.

RTS,S/AS01 has demonstrated the feasibility of developing a malaria vaccine, from which a second generation vaccine will likely benefit by shortened development times and reduced resource requirements. Nonetheless, innovative financial mechanisms will be required to guarantee success, in terms of implementation and impact, given the often under estimated costs of development, manufacturing and implementation.

8. Integrated end-to-end vision of malaria vaccine development: opportunities and challenges

In order to identify strategies to advance future malaria vaccines and expedite availability, the risks and benefits of a particular approach need to be evaluated from beginning to end, i.e. an end-to-end vision of vaccine development. This needs to consider the true value-drivers, prospects for access and programmatic feasibility, as expressed in the Immunization Agenda 2030: A Global Strategy to Leave No One Behind (8). The recent concept of a 'Full Public Value Proposition' evaluation to inform strategic investment aims to evaluate the comprehensive value of vaccines and balance the costs, including research and manufacturing, product pricing, and delivery considerations, with the full public health, economic and extended societal benefits. A more mature financial model can then be developed, with co-funding, risk-sharing and shared accountability.

Lessons can be learned from the technical, regulatory, policy and investment planning hurdles that have been identified. Support is needed for incremental step improvements to reduce burden, and disruptive approaches to achieve ambitious long-term public health goals (9). Overall, an inclusive approach is crucial, encouraging diversity and equity, and the engagement of younger scientists from affected countries.

9. Conclusions

Malaria continues to be a major public health problem. Progress with current interventions alone has stalled in recent years. New interventions are needed to reignite the fight against malaria.

The first generation malaria vaccine, RTS,S/AS01, is undergoing pilot implementation in three African countries with moderate-to-high malaria transmission intensity, demonstrating the possibility of a malaria vaccine. Its use in programmatic contexts will inform the potential value of malaria vaccines in combination with other tools.

Second generation malaria vaccines need to confer higher levels of protection, over a longer term. Advances in the understanding of host-parasite interactions and immune control should inform new strategies, targeting different parasite stages. Candidates under evaluation include the RTS,S-like vaccine candidate R21, whole organism-based approaches, the blood-stage RH5 and other single protein candidates including some targeting the sexual stage. New tools including mAbs are entering the field of malaria, guided by progress in molecular-level structural biology research. CHMI models provide opportunities for early testing of proof-of-concept of vaccines targeting all parasite stages.

Sustained investments in R&D are needed, guided by an end-to-end vision of the value of research, product development and potential health and societal impact. Costs and programmatic feasibility should be considered early. In line with ethical clinical research principles, late-stage research should reflect solid scientific justification, and a genuine intent and clear line of sight for access to the vaccine by the communities where research is undertaken.

The newly reconstituted WHO MALVAC argues that to maintain momentum towards malaria eradication, a malaria vaccine is a key addition to the malaria intervention toolkit. Two approaches are recommended: (1) promote the short to medium term deployment of first-generation vaccine candidates aimed at reducing malaria burden, and (2) support innovation and discovery to identify

and develop highly effective, long-lasting and affordable second generation and future malaria vaccines.

Meeting attendees

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Conflict of interest statements

The authors report no conflict of interest.

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Figure 1. Objectives of the malaria vaccine consultation

- Provide a landscape status of malaria vaccine R&D
- Discuss potential malaria vaccine use cases, considering recent changes and the heterogeneity of malaria epidemiology
- Consider key product profile attributes and programmatic suitability
- Discuss early and late development data packages for decision making
- Highlight challenges and opportunities in malaria vaccine evaluation pathways
- Provide a basis for subsequent MALVAC discussions and the development of updated WHO technical guidance.

Figure 2. Malaria seasonality in Africa. Markham seasonality index, depicted by the largest administrative areas within each country (14), is a ratio of monthly to annual rainfall and reflects the seasonality of malaria transmission.

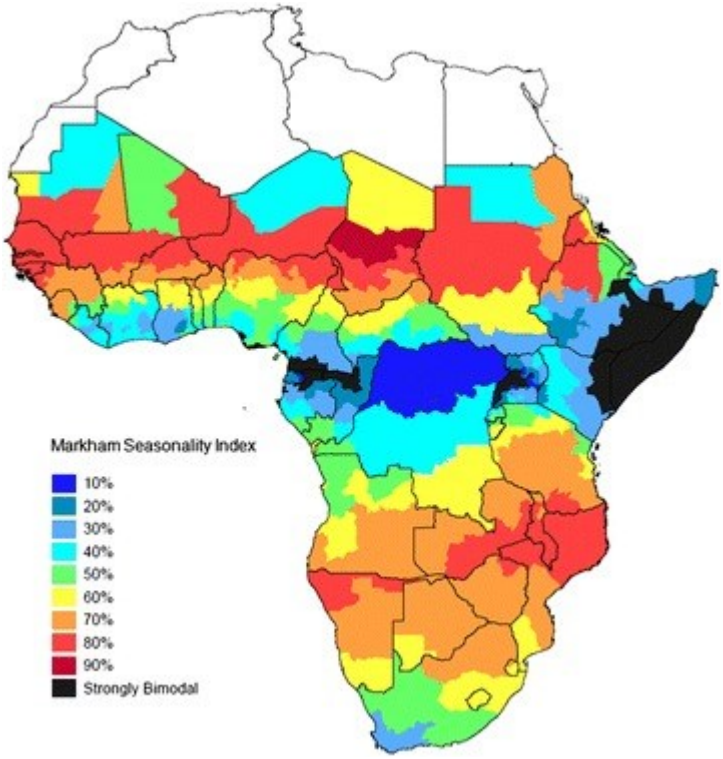

Figure 3. Potential pivotal endpoints (and approximate sample sizes) for malaria vaccine studies in conditions of natural malaria exposure

- **Infection** *(10s-100s of participants)*
  - Mainly useful for "proof-of-concept"
  - Requires periodic screening for infection, may be challenging (e.g. in healthy young children)
  - Unlikely to be acceptable for policy and public health deployment
  - Proportion of subjects free of infection may indicate potential to reduce transmission and contribute to elimination
- **Active surveillance for clinical malaria** *(100s-1000s of participants)*
  - Possible value in low intensity transmission settings
  - Difficult to interpret in higher transmission settings
  - May be acceptable for licensure, but of limited value for assessing public health use
- **Passive surveillance for clinical malaria** *(100s-1000s of participants)*
  - Preferred primary endpoint, likely to support licensure
  - Requires functional infrastructure for malaria diagnosis and treatment at health facilities
  - Provides incomplete assessment of public health impact, especially if moderate level of efficacy
- **Severe malaria** *(1000s-10,000s of participants)*
  - Not common, requires large sample size
  - Important to determine public health value
  - Evaluation post initial licensure potentially acceptable
- **(Death)** *(100,000s of participants)*
  - Important endpoint for estimating public health value and to support decisions on widespread use
  - Post-licensure assessment only`

Table 1. Phase 3 trial of the RTS,S/AS01 malaria vaccine: vaccine efficacy from month 0 to study end. Study end was median 48 months after first dose for 5-17 months age category and 39 months after first dose for the 6-12 weeks age category

	Infants 6-12 weeks at enrolment	Children 5-17 month at enrolment
	Vaccine efficacy % (95% CI); p-value vs comparator control group	
Clinical malaria*	25.9 (19.9, 31.5); p<0.001	36.3 (31.8, 40.5); p<0.0001
Severe malaria**	17.3 (-9.4, 37.5); p=0.16	32.2 (13.7, 46.9); p=0.0009
	Cases averted per 1000 participants (95% CI)	
Malaria hospitalisation***	18 (-8, 42)	40 (19, 64)
Blood transfusion	4 (-12, 23)	15 (1, 31)

* Clinical malaria primary case definition: illness in a child brought to a study facility with a measured temperature of ≥37.5°C and *P. falciparum* asexual parasitemia at a density of >5,000 parasites/mm^3 or a case of malaria meeting the primary case definition of severe malaria

** Severe malaria primary case definition: *P. falciparum* asexual parasitemia at a density of >5,000 parasites/mm^3 with one or more markers of disease severity (prostration, respiratory distress, a Blantyre coma score of ≤2 [on a scale of 0 to 5, with higher scores indicating a higher level of consciousness], two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of <5 g/dl) and without diagnosis of a coexisting illness (radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration)

*** Malaria hospitalisation case definition: a medical hospitalisation with confirmed *P. falciparum* asexual parasitaemia at a density of >5,000 parasites/mm^3.

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