unacceptable. A subsequent meeting among MCP and Jhpiego staff was held to review nine health systems areas to determine reasons for the low performance on malaria indicators. The group reviewed strategies and annual workplans and then ranked each health system area on a scale from 1 (low) to 4 (high) to reflect level of progress, and then the average score computed.. The highest scoring components were human resource capacity (3) and integration and coordination (3), based on findings such as integrated supportive supervision and the holding of monthly coordination and review meetings among partners at the state and local level. Community Involvement (1.9) and finance (1.8) scored lowest, based on lack of community outreach and engagement, in control efforts, and late/ sporadic release of funds for program implementation, respectively. In response, the group drew up action plans to address identified weaknesses and used monthly partners meetings for advocacy and learning. In conclusion Nigerian health workers can use health systems analysis and planning tools to identify best practices, address challenges, and create an action plan to help advance their state (and country) along the pathway to malaria elimination.

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REGULATORY T CELL-MEDIATED SUPPRESSION OF HUMAN IMMUNE RESPONSES TO INVESTIGATIONAL MALARIA VACCINES

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Natural malaria and helminth infections induce upregulation of Regulatory T cell (Treg) responses in humans. Increased Treg frequencies may play a role in causing the immunosuppression known to be associated with malaria infection and may contribute to the reduced immunogenicity observed for some experimental malaria vaccines when trialled in malaria-endemic sites in Africa. Increased total CD4+ CD25+ FoxP3+ CD127lo Treg frequencies at baseline, as measured by flow cytometry, negatively correlate with peak antigen-specific CD4+ T cell and antibody titres in the investigational vaccine regime ChAd63 ME-TRAP / MVA ME-TRAP, but only with antigen-specific CD4+ T cell responses to RTS,S in malaria-naïve European volunteers. Both vaccine regimes themselves induced antigen-specific Treg responses, however these do not correlate with decreased antibody or effector CD4+ T cell titres. Instead, high baseline Treg frequencies appeared to be suppressive of antigen-specific Treg induction as well, demonstrating that pre-existing Tregs might be most important in suppression of vaccine-induced immunity. Therefore, in a setting where populations have naturally higher circulating Treg frequencies due to parasite infections, responses to vaccines could be suppressed. Immunogenicity and Treg frequency data from a Kenyan cohort vaccinated with ChAd63 ME-TRAP / MVA ME-TRAP will be presented. Functional data from Treg suppression assays will also be presented to understand the mechanistic basis of the heterologous effects of Tregs on different experimental malaria vaccines.

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SAFETY AND IMMUNOGENICITY OF THE MALARIA VACCINE CANDIDATE R21 ADJUVANTED WITH MATRIX-M1 IN WEST AFRICAN ADULT VOLUNTEERS, BURKINA FASO

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A highly effective malaria vaccine would help reduce disease burden in malaria endemic countries. We have assessed the safety and immunogenicity of the malaria vaccine candidate R21, a virus-like particle comprising a fusion protein of part of the *P. falciparum* circumsporozoite protein with the hepatitis B surface antigen.A phase Ib randomised, controlled, single-blind study was conducted. Volunteers were randomly assigned in a 2:1 ratio to receive 3 doses of the malaria vaccine or the control (normal saline) intramuscularly 1 month apart. Participants were actively followed up at home daily during the 7 days following each vaccination to collect local and systemic solicited adverse events. Serious adverse events were recorded throughout the study duration. Venous blood samples were obtained for clinical safety and immunological evaluations. The study duration was 140 days for each participant.A total of 8 and 5 participants have received respectively 10µg of the malaria vaccine or a saline control immunisation. The most reported local solicited symptoms post vaccination were mild to moderate pain (25%, 2/8) and swelling (12.5%; 1/8) at injection site following each vaccination; all reported in the R21 vaccine group. Solicited systemic symptoms include moderate joint pain and headache. Neither severe adverse event nor serious adverse event was recorded. There was significant increase of anti-NANP IgG following vaccination in the R21 group compared to the controls.This was the first administration of R21 malaria vaccine candidate in Africa. The vaccine was immunogenic in semi immune adults with a good safety profile. These data are supportive for further development of the R21 malaria vaccine candidate.

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PROTEOMIC CHARACTERIZATION OF ERYTHROCYTE DERIVED MICROVESICLES FROM MALARIA INFECTED CHILDREN

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Red blood cells infected with *Plasmodium* parasites produce microvesicles containing parasite derived proteins and mRNA. Previous studies have shown that the production of red blood cell-derived microvesicles (RMVs) is increased during malaria infection, with a correlation between elevated RMV concentration and increased severity of disease. These microvesicles have been shown to have numerous effects, including induction of transmission, upregulation of inflammation and inter-parasite communication. Purified RMVs from infected individuals have previously been seen to elicit an acquired immune response and diminish lethality from *Plasmodium* infections in mice. The goal of this study is to explore the role of RMVs from infected erythrocytes in the development of humoral immune response to malaria. We hypothesize that RMVs play a role in displaying *Plasmodium* proteins to the host immune system, leading to the production of protective antibodies. To achieve this, RMVs from malaria-infected children's plasma were isolated and analyzed using electron microscopy and proteomic approaches. Proteomic analysis indicates that several *Plasmodium* proteins are enriched in the microvesicles. Conserved proteins indicated to be consistently present in RMVs will be recombinantly expressed for characterization and use in immunosurveillance studies. The presence of naturally acquired antibodies against putative *Plasmodium* antigens in RMVs is to be cross-referenced with reduction in parasite burden and protection against disease. Results from this immunosurveillance will indicate the viability of using antigens found to be enriched in RMVs as malaria vaccine targets.

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LYMPH NODE TARGETING NANOPARTICLE BASED PLATFORM FOR MALARIA VACCINE DELIVERY

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Transmission-blocking vaccines that disrupt malaria transmission between the human and the mosquito host are considered one of the key interventions in the global effort to eradicate malaria. A highly conserved *Anopheles* mosquito midgut surface glycoprotein, Alanyl aminopeptidase N (AnAPN1), is a promising malaria transmission-blocking vaccine candidate. The AnAPN1 antibodies have been shown to completely block the development of naturally circulating isolates of *Plasmodium falciparum* and *P. vivax*. The AnAPN1-based vaccine is safe and highly immunogenic, but lacks natural boosting because the target antigen is not naturally presented to the human immune system. To circumvent this problem and improve vaccine efficacy, we have developed a polymeric biodegradable nanoparticle-based vaccine delivery platform. These biodegradable nanoparticles target the draining lymph nodes to allow effective presentation of the antigen, AnAPN1, to generate a robust priming immune response. A high-energy, multi-inlet vortex mixer based flash nanoprecipitation method was developed to generate a series of tightly size regulated virus-like biodegradable nanoparticles loaded with near infrared and Alexa488 dyes. Several biodegradable nanoparticles with different hydrodynamic diameters (30, 50, 70, and >100 nm) were tested for safety, inflammation, and mistargeting in mice. *In vivo* mice imaging studies suggest that biodegradable nanoparticle size is a key determinant of trafficking and retention in the draining lymph nodes. Our studies show that the smaller biodegradable nanoparticles (30 and 50 nm) drained more efficiently than their larger counterparts (70 and >100 nm). The co-localization of smaller biodegradable nanoparticles with macrophages and dendritic cells suggest cellular uptake by lymph node resident antigen presenting cells. We will leverage the lymph node targeting biodegradable nanoparticles (30 nm) as part of a bimodal, nano-/microparticle vaccine delivery system to induce a long-lasting AnAPN1-specific immune response in vaccinated individuals.

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A NOVEL VIRUS-LIKE PARTICLE-BASED PLATFORM FOR MULTI-ANTIGEN MALARIA VACCINES

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Malaria remains a global health priority despite numerous interventions and is worsened by the emergence and spread of drug resistant *P. falciparum*. Currently, the most advanced vaccine, known as RTS,S, has only shown modest efficacy in clinical trials and new more efficacious vaccines are needed. The RTS,S vaccine is based on the presentation of a fragment of the sporozoite antigen CSP on the surface of virus-like particles (VLPs) based on human hepatitis B virus (HBV). However, a limitation of the HBV platform is that only small antigens or antigen fragments can be incorporated into VLPs, and not larger proteins that are typical of malaria vaccine candidates. We have developed and evaluated a novel VLP platform based on duck HBV (known as Metavax) for malaria vaccine development. This platform can incorporate large and complex proteins into VLPs and is produced in a *Hansenula* cell line compatible with cGMP vaccine production. We have established the expression of several leading *P. falciparum* malaria vaccine candidates as chimeric VLPs. This includes Pfs25 and Pfs230, which are candidate transmission-blocking vaccine antigens, the sporozoite antigen CSP, and a candidate vaccine antigens expressed during blood-stage infection. VLP formation and display of vaccine antigens was confirmed using super resolution microscopy with antigen-specific antibodies, and electron microscopy. Correct folding and antigen presentation was evaluated by western blotting and ELISA using defined antibodies. Initial studies demonstrated that the VLPs effectively induce antibodies to malaria vaccine candidates with minimal induction of antibodies to the duck HBV scaffold antigen, and that VLPs are more immunogenic than standard recombinant antigen. These results establish the utility of this VLP platform for malaria vaccines. The expression of multiple vaccine antigens in a single platform will facilitate the development of multi-stage multi-component vaccines to achieve high vaccine efficacy and transmission-blocking immunity.

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TRUNCATION OF PFRIPR REVEALS REGION THAT INDUCES ANTIBODY WITH THE MOST POTENT GROWTH INHIBITORY ACTIVITY AGAINST *PLASMODIUM FALCIPARUM*

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Blood-stage malaria vaccine candidates of high efficacy against *Plasmodium falciparum* remain elusive, mainly because of antigen polymorphisms and resultant allele-specific immunity in natural parasite populations. We recently reported *P. falciparum* reticulocyte binding protein homologue 5-interacting protein (PfRipr) as a promising blood-stage vaccine candidate, and highly conserved among Ugandan isolates. PfRipr is known to interact with previously reported conserved merozoite proteins, reticulocyte binding protein homologue-5 (PfRH5) and Cysteine rich protective antigen (PfCyRPA) in an invasion complex. PfRH5 binds to basigin receptor on the surface of red blood cells and is currently in clinical development. Antibodies against wheat germ cell-free system (WGCFS) expressed recombinant PfRipr based on Pf 3D7 sequences demonstrated potent growth inhibition assay (GIA) activity of both 3D7 and heterologous FVO. However, because of difficulties associated with synthesizing a large PfRipr immunogen that consists of 1086 amino acids (aa) and 83 cysteine residues, we attempted to identify the protein region(s) with functional epitope(s). The WGCFS successfully expressed 11 PfRipr antigen truncates, each containing approximately 200 aa. Rabbit antibodies against each truncate were generated, and performed GIA. We demonstrated that antibody against PfRipr region containing 215 aa had the highest GIA activity, and a promising blood stage vaccine candidate.

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ASSESSMENT OF *PLASMODIUM FALCIPARUM* PFS47 AS A TRANSMISSION BLOCKING TARGET FOR MALARIA

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Malaria transmission-blocking vaccines rely on functional antibodies that interact with proteins present on the surface of sexual/sporogonic stages of *Plasmodium* or in the mosquito midgut, and disrupt vector-parasite interactions critical for malaria transmission. We recently identified the female gametocyte surface protein *Pfs47*, a three domain 6-cys protein, as a key determinant of parasite immune evasion in the mosquito vector. Polymorphisms in the domain 2 of Pfs47 were shown critical to determine immune evasion by the parasite. We investigated whether monoclonal antibodies (mAb) to *Pfs47* have transmission blocking activity by decreasing infection of mosquitoes in a standard membrane feeding assay. Thirteen mAbs generated against the full length *Pfs47* showed modest and variable transmission-blocking activity but, through domain mapping, we observed that none of these mAbs reacted against the domain 2 of