a dose-escalating Phase Ia study in healthy UK adults (NCT02927145, unpublished). Here we report on the promising immunogenicity of the fractional dose group from the Phase Ia trial, where 12 volunteers received 2x 50 µg of RH5.1/ AS01B 4 weeks apart, followed by a delayed 10 µg dose 6 months later. We then present data on vaccine efficacy, assessed using a blood-stage controlled human malaria infection (CHMI) model against both primary and secondary homologous *Plasmodium falciparum* 3D7 clone challenge. 30 healthy malaria-naïve UK volunteers were recruited into this CHMI study. 15 received 3x 10 µg doses of RH5.1/ AS01B (4 weeks apart) and then received an intravenous injection of parasitized red blood cells in parallel with 15 control volunteers. Impact of the vaccine on qPCR-derived parasite multiplication rate (PMR) was the primary efficacy endpoint. 9 of these vaccinees and 8 controls have since undergone a second homologous CHMI to assess durability of immunity, compared to a third group of 6 new malaria-naïve controls. Results of both the first and second *P. falciparum* blood-stage challenges will be presented.

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ANTIBODIES AGAINST PYMIGS, A NOVEL TRANSMISSION-BLOCKING VACCINE CANDIDATE, REDUCE THE MOTILITY OF MICROGAMETES

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Malaria transmission-blocking vaccine aims to inhibit the development of malaria parasites in mosquitoes by antibodies targeting surface proteins of sexual stage parasites. We have previously identified PyMiGS, a protein expressed on the surface of microgametes of *Plasmodium yoelii (*Py) to elicit antibodies with potent transmission-blocking activity. In this study, we aimed to investigate the mode of action of anti-PyMiGS antibodies against parasite development. Activated male gametocytes in mosquito midguts first egress from the erythrocytes, followed by exflagellation soon after the blood meal. To mimic the *in vivo*environment, Py gametocytes were mixed with activation medium containing anti-PyMiGS antibodies or anti-GST (control) and subsequently processed for electron microscopy after 15 min incubation. We observed exflagellation in both anti-PyMiGS and control group. However, whereas most microgametes were released from the residual body of activated male gametocytes in the control group, a significantly reduced number of microgametes were released in the presence of anti-PyMiGS antibodies, with most left attached on the residual body. Moreover, anti-PyMiGS antibodies shortened the duration of the active movement of microgametes after the onset of exflagellation to a fifth of the control. Put together, these findings suggest that anti-PyMiGS antibodies bind to microgamete surface immediately after exflagellation, thereby reducing microgamete motility and inhibiting microgamete release from activated gametocytes.

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IN SILICO T CELL EPITOPE PREDICTION IDENTIFIES HIGH VALUE RH5 EPITOPES THAT CORRELATE WITH RESPONSE IN VACCINEES

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In silico epitope prediction and analysis tools EpiMatrix and ClustiMer were used to identify class I and class II epitopes providing broad HLA coverage in RH5, a highly conserved *Plasmodium falciparum* blood-stage antigen that has recently been assessed in a Phase I clinical trial with controlled human malaria infection (CHMI). In addition, sequence similarity to the human proteome regarding the potential for cross-reactive epitopes, which may induce regulatory T cell responses, was also analyzed using the JanusMatrix algorithm. In contrast to other well-studied *P. falciparum* antigens such as TRAP, CSP, and EBA-175, high levels of class I and class II T cell epitope content were found in RH5, including thirteen class II epitope clusters. Predicted epitopes were synthesized as peptides and validated in competition binding assays with soluble class I and class II HLA as well as in Interferon gamma ELISpot assays using PBMC from clinical trial vaccinees administered RH5.1, a full-length recombinant RH5 protein vaccine. Criteria for selection of high value vaccine candidate epitopes as well as data correlating T cell response with in silico and *in vitro* indicators of donor HLA-specific potential for inflammatory, regulatory or lack of response will be shown.

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CLINICAL ILLNESSES IN A HEALTHY POPULATION AT A MALARIA TRANSMISSION BLOCKING VACCINE TRIAL SITE IN MALI

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Malaria vaccine trials assess product safety, immunogenicity, and efficacy; these endpoints can be confounded by intercurrent illnesses that may be deemed adverse events or may mimic or aggravate clinical malaria episodes. Furthermore, concurrent illnesses, such as malaria or respiratory infections, can impair vaccine responses. Therefore, defining the prevalence of common diseases and their distribution in different socio-demographic stratifications is helpful to prepare a site for the evaluation of vaccine safety and efficacy. In preparation for malaria community transmission blocking vaccine trials, we initiated a study of Community Dynamics of Malaria Transmission and Mosquito Feeding in Bancoumana, Mali in February 2018. Bancoumana is a village located 60 km southwest of Bamako with a population of about 10,000 people, and malaria transmission is highly seasonal with low incidence during the dry season from approximately January through June. As part of this observational study, we assessed disease frequency at enrollment of all age groups. We enrolled 957 subjects who were screened, including clinical exam, baseline hematological parameters, and malaria parasite density, with diagnostic assays and assessments as appropriate for any ongoing illness.Out of all participants, 32.3% (309/957) presented with at least one clinical abnormality at enrollment. Respiratory infection were by far the most commonly reported disease [11.0% (105/957)], with highest frequency among children under 5 years old [26.1% (47/180)]. The second most common infection was uncomplicated malaria [2.8% (27/957)] followed by gastroenteritis [2.1% (20/957)], both again most commonly in children under five years old [3.9% (7/180); 5.0 % (9/180)]. No difference was observed between sexes regarding the distribution of reported diseases. Less than 25% of volunteers reported a hemoglobin value under 11.7 g/dl. Infectious diseases, which are known to modify human immunity, were prevalent at the Bancoumana clinical trial site but varied widely between age groups. These findings will be considered when designing vaccine trials at this site.