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Letter to the Editor

Towards validated assays for key immunological outcomes in malaria vaccine development

A first generation partially effective malaria vaccine, RTS, S/AS01, is scheduled to complete an ongoing Phase 3 trial in 2014. Intense efforts are underway to develop highly effective second generation malaria vaccines in accordance with the malaria vaccine technology roadmap [1]. An important aspect of this second generation development work is agreement on the key immunological outcomes for upcoming malaria vaccine trials, and agreed approaches on standardised measurement of these outcomes.

The protective mechanisms underlying immunity induced by malaria vaccines are not fully characterised and are distinct from those responsible for naturally acquired immunity. Vaccine-induced immune mechanisms are thought to differ according to life-cycle target stage for subunit vaccines. Over 30 malaria vaccine projects are under clinical evaluation or progressing towards the clinic [2]. Of these, about two-thirds have used IgG-based assays for immunogenicity, with the other third using T-cell based assays as the primary immunological readout. In most cases the immunoassays are used as a measure of immunogenicity of the vaccines as immune correlates of protection are not known. It is important to be able to accurately and reproducibly quantify whether desired immune responses have been induced. Whatever assay is used, comparison between immunogenicity of alternate formulations, adjuvants and platforms requires the availability of robust assays. “Harmonisation” of assays refers to use of consensus SOPs between networks of laboratories. “Standardization” is a further step which requires agreed-upon SOPs, reagents and equipment and implies confirmation that equivalent results will be obtained at different centers by different operators. “Validation” is a regulatory requirement for use of immunoassay data for licensure purposes and refers to a stringent quantification of assay performance including accuracy and reproducibility.

If the malaria vaccine field is to progress to the stage where assay results are known to correlate with vaccine efficacy and are comparable between laboratories and in different settings, progress in the above activities is desirable for key assays. It is also necessary to develop robust assays with quantified inter-laboratory variability in order to have confidence in down-selection decisions for progression into pre-clinical development pathways. Substantial funding is required for GMP manufacturing, GLP toxicology and regulatory submission; down-selection often rests on assay-based comparisons between platforms, adjuvants and antigenic constructs. The process of assay harmonization is underway in the malaria vaccine field [3], though a great deal of further work will be required before rational decision-making will be possible based on standardized key immunological outcomes (see Fig. 1). The assay classes thought to be of greatest relevance to immune protection are listed in Fig. 2.

Malaria Vaccine Assay Harmonization

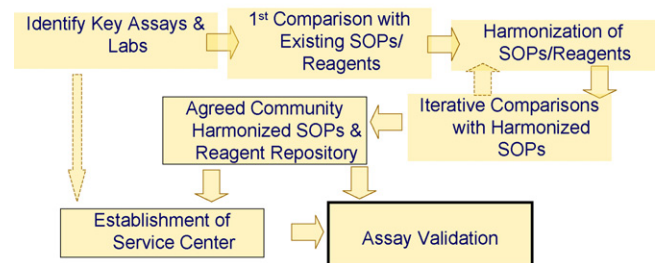


Fig. 1. Malaria vaccine assay harmonization.

Pre-erythrocytic malaria vaccine development benefits from the availability of a well developed clinical challenge trial. However immunological down-selection for progression to the clinic is based on non-harmonized pre-clinical IgG and T-cell based assays as well as pre-clinical challenge data. There are no well developed functional assays in the pre-erythrocytic area, making assay development in this area one of the priorities. There is good evidence for protective immunity through cellular responses in malaria, targeted at liver-stage antigens, but also for blood-stage antigens in different models. Both enzyme-linked immunospot (ELISpot) and intracellular cytokine staining (ICS) assays have been identified for harmonization on this basis. In the blood-stage field there are two functional assays of note: growth inhibition (GIA) and antibody-dependent cellular inhibition (ADCI) assays. Investigators proficient in GIA have participated in several harmonization efforts resulting in conformity in some aspects of the assay procedure, and selection and support of one intramural NIAID laboratory as a PATH MVI Reference center [3–5]. ADCI is more difficult to standardize, but has the advantage of requiring far lower IgG concentrations for activity [6] and has therefore been identified for harmonization, with the anticipation that this will be challenging. A PATH MVI ELISA Reference laboratory is funded for the performance of both blood-stage and pre-erythrocytic stage ELISAs at the Walter Reed Army Institute of Research (WRAIR).

In the spirit of growing coordination and collaboration between groups of funders and scientists, the OPTIMALVAC assay harmonization activity has been initiated (www.optimalvac.eu). This is a European Union funded project whereby funds have been allocated to harmonize the following assays: ICS, ELISpot, ADCI and blood-stage IFA. The European Vaccine Initiative provides project management and coordination expertise. The PATH Malaria Vaccine Initiative is closely involved with the project both through its steering committee and through targeted, complementary funding of certain components. PATH MVI also supports the NIAID GIA

Key Immunological Outcomes

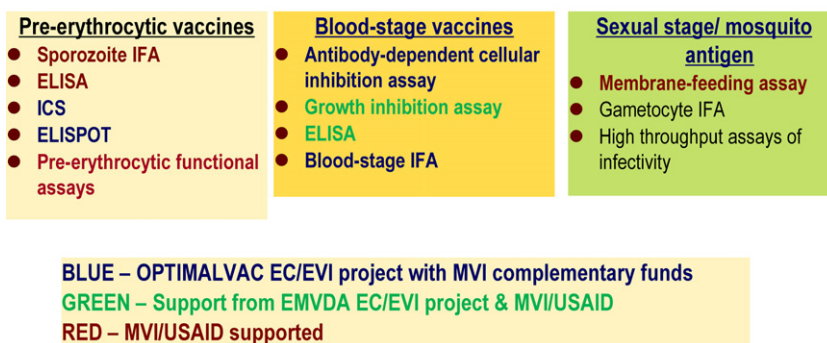


Fig. 2. Key immunological outcomes.

Reference Center as well as the WRAIR ELISA Reference Center along with USAID support. WHO Initiative for Vaccine Research (IVR) acts to identify and synergize other malaria vaccine assay harmonization activities with OPTIMALVAC and to link with other disease areas where appropriate.

PATH MVI is, in parallel, conducting comparisons of alternate pre-erythrocytic functional assays and assays of infectivity for sexual stage and mosquito antigen vaccine research. Thus, though choice of immunological outcomes is complex in malaria vaccination, a great deal of progress is being made. In the medium term, consensus harmonized SOPs should be available for the community and identification of laboratories with an interest in serving as additional central testing centers may be facilitated. There are currently no WHO designated reference centers. Ultimately a particular assay may progress to the stage where it has met the requirements of a WHO reference center and where establishment of such a center is appropriate and feasible in the malaria vaccine field.

To conclude, many different approaches to malaria vaccination are under clinical or advanced pre-clinical evaluation. Comparison of immunogenicity using robust standardized assays will be a major benefit for rational development decision-making, identification of correlates, and more rapid and focused product/candidate/concept advancement. Where partial clinical efficacy is demonstrated availability of standardised assay data will maximise the chances of identification of correlates of protection which can then be used to iteratively improve vaccine efficacy. Where efficacy is absent, confidence in immunological outcome data is equally important to allow developers to make conclusions about whether the vaccine concept has been tested to failure and can thus be confidently terminated. A coordinated multilateral approach to assay harmonization, standardization and identification of central testing centers is underway and will be critical for the development of a highly effective second generation malaria vaccine. Many in the malaria R&D arena feel that such a vaccine will be necessary if malaria transmission is to be successfully interrupted in high malaria transmission settings. Thus the drive towards validated assays for immunological outcomes in malaria vaccination may prove vital if malaria is ever to be eradicated globally.

Acknowledgments

The views expressed in this article are those of the authors and do not necessarily represent the views, opinions or stated policy of the World Health Organization.

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