GVIRF 2014: Plenary 1: Develop new and improved vaccines	
Rapporteurs: Vasee Moorthy (WHO) and Annie Mo (NIAID)	
Session Outline	**Chair: Charles Mgone (EDCTP)** **Presentations: Ashley Birkett (MVI), Peter Smith (LSHTM)**
Objectives of the session	Summarize status of malaria vaccine R&D.
Main outcome	While progress has been made with malaria control, malaria vaccine development remains a global public health imperative (SAGE 2013). A first generation product (RTS,S/AS01) is entering regulatory and policy evaluations in 2014-2015 for possible licensure and recommendations for use. The vaccine pipeline is well populated, but there are opportunities to make further progress with targeted investments. The malaria human challenge model is a valuable tool for screening candidate vaccines. Human vaccinology research offers a great opportunity to explore and accelerate platform and vaccine development and evaluation.
Summary	Dr Birkett indicated that despite the major progress with scale-up of available malaria control tools, an estimated 627,000 deaths occurred in 2012 with around 207 million cases. There remains an urgent need for effective malaria vaccines. The global malaria vaccine community agreed an update to the Malaria Vaccine Technology Roadmap during 2013. The update includes 2 strategic goals to develop highly efficacious vaccines to prevent malaria disease, and to develop vaccines to interrupt malaria transmission. The status of the RTS,S/AS01 malaria vaccine candidate was reviewed. Next steps include file submission to the European Medicines Agency in 2014, and possible policy decision by WHO in late 2015 (depending on the regulatory timings). The results to date indicate superior efficacy in those 5-17 months of age at administration compared to those 6-12 weeks of age. The healthy pipeline of earlier stage candidates was discussed with many possibilities 5-10 years or longer behind RTS,S/AS01 in development. The utility of the human challenge model was highlighted in P. falciparum malaria, where there is a well standardised model using a parasite clone that is fully drug sensitive, and treatment occurs after early diagnosis of infection. Challenges and opportunities presented included the development of WHO Preferred Product Characteristics so that developers can align with these to reduce risk, the need for strengthened developing country pharmacovigilance systems given the absence of dual market opportunities for many malaria vaccines, the regulatory approval strategies for malaria vaccines which act at the community level for transmission reduction, human vaccinology research opportunities to identify and evaluate effective vaccine delivery platforms especially for very young children, to define biomarkers of protection, and to validate targets for subunit vaccine development as well as overcome the limitations of current preclinical models through back-validation from clinical to preclinical data. PATH Malaria Vaccine Initiative confirmed that their future directions are well-aligned with the strategic goals and priority activity areas outlined in the 2013 Malaria Vaccine Technology Roadmap. Peter Smith reflected on the results from the pivotal Phase 3 trial which have confirmed that, in children vaccinated at ages 5-17 months, RTS,S/AS01 confers efficacy against clinical malaria in the range 40-77% across the 11 Phase 3 trial sites, when assessed over 18 months of follow-up, with consistent figures for reductions in severe malaria, malaria hospitalizations, and all-cause hospitalizations. Results when the vaccine was co-administered with EPI vaccines in infancy were showed lower efficacy. The possible reasons for this include interference from either co-administered vaccines or maternally acquired antibodies in the younger age group, or immunological immaturity. Prof Smith discussed the importance of the booster dose results, given the waning efficacy seen during the 18 months after vaccination. The effect of a fourth (booster) dose given 18 months after the primary immunization series will be available by the time of the expected WHO policy decision in late 2015. Prof Smith indicated that any WHO policy recommendations will be highly likely to reiterate the need to continue with ongoing scale-up of available WHO preventive, diagnostic, and treatment measures which have already had a significant impact in malaria endemic countries. With respect to second-generation malaria vaccines, there was a brief discussion about the possible trial design options in the event that a first-generation vaccine had been licensed. Important considerations for trial design will be the primary objective of the study, the trial setting, whether the first-generation vaccine is licensed in-country, whether it is recommended for use locally, and whether it is available. While placebo controlled trials are not ethically appropriate if the first-generation vaccine is in widespread use in a country, a recent WHO Expert

	Consultation on use of placebos in vaccine trials provides an ethical framework for national authorities to make decisions about appropriate trial design, when a first-generation vaccine is licensed in some jurisdictions but not in use locally.
Key references or quotes	"The global malaria vaccine community agreed an updated Malaria Vaccine Technology Roadmap during 2013." —Ashley Birkett "A first-generation malaria vaccine is now approaching its regulatory and policy assessments, and opportunities to develop second-generation products exist." —Ashley Birkett "The benefit from RTS,S/AS01 may be greatest in high transmission settings where the Phase 3 trial results indicate over two episodes of clinical malaria prevented per child vaccinated." —Peter Smith "Given the waning of efficacy seen so far, the effects of a booster dose given at 18 months after the initial course in the Phase 3 trial are going to be important." —Peter Smith