Introduction

The most advanced vaccine candidate against *Plasmodium falciparum*, known as RTS,S/AS01, is currently being evaluated in a Pivotal Phase 3 trial. This vaccine is being developed by GSK in partnership with PATH Malaria Vaccine Initiative (MVI) with funds from the Gates Foundation to MVI. There are about 20 other malaria vaccine projects in clinical testing; none of the other approaches have demonstrated proof of concept of efficacy in field settings.

The randomised controlled double-blind Phase 3 efficacy trial started in May 2009 and completed enrolment in January 2011 of 15,460 children in 7 countries in sub-Saharan Africa. These countries are: Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania. The children are in two age groups: 1) 5-17 months at first immunization without co-administration and 2) 6-12 weeks at first immunization (which is the target age group for this vaccine) in co-administration with routine infant vaccines. Each child is followed up for at least 30 months following the third dose of RTS,S/AS01. The three doses are given with 1 month intervals followed by an 18 month booster dose in one of the 3 trial arms. The control vaccine is rabies vaccine for 5-17 months olds and meningococcal C vaccine for 6-14 week olds. The trial is occurring in the context of LLIN use by most trial participants. The trial teams liaised with national authorities to maximise LLIN use in the trial settings.

Results available as of Oct 2011

Phase 3 results

The first of three sets of results from the Phase 3 trial were published in Oct 2011 in the New England Journal of Medicine. Efficacy against clinical malaria in 6000 infants/toddlers 5-17 months old during the 12 months following administration was about 55% depending on the analysis (95% CIs spanning 45-59%), comparable to results obtained in Phase 2 trials. Efficacy against first episode of malaria waned, being substantially higher than 55% at the start of the follow-up period post dose 3 and substantially less than 55% at the 12 month follow-up time point. Variation in efficacy against all episodes of malaria with time has not been presented.

The primary severe malaria analysis included both 5-17 month olds and 6-14 week olds. Here there was a mean follow-up of 11 months from first dose (range 0-22 months) and efficacy was 35% (95% CI 16 - 49%). In the 12 months following vaccination in the 5-17 month age category, the protective effect of the vaccine against severe malaria was estimated to be 47% (95% CI 22 to 64%). The 151 deaths were balanced between malaria vaccine and control groups.

Safety and reactogenicity: In terms of reactogenicity, there was a higher proportion of fever cases (31% vs 13%) in the 7 days after vaccination in the 5-17 months age category, among those receiving RTS,S when compared to controls; and an excess frequency of about 1 in 2000 vaccine doses for febrile seizure was observed within 7 days after RTS,S vaccination. There were also more cases of meningitis (as
defined by the investigator without proven aetiology) in the RTS,S/AS01 group (19 cases compared to 2 cases in the controls but note 2:1 randomization). No temporal association of meningitis cases with vaccination was observed. The Independent Data Monitoring Committee reviewed these data in an unblinded manner and concluded that there was no evidence of a safety concern at this time.

**Phase 2 results**

The earlier Phase 2 studies were done using a different adjuvant (AS02, an oil-in-water emulsion containing immunostimulants). Later studies were done with the AS01 adjuvant (a liposomal formulation containing the same immunostimulants) which appeared to give superior IgG and cell-mediated immune responses, as well as improved efficacy in the human challenge model. AS01 is the adjuvant that is being used in the Phase 3 studies.

The longest term efficacy follow-up from Phase 2 available to date is from a RTS,S/AS02 study in Mozambique. Efficacy from this study was 26% (95%CI 12 to 37) for all episodes of clinical malaria over 43 months following administration of the third dose, in children aged 1-4 years at vaccination.

Phase 2 efficacy data against all episodes of clinical malaria for RTS,S/AS01 are summarized in figure 1 (this figure was produced by WHO secretariat). These are per protocol estimates with follow-up starting 2 weeks from the third dose. The first column relates to an exploratory efficacy analysis from a three site safety and immunogenicity study conducted in Gabon, Ghana and Tanzania. The second and third column relate to pooled results from a study conducted in Kilifi, Kenya and Korogwe, Tanzania. The fourth column relates to extended follow-up in the Kilifi site only for the same trial.
Timing of further Phase 3 results

In Q4 2012 the GSK/MVI partnership will announce safety, immunogenicity and efficacy data from infants aged 6-12 weeks at first dose in co-administration with pentavalent vaccine.

In Q4 2014 WHO expects to receive the full 30 month analyses from both age groups, including additional pre-specified analyses requested by WHO including data on all episodes of malaria broken down by time since vaccination.

Intended target population for deployment, and final presentation

GSK has stated that the initial target group for deployment is infants aged 6, 10 and 14 weeks of age in co-administration with routine DTP or pentavalent vaccines. The Phase 3 trial has been conducted with pentavalent DTwP/Hep B/Hib and OPV. Co-administration data has also been generated with measles vaccine. The final presentation will be a 2-dose vial of lyophilized RTS,S antigen clipped to a 2-dose vial of liquid AS01 requiring storage at 2-8 degrees centigrade and to be discarded if the second dose is not used during a 6 hour period after reconstitution.

Other phase III and ancillary studies

An additional phase III co-administration study is underway with pneumococcal conjugate and rotavirus vaccines, powered to evaluate non-inferiority of immunogenicity in co-administration.
A phase III lot to lot consistency and bridging study is underway in Nigeria using anti-circumsporozoite antigen IgG responses in children to bridge the pivotal Phase 3 trial vaccine material (20 L manufacturing scale) with initial commercial scale material (1600 L manufacturing scale), and to demonstrate clinical consistency of 3 different lots produced from 1600-L scale material.

A phase III study in 200 HIV infected children, aged 6 weeks to 17 months, is underway to evaluate safety and immunogenicity in this special population.

A transmission intensity ancillary study is underway to assess the prevalence of asexual P. falciparum infection in communities related to each Phase 3 efficacy trial site in various age groups, together with serological exposure studies.

Timing for Policy recommendations

A Joint Technical Expert Group (JTEG) on Malaria Vaccines was first convened in June 2009 by the WHO Global Malaria Programme (GMP) and WHO Department of Immunization, Vaccines & Biologicals (IVB) (www.who.int/vaccine_research/jteg/en/index.html). JTEG determined that there should be sufficient data available to make a draft policy recommendation regarding RTS,S/AS01 in 2015 for subsequent consideration by the policy advisory committees in IVB (SAGE) and GMP (MPAC). The WHO policy recommendation will take into consideration safety and efficacy results from the current Phase 3 efficacy trial after 30-month follow-up of children receiving the malaria vaccine together with routine infant vaccines, as well as site-specific data on efficacy (where there is adequate power), 18 month booster dose efficacy and severe malaria efficacy. Not all sites will be powered for site-specific efficacy, although the highest transmission sites will be well powered for such an analysis.

Reviewing the Oct 2011 results, JTEG has confirmed the previously stated timings of a potential policy recommendation in 2015 depending on the results available to WHO in 2014. JTEG highlighted the essential need for follow-up data beyond 12 months. Given the apparent waning of efficacy reported during the trial, JTEG also highlighted the need for a further exploration of the duration of vaccine protection in the full trial results to be received by WHO in 2014.

Hepatitis B efficacy

The immunogen in the RTS,S/AS01 vaccine is a fusion protein between a malaria antigen and Hepatitis B surface antigen. RTS,S/AS01 may also be submitted for licensure as a Hepatitis B vaccine and it is already clear that RTS,S/AS01 would provide at least equivalent protection against Hepatitis B compared to available Hepatitis B vaccines.

How much longer term follow-up data will be available, and what phase 4 studies are planned?

Five-years of follow-up data has been requested by WHO from at least 3 of the 11 Phase 3 trial sites, with data collection planned for serious adverse events and clinical malaria only during the 30 month extension. The 3 sites were requested to be in different transmission intensity strata. In addition, the GSK/MVI partnership is currently planning to provide post-registration Phase 4 data on safety and effectiveness from both age groups. The Phase 4 safety studies are planned to occur in Senegal, Burkina...
Faso, Ghana, Kenya and Tanzania with about 40,000 individuals receiving RTS,S/AS01. The design of the Phase IV studies has been reviewed by JTEG, the WHO Global Advisory Committee on Vaccine Safety and the European Medicines Agency. WHO requested that adequate baseline data is collected on potential adverse events prior to Phase 4 administration of RTS,S/AS01, that Phase 4 studies are planned in close liaison with national authorities, and that studies are conducted in demographic surveillance system sites.

**What is the regulatory pathway?**

The European Medicines Agency (EMA), under a process known as article 58, will perform a scientific evaluation of this vaccine and issue what is called "a European scientific opinion". The submission timings are currently unknown. This would not result in a European license or registration, but provides a scientific opinion which African regulators may use to help their own regulatory processes. It will be African national regulatory authorities which will consider licensing the vaccine in their jurisdictions. Article 58 is a specific legal basis in the European pharmaceutical legislation, allowing the EMA to perform an evaluation of medicinal products, using the same processes as those used for marketing/registration of European Union (EU) medicinal products, but for medicines to be used outside the EU and intended to prevent or treat diseases of major public health significance in those countries. This evaluation is performed with WHO input and with involvement of the relevant national regulatory authorities as observers.

**What has WHO communicated to date about the potential role of RTS,S/AS01 in the context of existing WHO recommended malaria control measures?**

There is a detailed WHO “Questions & Answers on Malaria Vaccines” document available here:  

[http://who.int/entity/vaccine_research/diseases/malaria/WHO_malaria_vaccine_q_and_a_July_2012.pdf](http://who.int/entity/vaccine_research/diseases/malaria/WHO_malaria_vaccine_q_and_a_July_2012.pdf)

WHO has stated on its website the following: “Contingent on the completion of the on-going phase 3 trial and submission of data supportive of use, WHO will review the evidence for policy recommendation in 2015. The recommendations on RTS,S/AS01 will consider its potential as an addition in some settings to existing preventive measures, such as long-lasting insecticidal nets and indoor residual spraying. The priority need for high quality artemisinin-combination treatments should continue regardless of availability and use of RTS,S vaccine. Based on currently available data the vaccine will be considered as an addition to, not a replacement for, existing preventive and treatment measures.”

Depending on the results in Q4 2012, WHO may engage in further communications activities to provide WHO’s perspective on the possibility of RTS,S availability in 2015 and later. This would include the implications of an efficacy at around the 50% level including the imperative to continue with preventive, diagnostic and treatment measures, and the fact that vaccinated children cannot be considered to be fully protected from malaria.
For the last 2 years, WHO has been giving presentations at multiple fora including sub-regional malaria programme and EPI meetings in AFRO to present these concepts, and to communicate the potential 2015 policy timings.