SUMMARY FOR STRATEGIC ADVISORY GROUPS OF EXPERTS (SAGE) RE: RTS,S/AS01 MALARIA VACCINE

February 2013: written by WHO secretariat with input from JTEG

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 GlaxoSmithKline (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 III 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 in co-administration with DTwP/HepB/Hib and OPV. Each child is followed for at least 30 months following the third dose of RTS,S/AS01. The three intramuscular doses are given in 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 conjugate vaccine for 6-12 week olds. The trial is occurring in the context of insectidice-treated bednet (ITN) use by most trial participants. The trial teams liaised with national authorities to maximise ITN use in the trial settings.

Phase 3 Results

The first of the three sets of results from the Phase III trial were published in October 2011 in the *New England Journal of Medicine* (NEJM)[1]. At that time clinical malaria efficacy data was reported on 6,000 infants/toddlers 5-17 months old at first immunization with RTS,S/AS01.

There was a Joint Technical Expert Group (JTEG) on Malaria Vaccines meeting on 9-10 October 2012. At this meeting GSK and MVI presented the second set of results from the Pivotal Phase 3 trial of RTS,S/AS01. These results were then published in a second NEJM article[2], which reports data from 6,537 infants aged 6-12 weeks of age randomized 2:1 to receive RTS,S/AS01 or Meningococcal C conjugate vaccine (control) in co-administration with DTwP/HepB/Hib and OPV. Duration of follow-up reported to date for both age groups is 12 months post dose 3.

[1] N Engl J Med 2011; 365:1863-1875 . November 17, 2011. www.nejm.org/doi/full/10.1056/NEJMoa1102287
[2] N Engl J Med 2012; 367:2284-2295. December 13, 2012. www.nejm.org/doi/full/10.1056/NEJMoa1208394

Efficacy & Immunogenicity: Summary Table of Per Protocol Analyses for RTS,S/AS01 Phase III Trial.

	6-12 week age group **(published Nov 2012)**	5-17 month age group **(published Oct 2011)**
Efficacy, first or only episode of clinical malaria	31%(97.5% CI 24-38)	56% (97.5% CI, 51 to 60)
Efficacy, all episodes of malaria	33% (95% CI 26-39)	55% (95%CI 50-59)
Efficacy, severe/ hospitalized malaria	37% (95% CI 5-58)	47% (95% CI 22-64)
Immunogenicity (antibody, elisa units per ml to malaria antigen).	209 (95%CI 197-222)	621 (95% CI, 592 to 652).

While much of the discussion following publication is likely to focus on the apparent difference between the efficacy figures in the 2 age groups, JTEG advised that the two age groups are not strictly comparable. This is because the numbers enrolled by site across the 11 sites differs between the 2 age groups, as does the number of malaria events. Malaria transmission intensity varies greatly across the sites. JTEG advised that site or transmission strata specific efficacy analyses are necessary to interpret the new results, and this was communicated to GSK/ MVI. Such analyses will be available to WHO by late 2014.

A potentially important finding is the three-fold lower antibody concentrations by ELISA to the malaria antigen in the younger age group. The apparent difference in efficacy between the two age groups may relate to some or all of the following factors: interference from co-administration, maternally acquired antibodies to the malaria antigen in RTS,S/AS01, differences in the prior exposure of the children to malaria, transmission intensity and seasonality. A further factor raised by the GSK/MVI partnership is that the children in the 5-17 month age category had almost all received three prior doses of hepatitis B vaccine, and this may act to prime for higher malaria antibody responses given that RTS,S is a fusion malaria-hepatitis B vaccine.

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.

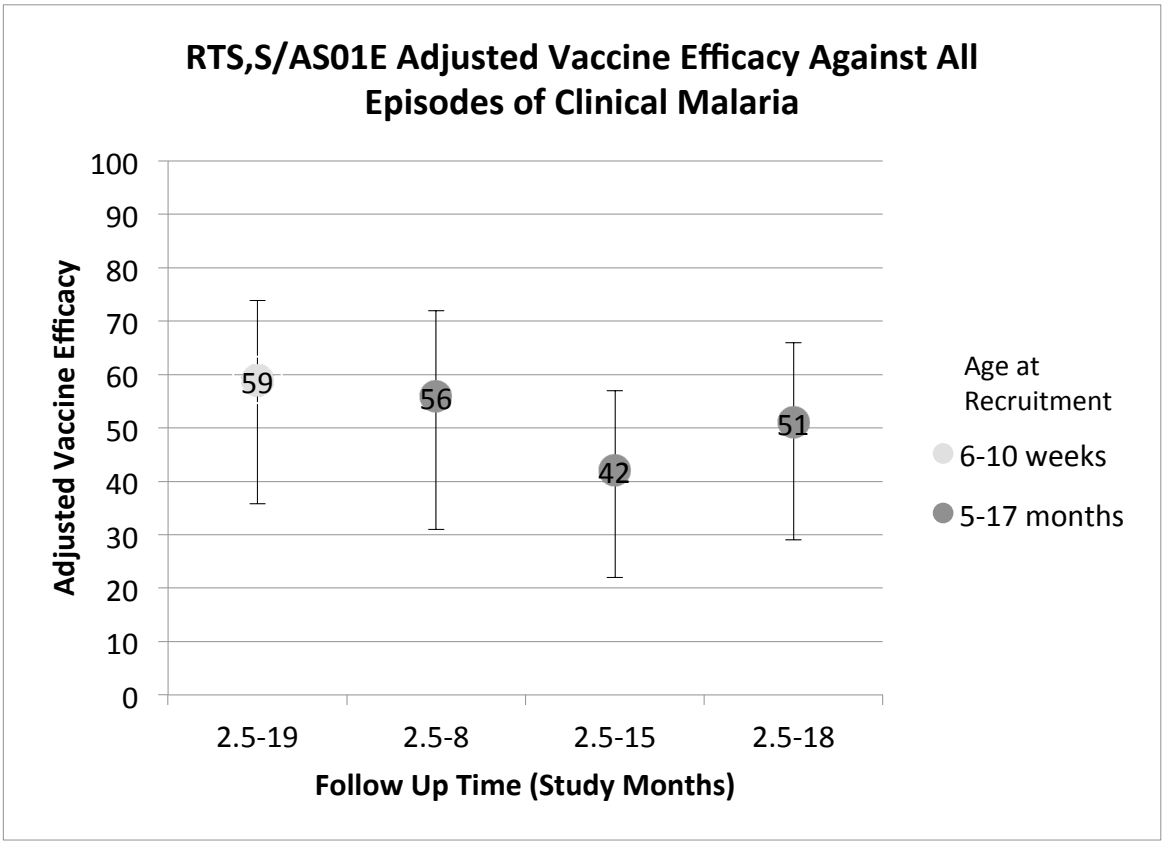
No new safety concerns were raised by the second set of results in infants aged 6-12 weeks at first dose, with no excess of febrile seizures reported in this age group. The full Phase III data will be reviewed by the Global Advisory Committee on Vaccine Safety (GACVS) prior to the "For Decision" session in 2015.

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, ie monophosphoryl lipid A and QS21) which

appeared to give superior IgG and cell-mediated immune responses, as well as an indication of 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 late 2014, WHO expects to receive the full per-protocol 30 month analyses from both age groups, as well as additional pre-specified analyses requested by WHO, including data on all episodes of malaria broken down by time since vaccination and additional site or transmission strata specific analyses.

Likely timing of For Decision Joint Session of SAGE and Malaria Policy Advisory Committee (MPAC)

The new results re-emphasise the previously stated policy timings: WHO policy recommendations are expected in 2015 based on the outcome of a joint SAGE/MPAC session. This session is tentatively scheduled for Q4 2015, depending on the final regulatory submission timings. The recommendations will be based on all data available up to 2014, including the site-specific efficacy, duration of protection and 18-month booster dose data. GSK/MVI have agreed that additional analyses requested by JTEG will be performed in late 2014.

The GACVS safety review of RTS,S/AS01 data is tentatively scheduled for June 2015.

Assessment of severe malaria age patterns, in order to inform discussions about immunization schedules

IVB is working jointly with WHO Global Malaria Programme to perform an assessment of the available data on severe malaria age patterns in sub-Saharan Africa. In work with some analogies to the rotavirus schedule expansion assessment, it is planned that the age patterns for given malaria transmission settings, will be combined with immunization coverage data to provide modeled estimates of the percentage of severe malaria disease burden that would be missed by different possible schedules within the age ranges of immunization covered by the pivotal Phase 3 trial. The outcome of this work will be presented to SAGE as part of the 2015 For Decision session.

Summary of Ongoing Phase II, Phase III, and ancillary studies for the RTS,S programme

See separate 2 page document

October 2012 JTEG Recommendations to WHO
JTEG indicated that the new data that have become available in Q4 2012 do not change the previously communicated policy timings. WHO policy recommendations can be expected in 2015, depending on the data available in 2014 and on the timing of regulatory submission.
Depending on the results in late 2014, RTS,S/AS01 will be evaluated as an addition to, not a replacement for, existing malaria prevention, diagnostic and treatment measures. There is a range of policy decisions possible in the 2015 timeframe, depending on the 2014 results.
JTEG highlights the following to be considered as part of the additional analyses for late 2014. These will also be revisited in review of the analysis plan for the Q3 2013 analyses. It is appreciated that GSK/MVI have stated that additional analyses cannot be performed before 2014: • Site-specific and transmission strata specific efficacy analyses • Rates of disease in the vaccine vs control group broken down by time since vaccination • Explorations of correlation between immunogenicity and efficacy • Exploration of the interaction between seasonality and vaccine efficacy • Correlation between pre-existing maternally acquired antibody to CS and immunogenicity • Correlation between anti-CS and anti-Hepatitis B antibody titres
Given the results to date, contingency plans for alternative schedules should be included, minimizing the number of additional routine immunization visits whilst maximizing expected efficacy. However it is unlikely that policy recommendations for use can be made on alternative schedules without clinical trial data on those schedules.
JTEG recommends the Secretariat present to MPAC and SAGE: • Available data (as soon as embargo period is over) • Summary of issues JTEG has identified • Pipeline of additional work that is ongoing or planned
JTEG supports WHO's effort on communication about these results. JTEG could be included in such communication efforts by provision of slides.
JTEG supports in concept a systematic review of the age pattern of severe malaria in sub-Saharan Africa if possible to do, noting that age-spectrum of hospitalizations can change at the same location as transmission changes, and this must be taken into account. This work may support considerations of alternate schedules during the 2014-2015 policy discussions.