SUMMARY FOR MALARIA POLICY ADVISORY COMMITTEE RE: RTS,S/AS01 MALARIA VACCINE

February 2012. Written by WHO secretariat with input from JTEG Chair

For an introduction on the design of the Phase III trial, and an overview of the timings of availability of different data packages, please refer to the Briefing document on RTS,S/AS01 prepared for the September 2012 MPAC meeting

There was an in-confidence Joint Technical Expert Group (JTEG) on Malaria Vaccines meeting on 9-10 October 2012. At this meeting GSK (GlaxoSmithKline) and PATH Malaria Vaccine Initiative (MVI) presented the second set of results from the Pivotal Phase 3 trial of RTS,S/AS01.

These results were published in a New England Journal of Medicine article, available online from 9 Nov 2012. The article reports data from 6,537 infants aged 6-12 weeks of age randomized 2:1 who received RTS,S/AS01 or Meningococcal C conjugate vaccine (control) in co-administration with DTwP/HepB/Hib and OPV. The duration of follow-up reported is 12 months post dose 3.

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

<table>
<thead>
<tr>
<th></th>
<th>6-12 week age group (published Nov 2012)</th>
<th>5-17 month age group (published Oct 2011)</th>
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</thead>
<tbody>
<tr>
<td>Efficacy, first or only episode of</td>
<td>31% (97.5% CI 24-38)</td>
<td>56% (97.5% CI, 51 to 60)</td>
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<tr>
<td>clinical malaria</td>
<td></td>
<td></td>
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<tr>
<td>Efficacy, all episodes of malaria</td>
<td>33% (95% CI 26-39)</td>
<td>55% (95%CI 50-59)</td>
</tr>
<tr>
<td>Efficacy, severe/ hospitalized</td>
<td>37% (95% CI 5-58)</td>
<td>47% (95% CI 22-64)</td>
</tr>
<tr>
<td>malaria</td>
<td></td>
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<tr>
<td>Immunogenicity (antibody, elisa</td>
<td>209 (95%CI 197-222)</td>
<td>621 (95% CI, 592 to 652).</td>
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<td>units per ml to malaria antigen)</td>
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No new safety concerns are raised by this set of results, and it remains the case that the full Phase III data will be reviewed by the Global Advisory Committee on Vaccine Safety prior to the SAGE/MPAC decision session in 2015.

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 two 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/PATH Malaria Vaccine Initiative (MVI).

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In 2012, GSK/MVI stated that they could not perform such analyses until a protocol amendment was passed by ethical committees. The site-specific analyses will proceed during 2013 as the protocol amendment had passed as of March 2013.

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 with EPI vaccines, maternally acquired antibodies to the malaria antigen in RTS,S/AS01 and differences in the prior exposure of the children to malaria. If efficacy varies with transmission intensity, and the distribution of enrolled cases between sites with various transmission intensities is different between the 2 age groups, this could be a contributory factor. The time over which enrolment was completed was longer for the younger age group. Thus seasonality of transmission could also have impacted vaccine efficacy differently in the 2 age groups. 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.

WHO is starting preparatory work to inform policy discussions on choice of immunization schedules for RTS,S/AS01. This is expected to be a major policy question. 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 and MPAC as part of the 2015 session at which a decision on a policy recommendation will be made. There is an ongoing discussion as to whether available published data from a recent systematic review and meta-analysis is sufficient to provide the severe malaria age patterns in sub-Saharan Africa as the basis for this planned work, or WHO should extend the previous systematic review by performing an assessment of whether additional datasets should be included, and by incorporating health facility data on hospitalized confirmed malaria cases in addition to published epidemiological studies.

Expected Policy Timings

The new results re-emphasize the previously stated WHO policy timings: WHO will issue policy recommendations in 2015 based on advice from JTEG through SAGE and MPAC. These recommendations will be based on all data available up to 2014, including the site-specific efficacy data and 18-month booster dose data. GSK/MVI have agreed that additional analyses requested by WHO will be performed in late 2014.

The initial WHO policy decision on RTS,S/AS01 is now tentatively scheduled for Q4 2015 at a planned joint MPAC/SAGE “for decision” session. The change in timing from Q2 2015 is due to a planned change in the GSK/MVI partnership’s regulatory submission timing. A scientific opinion from the European Medicines Agency is necessary prior to policy recommendation.
**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.

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 2013 analyses:

- 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.