

RTS,S/AS01: JTEG Assessment and Preparations for Policy Recommendations

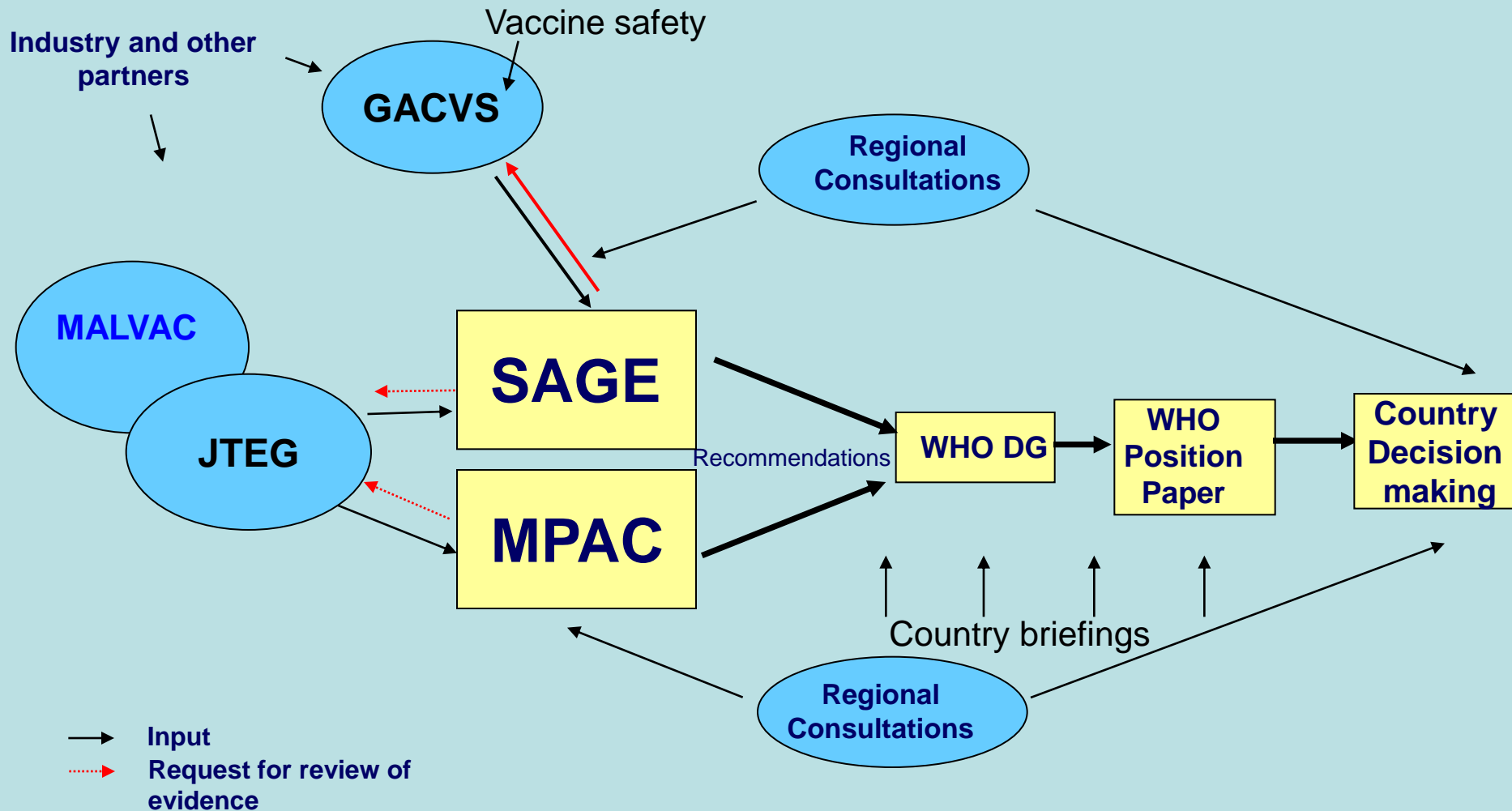
Peter Smith, Chair JTEG

JTEG members

- Chair, Peter Smith
- Fred Binka (MPAC member)
- Kamini Mendis (MPAC member)
- Malcolm Molyneux
- Paul Milligan
- Kalifa Bojang
- Mahamadou Thera
- Blaise Genton
- Janet Wittes
- Robert Johnson
- **Zulfiqar Bhutta (SAGE member)**
- **Claire-Anne Siegrist (SAGE member)**

Observers from NRAs of Kenya, Tanzania, Ghana, Malawi and European Medicines Agency

Pathways for WHO Policy Recommendations on Malaria Vaccines



Phase III
Results



Regulatory



Policy

The data from the pivotal Phase III trial is critical for both regulatory submission and policy consideration. This has caused some delays in GSK/MVI partnership in responding to WHO/JTEG requests in interim analyses

WHO/JTEG dialogue with GSK/MVI

The JTEG process has facilitated WHO's technical interaction with GSK/MVI.

GSK/MVI has agreed to conduct some of the key analyses that JTEG requested during the 2013 analyses of the 18 month follow-up data.

JTEG Assessment of One Year Follow up Results

The distribution of children and cases between sites is different in the 2 age groups and thus the pooled VE results for each of the 2 age groups are not strictly comparable (if there is heterogeneity of efficacy).

Pooled results are usually presented which is reasonable if some sites do not have markedly different efficacy to others.

JTEG advised that site or transmission strata specific analyses are required to aid interpretation of the results: GSK/MVI have agreed to provide these during 2013

Scientific questions raised by the recent results

- How does efficacy change with time since vaccination?
- Does efficacy vary with transmission intensity?
- Does the presence of marked seasonality affect measured efficacy, especially if efficacy declines rapidly?
- Does co-administration with pentavalent vaccine reduce efficacy?
- Does maternally acquired antibody present during vaccination affect efficacy?
- Does prior Hepatitis B immunization increase RTS,S efficacy?
- Does age or prior exposure to malaria affect efficacy?

WHO encourages exploration of all these questions as a high priority to guide policy discussions in 2015

Some information on all questions expected by 2015

Overview of analysis timepoints

Q4 2011 12 m follow-up post dose 3	Safety, Immunogenicity & Efficacy 6,000 children aged 5-17 months.
Q4 2012 12 m follow-up post dose 3	Safety, Immunogenicity & Efficacy 6,537 infants aged 6-12 weeks in co-administration with DTwP/Hep B/Hib
2013 18 m follow-up post dose 3	Both age groups
2014 30 m follow-up post dose 3	Both age groups, including 18 month booster dose

Key analyses expected in 2013 after 18mo follow up

- Duration of protection, including JTEG request to analyse all episodes of malaria in 6 month time intervals post vaccination
- Site-specific efficacy analyses
- Associations of efficacy with immunogenicity
- Association between pre-existing maternal antibodies and immunogenicity
- Cases averted analyses

Key data expected during 2013 from additional Phase III trials

- Pneumococcal & rotavirus vaccine co-administration
- Safety in HIV infected children

Key analyses expected in 2014

- As for 2013 with 30 months follow-up
- Effect of a booster dose at 18 months
- Analyses of the effect of seasonality
- Further analyses requested by WHO not yet confirmed, but including after seeing initial analyses.

Public Health Impact/Cost Effectiveness

- Second WHO meeting to assess status of malaria vaccine health economic models: 7-8 May 2013
- Will document status of multiple modeling groups working in this area
- Will propose role for such work in policy process
- Policy recommendations will be based on clinical trial data. In some areas a contribution from modeling may be beneficial e.g. guidance for Phase IV design

Key policy question: age group and schedule

- While original target group was infants aged 6,10,14 weeks, the published results raise the question of implementation in children aged 5-17 months
- WHO is commissioning work to model the proportion of malaria hospitalizations “missed” by schedules ending at different ages. Range from DTP3 up to 18 months of age being explored.
- Costing of adding new visits will also be requested in health economic work

Key policy question: role of RTS,S in context of other malaria control measures

- Available data indicates that efficacy is in addition to high level insecticide-treated bednet use
- Also possible that efficacy will be higher at low to moderate transmission levels
- Thus policy recommendations are highly likely to encourage sustained insecticide-treated bednet use together with any RTS,S introduction

Timing for policy recommendations

- Following review of the 2014 analyses, JTEG will draft candidate policy recommendations for review by SAGE and MPAC in joint session in Q4 2015
- The joint session has been deferred by 6 months due to a change in the planned regulatory submission timings by GSK/MVI

Messages from WHO

- Detailed Q&A available on WHO website
- RTS,S/AS01 will be evaluated as an addition to, not a replacement for, existing preventive and treatment measures
- It is too early to draw conclusions about the public health role of RTS,S/AS01
- Depending on the results expected in 2014, and on the regulatory submission timings, WHO will make the first malaria vaccine policy recommendations in late 2015.

Conclusions & Key Question for SAGE

- GSK/MVI have proved responsive to WHO's requests for data and analyses needed to formulate policy recommendations
- JTEG is now confident we will have information necessary for SAGE and MPAC to make a decision in Q4 2015 (assuming regulatory timings allow).
- Do you have suggested additional work for WHO & JTEG in preparation for the 2015 "For Decision" session?