Status of Malaria Vaccines: Update from JTEG Chair and Secretariat

Peter Smith, Chair JTEG

Vasee Moorthy, WHO Secretariat
Pathways for WHO Recommendations on Malaria Vaccine Use

Industry and other partners

GACVS

Vaccine safety

Regional Consultations

WHO DG

WHO Position Paper

Country Decision making

www.who.int/vaccine_research/jteg/en/index.html
Process for WHO policy recommendation

- MPAC will have key role for decision on addition to range of malaria prevention measures, on relation to other malaria control measures, and range of transmission settings for recommendation.

- SAGE will have key role for decision on addition to routine EPI programmes, for schedule, and ensuring satisfactory co-administration data.

- Joint MPAC/SAGE session is agreed at time of possible policy recommendation 1\(^{st}\) April 2015.
Global Malaria Vaccine Portfolio

Phase 3: One project RTS,S/AS01

Phase 2 field: Three ongoing Pf projects. GMZ2, MSP3, ME-TRAP

Phase 1: One Pv, One Pf TBV, 20 Pf PEV & Pf BSV
Introduction to RTS,S

- Development partnership is GSK with PATH Malaria Vaccine Initiative (MVI) with funds from Gates Foundation to MVI

- $200 million funds so far from BMGF and over $200 million from GSK over last 20 years
Malaria-Hep BsAg fusion VLP
Lyophilised
Point-of-use reconstitution with AS01 adjuvant: liposomes, MPL, QS21
Terms of Reference: “Provide recommendations to the secretariat of GMP and IVR on:

1) clinical trial data necessary and desirable for evaluation of public health impact of a malaria vaccine in malaria endemic countries, and

2) the design, conduct, analyses and interpretation of Phase 2, Phase 3 and Phase 4 trials of malaria vaccines.”
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
European Medicines Agency Observer attends
Three Previous JTEG meetings


Meeting 2 Nov 2010: Feedback on regulatory submission plans and Phase 4 study design

Meeting 3 23-24 Feb 2012: Review of Phase 3 data to date, planning for first data on target population to be received Q4 2012
Fourth JTEG

- During Q4 2012
- In confidence meeting, for JTEG to review second set of results
Phase 3 multi-centre efficacy trial

11 participating centres in 7 African countries

Also Nigeria, 2nd site in Malawi

WHO Recommendations: Vaccine. 2007 Jul 9;25(28):5115-23
Phase 3 Trial Study design

- Designed to provide both data for filing and to support assessment of public health impact for possible implementation
- 15,460 children in 2 age categories:
  - 6 to 12 weeks in co-administration with infant vaccines
  - 5 to 17 months
  - 0,1, 2 month schedule
- 1:1:1 randomisation to include an arm with booster immunization at 20 months
- Total trial duration per child 32 months

Hum Vaccin. 2010 Jan;6(1):90-6
First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

First or only episode

\[ \text{VE} = 55.8\% \ (97.5\% \ CI \ 50.6 \text{ to } 60.4) \]

All episodes of malaria

\[ \text{VE} = 55.1\% \ (95\% \ CI \ 50.5 \text{ to } 59.3) \]
SEVERE MALARIA (per protocol analysis)

Case-driven analysis – both age groups (12961 children) (263 cases)

VE = 34.8% (95% CI 16.2 to 49.2)
Ave. duration of follow-up (5-17mo) 16mo (Range 0-22mo)
(6-14wks) 7mo (Range 0-15mo)

5-17mo followed for 1 year (4296 children) (113 cases)

VE = 47.3% (95% CI 22.4 to 64.2)

DEATHS

151 deaths, balanced between groups (10 deaths attributed to malaria)
A Per-Protocol Population

Proportion of Participants with Malaria

Control vaccine
RST,S/AS01

P<0.001 by log-rank test

No. at Risk
RTS,S/AS01 2830 2602 2279 1885 698
Control vaccine 1466 1137 909 712 274

Months since 14 Days after Dose 3
Variation in efficacy with time

- Analyses performed by trial team support waning of efficacy during the first year in the 5-17 month age group for first or only episode of malaria.

- In work by Paul Milligan (JTEG member) and others, under many scenarios heterogeneity of risk will tend to lead to underestimates of vaccine efficacy over time.

- Efficacy against all episodes of malaria with time is more relevant to public health, but has not been presented.
**Efficacy with time for all episodes of malaria**

<table>
<thead>
<tr>
<th>Time period</th>
<th>Vaccine group</th>
<th>Control group</th>
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<tbody>
<tr>
<td></td>
<td>Malaria episodes</td>
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This additional analysis requested by JTEG will be provided with month 32 analyses in late 2014.
A reactogenic vaccine with 31% vs 13% fever cases within the 7 days after vaccination in the 5-17 month age category in those receiving RTSS compared to controls.

Excess frequency of about 1 in 2000 vaccine doses for febrile seizure was observed in 7 days after vaccination.
First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

The RTS,S Clinical Trials Partnership*

- 19 cases of meningitis versus 2 in controls (but note 2:1 randomization)

- Investigator defined, some with no microbiological confirmation.

- No temporal association of meningitis cases with vaccination.

- IDMC assessment: no safety concern at this time
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**RTS,S: Availability of Further Phase 3 results**

- **Phase 3 efficacy study**
  - *Children 5-17 months* 12 M post dose 3
  - *Infants 6-12 weeks, EPI* 12 M post dose 3

**Public health efficacy endpoints in both age-groups**
- 30 M post dose 3
Reporting and Analysis

- GSK/MVI have provided statistical analysis plans for the 12-month analyses in the two age groups.
- GSK/MVI have agreed to perform additional analyses at the request of WHO, in late 2014 at the time of the 32 month analyses.
- JTEG will provide guidance to WHO on the nature of these additional analyses including all episodes of malaria broken down by time period, by site and seasonality.
Reporting and Analysis

- The details of GSK/MVI’s plans for the analyses at month 32 have not yet been presented to WHO.

- An additional set of analyses at month 20 (18 months post dose 3) in both age groups will occur if a protocol amendment passes all ethics committees. Application in process.
Phase 2 results

- Earlier studies done with different adjuvant, AS02.

- Phase 3 studies with RTS,S/AS01 giving superior efficacy in human challenge model, and higher antibody and cell-mediated immune responses.

- Longest term efficacy follow-up from Phase 2 studies is from Mozambique with RTS,S/AS02.

- Efficacy from this study was 26% (95%CI 12 to 37) for all episodes of malaria over 43 months following 3 doses in children aged 1-4 years at vaccination.
Phase 2 Efficacy

RTS,S/AS01E Adjusted Vaccine Efficacy Against All Episodes of Clinical Malaria

Adjusted Vaccine Efficacy

Follow Up Time (Study Months)

Age at Recruitment
- 6-10 weeks
- 5-17 months
Intended target population

- GSK have stated that the initial target group is infants aged 6, 10, 14 weeks
- The Phase 3 trial conducted in this age group in co-administration with DTwP/HepB/Hib and OPV
- Measles and yellow fever co-administration data has also been generated
GSK/MVI Responses to Requests

- GSK/MVI have responded to multiple areas of guidance from WHO
  - Phase 4 design: include DSS sites, liaison with national authorities, and baseline data
  - Information-sharing: JTEG meeting held in-confidence prior to public release of infant data. Phase 3 Trial Protocol and Study Report shared with WHO.
  - Published methods papers at WHO’s request
Messages from WHO

- Detailed Q&A available on website

- Key message: the WHO policy decision in 2015 will reflect data available up to 2014

- Key message: RTS,S will be considered as an addition to, not a replacement for, existing preventive and treatment measures

- WHO presentations at AFRO subregional and national meetings for last 2 years on these issues
Further communications

- Plans to increase intensity of communications work depending on Q4 2012 data to include the following

- Meaning of 50% efficacy in this context: many vaccinated children would still experience clinical malaria, must use other preventive measures, consider malaria diagnosis when febrile and seek treatment

- Communities will need to understand meaning of 50% efficacy
Timing for policy recommendations

- JTEG advised that 32 month analyses are required prior to possible policy recommendation.

- Following review of these analyses in late 2014, JTEG will draft candidate policy recommendation for review by MPAC and SAGE in early 2015.

- Given apparent waning of efficacy for first or only episode of malaria JTEG has highlighted the need for further analyses to explore duration of protection in the full trial results to be received in 2014.
Discussion, Questions and Comments