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

Peter Smith, Chair JTEG

(Vasee Moorthy: WHO staff)
JTEG members

- Chair, Peter Smith
- Fred Binka (MPAC member)
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Observers from European Medicines Agency and National Regulatory Agencies of Kenya, Tanzania, Ghana, Malawi
Pathways for WHO Policy Recommendations on Malaria Vaccines

Industry and other partners

GACVS

MALVAC

JTEG

Vaccine safety

SAGE

MPAC

Regional Consultations

Recommendations

WHO DG

WHO Position Paper

Country Decision making

Vaccines Dept. (IVB)

Regional Consultations

Country briefings

GMP

Input

Request for review of evidence
Design of RTS,S Trial

- **5 to 17 months**
  - RTS,S
  - RTS,S
  - control

- **6 to 12 weeks**
  - RTS,S
  - RTS,S
  - control

- **RTS,S**
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- **RTS,S**
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- **RTS,S**
- **control**
Vaccine efficacy over 18 months

<table>
<thead>
<tr>
<th></th>
<th>VE* in children [95%CI]</th>
<th>VE* in infants [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical malaria</td>
<td>46% [42 to 50]</td>
<td>27% [20 to 32]</td>
</tr>
<tr>
<td>Severe malaria</td>
<td>36% [15 to 51]</td>
<td>15% [-20 to 39]</td>
</tr>
<tr>
<td>Malaria hospitalization</td>
<td>42% [29 to 52]</td>
<td>17% [-7 to 36]</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>19% [9 to 28]</td>
<td>6% [-7 to 17]</td>
</tr>
</tbody>
</table>

- For every 1,000 children/infants, vaccination averted:
  - In children (ITT): 37 to 2365 [average: 829] cases of clinical malaria; -1 to 49 [average:18] cases of severe malaria
  - In infants (ITT): -10 to 1402 [average: 449] cases of clinical malaria; -13 to 37 [average: 6] cases of severe malaria
Vaccine efficacy against clinical malaria over 18 months

<table>
<thead>
<tr>
<th>Time since vaccination</th>
<th>VE* in children [95%CI]</th>
<th>VE* in infants [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>68% [64 to 72]</td>
<td>47% [39 to 54]</td>
</tr>
<tr>
<td>6-12 months</td>
<td>41% [36 to 46]</td>
<td>23% [15 to 31]</td>
</tr>
<tr>
<td>12-18 months</td>
<td>26% [19 to 33]</td>
<td>12% [1 to 21]</td>
</tr>
</tbody>
</table>

- Results for 1 year follow-up after booster dose at 18 mo. will be available later in 2014
- Will booster dose restore efficacy to level seen after primary course?
- Will decline in efficacy after booster dose mirror that seen after primary course?
- Will booster dose to those with primary course in infancy bring efficacy up to level of that seen in those who received primary course as child?
**Pivotal Phase III RTS,S malaria vaccine efficacy trial**

- Phase 3, randomized, controlled, double-blind trial conducted in 11 centers in 7 African countries
- 15,460 children enrolled in two age categories:
  - Children aged 5–17 months
  - Infants aged 6–12 weeks
- Co-primary endpoint: Vaccine efficacy against clinical malaria during 12 months of follow-up in each age category.
- Wide range of malaria transmission intensities (0.01 to 2.0 clinical episodes per child per year)
- Efficacy measured in presence of other malaria control interventions: 86% ITN coverage in 6-12 weeks and 75% in 5-17 months
Vaccine efficacy over 18 mo by site – all episodes of clinical malaria

<table>
<thead>
<tr>
<th>Children 5-17 months</th>
<th>Infants 6-12 weeks</th>
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<tbody>
<tr>
<td>Kilifi</td>
<td>Kilifi</td>
</tr>
<tr>
<td>77.4</td>
<td>-56.5</td>
</tr>
<tr>
<td>26.4</td>
<td>-598.9</td>
</tr>
<tr>
<td>93.1</td>
<td>65</td>
</tr>
<tr>
<td>61.1</td>
<td>48.5</td>
</tr>
<tr>
<td>34.8</td>
<td>-6.9</td>
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<tr>
<td>76.8</td>
<td>75.2</td>
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<tr>
<td>42.5</td>
<td>20.2</td>
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<tr>
<td>11.2</td>
<td>-31.8</td>
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<tr>
<td>62.7</td>
<td>51.6</td>
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<tr>
<td>65.4</td>
<td>8.7</td>
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<tr>
<td>46.2</td>
<td>-112.5</td>
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<tr>
<td>77.7</td>
<td>60.8</td>
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<td>40.3</td>
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<td>63.8</td>
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<td>40.2</td>
<td>19.5</td>
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<td>28.5</td>
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<td>49.9</td>
<td>36.9</td>
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- No clear variation in efficacy according to transmission level.
- Benefit of the vaccine (episodes prevented) likely to be greatest in high transmission settings.
- 3-fold higher immunogenicity for anti-CS IgG in older age group.
  - Immunological immaturity?
  - Interference from maternal antibodies?
  - Interference from co-administration with other vaccines?
Key findings: safety

- No new safety issue has arisen since the previous 2 sets of results from the Phase III trial
- To be assessed by Global Advisory Committee on Vaccine Safety
In general the efficacy is superior in the 5-17 month age group compared to the 6-12 week age group.

Efficacy is waning substantially by 18 months, and hence the booster dose data will be important for the policy assessment.

The increased frequency of febrile convulsions and meningitis in vaccine versus control groups will be assessed by the Global Advisory Committee on Vaccine Safety.
If any recommendations for use are proposed by JTEG for SAGE/MPAC decision, it is likely that JTEG will propose a cut-off for the lower limit of transmission below which recommendations for use are not advisable.

JTEG notes that until data are available for VE against infection in a wider population age range, JTEG cannot propose any recommendations for purposes of transmission reduction.
JTEG Assessment of Results

- JTEG further noted that any proposed policy recommendations in 2015 will be geographically restricted to sub-Saharan Africa, as no RTS,S data are available from other malaria endemic regions.

- In the scenario that recommendations for use are made, post-licensure district-scale studies appear desirable to better characterise risk/benefit and to allow initial recommendations to be broadened or narrowed through use of a larger dataset than will be available in 2015.
Key analyses expected in 2014

• 30 months follow-up
• Effect of a booster dose at 18 months
• Analyses of the effect of seasonality
• Breakdown of efficacy within 5-17 month age range
• Further analyses as requested by WHO.
Public Health Impact/Cost Effectiveness

- Ongoing work to assess range of predictions between 4 modeling groups, given harmonized inputs.

- Consensus indications of predicted cost-effectiveness of RTS,S/AS01 will be available by time of policy decision.

- 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.
Available data indicates that the demonstrated efficacy is in the presence of a high level of use of insecticide-treated bednets.

Thus any policy recommendations will include wording on continued scale-up of preventive, diagnostic and treatment measures in the context of any RTS,S introduction.
Planned EMA filing date June 2014

Earliest EMA regulatory decision timing is early Q3 2015.

Tentative MPAC/SAGE date ?Oct 2015 – could be deferred if regulatory timings lengthen

Possible WHO PQ ?Q1 2016 assuming PQ submission in Oct 2015.
Key Messages from WHO

- Detailed Q&As available on WHO website

- RTS,S/AS01 will be evaluated as an addition to, not a replacement for, existing preventive and treatment measures

- 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.