WHO Immunization, Vaccines & Biologicals (IVB)/Global Malaria Programme (GMP)

Report of the Fourth Meeting of the Joint Technical Expert Group (JTEG) on Malaria Vaccines in Pivotal Phase 3 Trials and Beyond

9-10 October 2012

Geneva, Switzerland

This report presents a summary of the discussions by the committee members and recommendations proposed by the JTEG.

LIST OF ABBREVIATIONS

ART: Anti-retroviral therapy
ASTMH: American Society of Tropical Medicine & Hygiene
CS: Circumsporozoite
DOI: Declaration of interest
DTwP/HepB/Hib: Diptheria, tetanus, whole cell pertussis, hepatitis B, *H. influenzae* type b
EMA: European Medicines Agency
EPI: Expanded programme on immunization
GSK: GlaxoSmithKline
MPAC: Malaria Policy Advisory Committeee
MVI: Malaria Vaccine Initiative
OPV: Oral polio vaccine
PATH: Program for Appropriate Technology in Health
SAE: Serious Adverse Event
SAGE: Strategic Advisory Group of Experts on Immunization
VE: Vaccine Efficacy

Joint Technical Expert Group (JTEG) Meeting
October 10, 2012
Summary of Topics Discussed and Key Points

Session 1. Welcome, Meeting Background and Objectives/Introduction from secretariat

This was the fourth meeting of JTEG. Objectives were outlined:

- Discussion with the Malaria Vaccine Development Partnership to help interpret the new data,
- To consider additional work required by the Secretariat to prepare for upcoming data,
- To determine if additional analyses should be requested,
- To receive JTEG input on external messages that will be available around the release of new data.

With the new results, WHO policy process remains the same: no policy decisions will be made prior to 2015, based on data to become available in late 2014, and on additional analyses to be performed at WHO's request. All results are confidential and should not be discussed outside the meeting. Submitted DOIs were deemed not to represent real or perceived conflicts requiring exclusion of any members.

Session 2. Presentation of Phase III data

Overview and Clarifications

Phase III study results from two analyses were shared:

- efficacy against clinical and severe malaria, and SAEs in 6,537 infants in the 6-12 week age group with one year of follow up, and
- immunogenicity for anti-CS, unsolicited AEs and rash, and solicited reactogenicity in 2200 (200 at each site) in the 6-12 week age group.

Neither numbers of children enrolled nor numbers of malaria cases occurring were distributed evenly across sites. For example, two sites taken together were responsible for over 50% of total malaria cases from the 11 sites in the older age group (5-17 months of age).

It was clarified that all analyses are stratified by site, in the Cox regression analyses. A test for heterogeneity of efficacy by site was not performed. The protocol was written such that site-specific effects would be examined only at the end of the study. The Partnership stated that this reasoning was based on an assumption that there would be insufficient cases for earlier site-specific analyses, although the actual numbers of cases to date have been higher than the pre-trial assumptions about incidence rates. It was clarified that in the graphs of cumulative malaria incidence, the drop in the denominator at 12 months was due to some participants having their one-year follow-up at slightly less than 12 months at the time of this analysis.

Changes in VE with time since vaccination have not been analysed for all episodes of malaria but may be incorporated into analyses in 2014. For severe malaria, 65 of the 104 cases included were analyzed in the February 2012 presentation of results.

Key Discussion Points

Potential explanations for the results were discussed, as were strategies for aiding in their interpretation. It was posited that subdividing the 5-17 month age group help clarify the differences seen between the 6-12 week and 5-17 month groups. There was much discussion about the possibility of heterogeneity of efficacy by site, and what bearing the lack of analysis examining such heterogeneity may have on interpreting the current data. JTEG indicated having site or transmission strata-specific VE estimates was very important, as the results from one or two high transmission sites could greatly affect the pooled estimate of effect. GSK/MVI Partnership stated that for any additional analyses or altered timing, the protocol must be amended, and this must be reviewed by many ethical and scientific review committees. An amendment that will include VE by site (for 18 months follow up) has been submitted and, if approved, will allow for these analyses to be done by 2013[Post-meeting note March 2013: this amendment has passed. Thus all analyses dependent on the amendment will occur in 2013]. It was clarified that even this amendment will not explore VE by site over 12 months. VE will be provided by site only over the full 18 month period, not including any breakdown by time period. The VE breakdown by time period will only be available in late 2014 [Post-meeting note March 2013: the 2013 analyses will include VE by site and broken down by time period, as GSK/MVI included these requests in line with JTEG's feedback].

The substantial difference in the pooled VE estimate between the older and younger age groups was noted, and it was suggested that one possible partial explanation could be that if VE wanes with time since vaccination, then the period of highest VE would coincide with lowest incidence of malaria due to the reduced malaria risk in young infants related to maternally acquired antibodies. Another difference between age groups discussed was that the older age group was enrolled more quickly while infants were enrolled over a longer period. Thus seasonality of malaria could impact VE in the 2 age groups differently. Furthermore, different sites contributed different proportions of cases for the two age groups. Indeed two sites did not contribute any children to the previously published analysis in 5-17 month olds.

It was observed that the Kaplan-Meier curves appear different in Phase III compared to Phase II data; one possible reason was speculated to be the different transmission levels. Transmission in some sites in the Phase III trial is much higher than in any Phase II studies.

In the Phase III trial, seasonality of malaria was not taken into account in the analyses to date. Most sites show some peaks in malaria but are considered perennial, with the exception of Nanoro in Burkina Faso where malaria is both highly seasonal and there is high transmission. It was proposed that analyses of the effect of seasonality on vaccine efficacy be included in future analyses. Broader issues were also raised, such as whether RTS,S should be delivered in the routine EPI schedule or potentially outside this schedule.

Discussion of Phase III data including available data on alternative schedules, including 4 doses.

Overview and Clarifications

Key differences between the 5-17 month age group and 6-12 week age group were highlighted including:

- Approximately three-fold higher anti-CS IgG responses to vaccination in the older age group
- Co-administration with DTwP/HepB/Hib and OPV in the younger age group
- Higher proportion with presence of maternally acquired antibodies to the CS sporozoite antigen in the younger age group (as measured by pre-vaccination anti-CS IgG)
- Greater naturally acquired immunity, and higher previous exposure to malaria in the older age group
- Prior Hepatitis B priming at the time of RTS,S/AS01 vaccination in the older age group (as part of prior pentavalent immunization)

There has not been an examination of an association between immunological response and birth weight or other anthropometric indicators, but this can be done at the end of the study as the data are being collected. There are few data looking at the correlation between anti-HepB and anti-CS. There is some evidence from phase II trials that co-administration with DTwP/Hep B/Hib and OPV may adversely affect immunogenicity. The potential role of HepB as a prime for the anti-CS response was also discussed. A JTEG member pointed out that kinetics of decline of antibody responses could differ by age even when peak responses do not differ. Decline can be more rapid in infants compared to older children with some other vaccines.

Key Discussion Points

The distribution of children and cases is different between the 2 age groups and thus the pooled VE results for each of the 2 age groups are not strictly comparable. Site specific weighting in the analyses presented to date is imposed by the Cox regression model.

An important question still being explored is the relationship between anti-CS titers and vaccine efficacy. No established correlate of protection currently exists for RTS,S/AS01, but a sense of the correlation (or lack of correlation) between titer and risk of disease would be helpful from the Phase III data. Challenge studies and Phase II field trials have found consistent statistically significant associations between total IgG titers and vaccine efficacy against infection but not consistently for morbidity.

With this vaccine, it appears that the most useful immunological measure for associating with efficacy may not be peak titer, but IgG titers at the time of infection. Antibody levels at the time of infection could vary by age group. Because of the short time interval before the sporozoite reaches the liver, there is insufficient time to mount an anamnestic immune response. The Olutu et al. study in Kilifi was raised exploring the relationship between CS antibody titers and protection to assess whether it was a linear or a stepwise function/threshold effect. In that

particular setting, it appeared to be a step-wise function. However, these results have not been confirmed in other settings.

The possible contribution of immune interference from EPI vaccines was discussed. A JTEG member stated that, even in 2-week staggered schedules (done with AS02 studies), interference can occur. Adjuvant use in different vaccines given could also have an effect, but since all co-administered parenteral vaccines given were alum-based, there are unlikely to be concerns about non-specific effects that would apply differently in the studies under discussion. There is evidence that RTS,S does not affect measles titers, but no evidence was available at the meeting on the effect of the measles vaccine on RTS,S response. A JTEG member indicated that interference between RTS,S and measles is unlikely, due to the contrast between live and subunit vaccine kinetics for induction of immunogenicity.

Further analyses of association between immunogenicity and pre-existing maternal antibodies could be informative.

The issue of timing between vaccination and infection was raised as an additional complexity that has not been fully looked at. The time interval between completion of the vaccination schedule and seasonal transmission is relevant if efficacy wanes. The relationship between vaccination and seasonality is likely different by age group given the rapid enrollment of the 5-17 month age group and the longer enrollment of 6-12 week age group.

There was a discussion about RTS,S kinetics of immunogenicity, suggesting that the vaccine does not appear to induce high, long-lived plateaus of immunogenicity, with boosters perhaps likely to provide multiple primary vaccination kinetics. The reasons for this are unclear, although it was raised that with RTS,S the malaria response may be subdominant to the Hepatitis B response (note that a plateau of anti-Hep B IgG is obtained with RTS,S vaccination).

The Partnership was asked whether there were plans to test RTS,S in adults. For the moment the Partnership is prioritizing infants. The site-specific analyses should give a sense of what the potential role could be in a range of settings. Thus, the data to become available in late 2014 will only allow assessment of direct benefits against morbidity, but there may be advantages to generation of data in broader age ranges, so that whether or not there may be a role for RTS,S/AS01 as a contribution to elimination in some settings can be assessed after 2015.

Availability of next data packages

Overview and Clarifications

Assuming the current protocol amendment is approved, 18 month post dose 3 results are expected in 2013 and will include efficacy pooled and by site over 18 months. The statistical analysis plan is under development and will be sent to JTEG for input in the beginning of 2013. The last child's last visit will occur in December 2013 (all children are followed for at least 12 months post booster). The final analyses in late 2014 will include WHO pre-specified requests, i.e. additional analyses that WHO indicated would be necessary for a policy decision in 2015. A

single-blind extension has been arranged to follow up all children to 49 and 41 months post dose 1 in the 5-17 month age category and 6-12 week age category, respectively.

Key Discussion Points

There was intense discussion about the process for requiring an amendment, timelines and regulatory limitations to doing unplanned analyses. It was clear that additional clarification on all of these issues would be of use.

JTEG has previously emphasized the need for longer follow up. However, if a decline in vaccine efficacy is apparent in one year of follow up and there is evidence of low vaccine efficacy after a year or two, the pressure to follow participants longer is reduced.

Update on regulatory status & Phase 4 plans

Overview and Clarifications

Prior to the availability of these new data to the Partnership, much scenario planning and decision tree analysis had already been done by GSK/MVI in anticipation of the results. Both co-primary endpoints were met, but many questions remain as to what the optimal indication and the schedule (EPI co-administration with DTP1-3 or alternative) would be, which are important considerations for filing. The timing of regulatory submissions are under assessment. Plans for Phase IV studies are also under revision, as they will depend on the results of the Phase III trial and the indication of the vaccine.

There was clarification about the impact modeling, which is based on the Swiss Tropical and Public Health Institute model and has been reviewed by a joint QUIVER/JTEG group. A JTEG member expressed caution in some of the assumptions used by the mathematical models [Post-meeting note: a second WHO meeting to assess the status of public health impact and cost-effectiveness models for malaria vaccines is being held in May 2013].

Key Discussion Points

There was much discussion about the pros and cons of doing additional analyses not yet specified in the data analysis plan. Conducting a study in the context of submission to a stringent regulatory authority was noted to add a layer of complexity that makes data exploration more difficult. There are opportunities for scientific consultations with European Medicines Agency (EMA), but the Partnership has concerns that actions taken without a careful approval process could invalidate the file when submitted to a regulatory agency. Because of the time it takes to go through the approval process, quick answers cannot be easily obtained despite the potential usefulness of additional analyses with interpretation of the latest results. Although there do not appear to be ethical issues with the requested clarifying analyses (e.g. site-specific data), recently an ethical committee raised questions to even the 18 month analysis in the amendment, so it is not a given that such unplanned analyses would be approved [Post-meeting note March 2013: all ethical committees and national regulatory authorities did approve the amendment]. This is the only pivotal Phase III trial, and it is important not to call into question its integrity. At the same

time, waiting a year for the ability to do new analyses is a highly inefficient way to explore the important scientific questions raised by these results. It would be an ethical problem, it was argued, to have a vaccine that could save lives but was withheld because analyses were not done in a timely fashion that could have been. Furthermore some analyses could be done now, which could lead to generation of additional data that could accelerate timelines.

There were also discussions of the potential impact on sites if site-specific vaccine efficacies were known. Theoretically, this knowledge could impact how investigators at a site follow up their patients. Many meeting participants did not think this would be a problem, but did acknowledge the theoretical possibility.

The Partnership agreed to consider if there could be a different course of action that would satisfy JTEG, regulatory agencies, involved scientific and ethical review committees, and the Partnership to conduct analyses that would allow for better understanding of the latest results. It was noted that the Partnership's decision to defer the regulatory submission, will also delay policy recommendation timelines by 6 months.

Given the many questions that are raised by the latest results, it was suggested that publishing these results without further context and explanation could be misleading and confusing to the scientific community. GSK considers it is very important to publish data when they are available so no one accuses them of with-holding data, particularly data that are different than what was hoped for.

In summary, there was strong support for looking at ways to improve flexibility for additional analyses that may help explain results or suggest further analyses or studies that are needed. Delay of these additional analyses could postpone timelines and access to the vaccine, depending on the results not yet to hand. It was appreciated that regulatory considerations are paramount. There was frustration that the publication speculates on questions that could be answered by analyses that could be performed on available data.

Review of status of other Phase III and ancillary studies

Malaria Transmission Intensity Study

Overview and Clarifications

Annual cross-sectional surveys will collect blood from 800 randomly selected children and adults for four years at eight sites. The results after one annual survey were presented. The peak prevalence of *P. falciparum* infection varied from over 60% to less than 5% across the range of sites, with different age patterns for prevalence of infection in the different sites. Bednet coverage also varied by site and impacted the odds of parasitemia differently by site. The results confirm the large heterogeneity in transmission intensity by site.

Key Discussion Points

The transmission intensity study is a useful contribution that should facilitate extrapolation from the Phase III trial to non-trial settings in terms of transmission intensity. Such extrapolation may be necessary at the policy stage if VE varies with transmission intensity.

Lot-to-lot consistency study

Overview and Clarifications

The first primary objective was to establish consistency of immunogenicity between three consecutive commercial scale lots of RTS,S/AS01, and the second primary objective was to establish non-inferiority of commercial scale lots to the pilot scale lot. Both were demonstrated.

Key Discussion Points

It was pointed out that the antibody titers seen in this study were lower than seen in other studies of the same age group. The study population was 5-17 month old Nigerian children thought to be living in an area of fairly high malaria transmission (although no data on the transmission intensity was presented). There may be several reasons that immunogenicity will vary by site or even within a site. These sites were chosen in Nigeria to support a filing that would include Nigerian data, which is required for licensure in that country.

Hepatitis B indication, co-administration with Rotavirus and S. pneumoniae

Overview and Clarifications

This study, the goal of which is to establish the non-inferiority of the Hepatitis B response, is fully enrolled and in progress. Secondary objectives include establishing non-inferiority of immunogenicity in co-administration with pneumococcal and rotavirus vaccines. The results should be available in 2013.

Study in HIV-positive children

Overview and Clarifications

The primary goal of this study is safety for 14 months post dose 1. Two sites in Kenya are participating with a total of 200 study participants, and results should be available in 2013. Children are diagnosed before entering the study, and thus are on ART treatment. There is a subset of children in the Phase III trial who are now known to be HIV positive but were not diagnosed at the time of vaccination and were not on treatment. A case-control study will be done to look at safety and immunogenicity in this group of 125 children.

Immunology study

Overview and Clarifications

This study will follow the model of the HIV RV144 prime boost vaccine trial in Thailand to better understand vaccine-induced protection against malaria and identify a correlate of protection. Three working groups are involved in drafting a proposal for the study, which will be thoroughly reviewed by a number of experts. The study is framed in the larger systems biology context. Because samples are taken at a fixed time, they are not obtained at the time when infection occurs.

Key Discussion Points

It was noted that having serology at the time of infection would be helpful given the assumption that the immunological response changes over time since vaccination. Such samples will not be available, and analyses will be done using fixed timepoints for the sampling.

Genotyping study

Overview and Clarifications

The aim of the study is to better understand the mechanism of action of RTS,S/AS01 and to evaluate whether the vaccine puts selective pressure on parasites resulting in variants that may be resistant to the vaccine or lead to a change in the number of parasite types. The study, to be performed in collaboration with the Harvard School of Public Health, will occur post-unblinding of the pivotal Phase III trial.

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 [Post-meeting note March 2013: some recommendations listed here were taken into account by GSK/MVI when the list of analyses to be conducted in 2013 was finalized] . • 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.

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