RTS,S MEDICAL AND SCIENTIFIC QUESTIONS & ANSWERS

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Disclaimer

The primary focus of this resource is to be an internal training tool for RTS,S malaria vaccine candidate, containing related data in the format of a Q&A for Medical Affairs personnel. Information presented here is not for external distribution.

Whilst this document can be inspirational for reactive responses to experts or medical enquiries, local regulations, the GSK Code of Practice, scientific engagement principles and/or medical information processes should be followed appropriately.

Please Note

- For media enquiries, please refer to the specific reactive Q&A for Media Enquiries and notify the Global Pipeline Communications team before you respond to a request for an interview so that they can help you to prepare (contact person: Aoife Pauley at aoife.x.pauley@gsk.com).
- The vaccine RTS,S/AS01 has completed phase 3 clinical program and positive regulatory assessment from the European Medicines Agency, but is not yet authorized for marketing in any country. The RTS,S vaccine is being developed in Public Private Partnership with PATH-MVI, as an additional tool to be added to the currently available malaria preventive interventions and for implementation through the national immunization programs in malaria endemic regions in sub-Saharan African countries.
- When referencing clinical data on RTS,S any statements should be prefaced by "In this study...", to make it clear that it is too early to make any general statement on the vaccine profile outside the context of the ongoing clinical trails.
- Have you found what you were looking for? If you have any suggestions for information which should be included in this tool please contact us at the following address: Carys Calvert at carys.calvert@gsk.com.

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What is the efficacy of RTS,S in infants 6-12 weeks old at first vaccine dose?

Key messages:

- **Over the first year after vaccination, RTS,S reduced the number of malaria cases in infants by a third.**
- **Vaccine efficacy as highest shortly after vaccination, but could be enhanced by a 4th dose**
    - Vaccine efficacy waned over time, but the VE against clinical malaria remained statistically significant over the 3 years follow up period and was enhanced by a 4th dose.
- Vaccines were given in co-administration with routine EPI vaccines (DTPw-HepB-Hib, OPV)
- Efficacy results were achieved in context of good access to health care and on top of existing malaria interventions, such as insecticide-treated bed nets used by 86% of study participants, demonstrating that RTS,S can provide protection in addition to that provided by existing malaria control interventions.

More detailed information:

The co-primary objective of the trial demonstrated a vaccine efficacy of 31% (97.5%CI: 24;38) over the first 12 months after dose 3 (ATP cohort) against the first episode of clinical malaria. [(a)] These results are not aligned with phase II results where efficacy against first episode of clinical malaria over 12 months was 62% [95% CI: 36 to 77] [(d)]

In the Phase III efficacy trial, VE was similar between the According-to-protocol and Intention-to-treat populations. [(a,b,c)]

The difference in VE between study sites was not statistically significant. [(b)]

VE waned over time, and although it remained statistically significant for clinical malaria until study end, no efficacy was observed during the last study period (month 21 to study end) in the absence of a booster dose. No significant protection was seen against severe malaria beyond the first year of follow-up, whether with or without a fourth dose [(d)]

Vaccine efficacy (as described in European SmPC [(e)])	**clinical malaria** (95% CI)	**severe malaria** (95% CI)	**hospitalisation caused by malaria** 95% CI)
Over 12 months follow-up from dose 3 (ATP* cohort, N = 6003)	33% (26; 39)	37% (5; 58)	32% (7; 50)
Over 18 months follow-up from dose 3 (ATP* cohort, N=6003)	27% (20; 32)	15% (-20; 39)	17% (-7; 36)
3 doses only (ATP* cohort, N=5997)			
Over 30 months follow-up from dose 3	20% (13; 27)	11% (-22; 35)	10% (-15; 30)
Over 36 months follow-up from dose 3**	18% (11; 25)	13% (-17; 35)	13% (-9; 31)
3 doses + 4th dose (ATP* cohort, N=5997)			
Over 30 months follow-up from dose 3	28% (22; 34)	17% (-14; 40)	25% (3; 42)
Over 36 months follow-up from dose 3**	27% (21; 32)	21% (-7; 42)	27% (7; 43)

*ATP: Subjects who received all vaccinations According-To-Protocol procedures within specified intervals, with period at risk starting 14 days after dose 3, N= total number in all 3 study groups
** All subjects were followed up over 32 months post dose 1. In addition, follow-up continued until Dec 31, 2013 leading to a median follow-up of 38 months for infants post dose 1.

VE was not demonstrated against all-cause mortality, malaria mortality, hospitalized pneumonia, septicaemia or prevalent anaemia, nor was there a detectable effect on nutritional status or growth. Case fatality rate for malaria and all-cause mortality was low [(b)]. This may, in part, be explained by the very high standard of care throughout the trial and low mortality.

a. *The RTS,S Clinical Trial Partnership. NEJM 2012, 367: 2284-95.*

b. *RTS,S Clinical Trial Partnership. PloS Medicine 2014; doi/10.1371/journal.pmed.1001685*

c. *The RTS,S Clinical Trial Partnership. The Lancet, 2015. dx.doi.org/10.1016/S0140-6736(15)60721-8*

d. *Asante, KP. et al, Lancet Infect Dis 2011; 11:741-9.*

e. *European Medicines Agency, ema.europa.eu/ema/*