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 children 5-17 months old at the first vaccine dose?

Key messages:

- **Over the first year after vaccination, RTS,S reduced the number of malaria cases in children by half.**
- **Vaccine efficacy was 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 4 years follow up period and was enhanced by a 4th dose.
- 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 78% 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 56% (97.5% CI: 51-60) over the first 12 months after dose 3 (ATP cohort) against the first episode of clinical malaria in the first 6000 children.[a] These efficacy results are aligned with phase II POC results where the vaccine efficacy against the first episode of clinical malaria in 5-17 months over 12 months was 39 % [95% CI: 20-54].[d]

In the Phase III efficacy trial, VE was similar between the According-to-protocol and Intention-to-treat populations as well as across case definitions (>0 to >5000 parasites/µl). [a,b,c]

Vaccine efficacy was similar in children vaccinated at 5-11 months of age or 12-17 months of age. [c] Vaccine efficacy varied between the 11 study sites.[b] This heterogeneity was statistically significant over the first 20 months of follow-up (range 41-70%) [b], but not when compared over the entire study period. [c]

Vaccine efficacy waned over time ($p<0.01$). [b] However, efficacy remained statistically significant for clinical malaria over the entire study period. [c]

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=6880)	51% (47; 55)	45% (22; 60)	48% (35; 59)
Over 18 months follow-up from dose 3 (ATP* cohort, N=6885)	46% (42; 49)	36% (15; 51)	42% (29; 52)
3 doses only (ATP* cohort, N=6918)			
Over 30 months follow-up from dose 3	34% (29; 39)	2% (-28; 25)	18% (1; 32)
Over 46 months follow-up from dose 3**	26% (21; 31)	-6% (-35; 17)	12% (-5; 26)
3 doses + 4th dose (ATP* cohort, N=6918)			
Over 30 months follow-up from dose 3	46% (42; 50)	32% (10; 50)	40% (26; 52)
Over 46 months follow-up from dose 3**	39% (34; 43)	29% (6; 46)	37% (24; 49)

*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 48 months for children post dose 1.

In children not receiving a booster dose, a negative VE against severe malaria was observed during the follow-up period between month 21 and study end. (-44% [95% CI: -119 to 4]). [(c)] This temporary increase in incidence of severe malaria in children receiving a primary schedule of RTS,S (73 severe malaria cases out of 2,057 children) as compared to controls (48 out of 2,051) could be a chance finding, but could also be compatible with a rebound effect, ie age shift. Such rebound effect has been noted after withdrawal of other malaria preventive interventions, eg seasonal malaria chemoprophylaxis (SMC).

Vaccination with RTS,S/AS01 also significantly reduced overall hospital admissions, severe anaemia and the need for blood transfusion, with these protective effects being more marked in those who received a 4th dose.

VE was not demonstrated against all-cause mortality, malaria mortality, hospitalized pneumonia, septicaemia or prevalent anaemia, childhood nutritional status or growth.. This may, in part, be explained by the very high standard of care throughout the trial and low mortality [(b,c)]

a. *The RTS,S Clinical Trial Partnership. NEJM 2011, 365: 1863-75.*
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. *Lusingo, J, PLoS ONE 2010, 5(11): e14090. Doi:10.1371/journal.pone.0014090.*
e. *European Medicines Agency, ema.europa.eu/ema/*