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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Does the vaccine efficacy wane over time? How long does RTS,S protection last?

In the Phase III efficacy trial, vaccine efficacy was highest shortly after vaccination and remained significant against clinical malaria over the 3-to-4 years follow-up period. Vaccine efficacy was enhanced by a fourth dose., [a,b]

Estimation of duration of vaccine efficacy is complex as the children in the control group were exposed to more episodes of malaria (especially in higher transmission areas) and thus acquired natural immunity more rapidly.

Malaria-076, is an open-label study to follow-up children from three sites from Malaria-055 to further evaluate efficacy and safety over an additional 3 years (January 2014 to December 2016). [c]

Detailed analysis from Malaria-055 (Data on file):

An analysis by periods showed a progressive decline in the efficacy against clinical malaria. Although the study groups were well matched during the first 6-month period this was no longer the case subsequently as children in the control group experienced more clinical malaria than children in the RTS,S/AS01 group, and thereby may have acquired natural immunity, making the vaccine appear less effective by comparison.

VE against all episodes of clinical malaria (ITT cohort)	**6-12 weeks old category**		**5-17 months old category**	
Months 0 to 8	44% [a]		60% [a]	
Months 9 to 14	23% [a]		41% [a]	
Months 15 to 20	12% [a]		28% [a]	
Months 0 to 20	**27%** [a,b]		**45%** [a,b]	
	Primary	**+ 4th dose**	**Primary**	**+ 4th dose**
Months 21 to 32	8% [b]	28% [b]	16% [b]	37% [b]
Months 33 to study end	3% [b]	12% [b]	3% [b]	12% [b]
Months 0 to 32	**20%** [b]	**28%** [b]	**35%** [b]	**44%** [b]
Months 0 to study end	**18%** [b]	**26%** [b]	**28%** [b]	**36%** [b]

ITT cohort: Intention-To-Treat subjects received at least one dose of vaccine, with period at risk starting the day of the first dose

These results are in alignment with previous Phase II studies which have investigated the long-term efficacy and safety of RTS,S. Sacarlal *et al* [d] reported clinical benefit for up to 42 months after the initial vaccination of children 1-4y of age. Olotu *et al* [e] reported a waning of vaccine efficacy in children 5-17 months of age from an initial 43.6% to zero per cent four years after vaccination and indicated possible rebound. However, over this 4-year period, 650 clinical cases were averted per 1000 vaccinees. A multivariate statistical analysis on pooled data from seven clinical studies reported by Bejon *et al* [f]indicated that vaccine efficacy varied significantly according to time since vaccination from 36% to zero per cent after 3 years across different transmission settings and adjuvants used.

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

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

c. *GSK study ID 200599; clintrials.gov NCT number NCT02207816*

d. *Sacarlal J, et al. J Infect Dis 2009; 200: 329-36.*

e. *Olotu A, et al. NEJM 2013; 368:1111-20*

f. *Bejon P. et al. Lancet ID 2013; 13: 319–27*