

RTS,S MEDICAL AND SCIENTIFIC QUESTIONS & ANSWERS

For internal use only - NOT FOR DISTRIBUTION

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 trials.
- 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.

RTS,S MEDICAL AND SCIENTIFIC QUESTIONS & ANSWERS

For internal use only - NOT FOR DISTRIBUTION

Did RTS,S increase the risk for meningitis in the Phase III efficacy trial?

The significant imbalance in cases of meningitis in children vaccinated at the age of 5-17 months between the RTS,S/AS01 and control group reported early, remained throughout the study. The imbalance in cases of meningitis was not seen in young infants. This imbalance in cases of meningitis of many different aetiologies in children could be a chance finding as comparisons were made across groups for many different diagnostic classifications of SAE, confidence interval was high, most of the cases were clustered in two sites (Lilongwe, Malawi and Kombewa, Kenya), and there was no temporal relationship to vaccination. If children who received RTS,S/AS01 do have a true increased risk of meningitis, it is difficult to understand the mechanism that could have brought this about. If RTS,S/AS01 is licensed, post-registration studies will be performed to determine the significance of this finding.

Meningitis cases and aetiology reported in both age groups (total vaccinated cohort) ^(a):

Month 0 to month 20						
	Children 5-17 months			Infants 6-12 weeks		
	R3R N=2976	R3C N=2972	C3C N=2974	R3R N=2180	R3C N=2178	C3C N=2179
Meningitis	4	5	1	2	2**	2
Meningitis haemophilus	1	0	0	0	0	0
Meningitis meningococcal	3	1	0	0	0	0
Meningitis pneumococcal	0	1	0	1	2	1
Meningitis viral	1	0	0	0	0	0
Meningitis salmonella	0	0	0	2	1	0
Meningitis total	9	7	1	5	5**	3
Month 21 to study end						
	Children 5-17 months			Infants 6-12 weeks		
	R3R N=2681	R3C N=2719	C3C N=2702	R3R N=1996	R3C N=1996	C3C N=1976
Meningitis	1*	0	0	0	1	1
Meningitis haemophilus	0/td>	2	0	0	1	1/td>
Meningitis meningococcal	0	1	0	0	0	0
Meningitis tuberculous	1	0	0	0	0	0
Meningitis pneumococcal	0	0	0	0	0	1
Meningitis total	2*	3	0	0	2	3

* This case did not receive a booster dose

**one case of meningism was recoded as meningitis by the investigator after analysis at month 20, resulting in one additional case of meningitis in the R3C group at final analysis as compared to analysis at month 20

RTS,S MEDICAL AND SCIENTIFIC QUESTIONS & ANSWERS

For internal use only - NOT FOR DISTRIBUTION

The 20-month FU analysis showed an imbalance for meningitis of any aetiology mainly in the 5-17 month age group (RR=8.0 (95%CI 1.1-60.3)) although the confidence intervals are wide, and that this imbalance might be a chance finding due to the number of analyses conducted and non-adjustment for multiplicity. The imbalance was less pronounced in the 6-12 weeks age category (RR=1.5 (95%CI: 0.4-5.5)).

The low incidence of meningitis in the control group (C3C) of the 5-17 months of age category is not explained. The 5-17 months control group appears as an outlier in term of number of meningitis cases accrued compared to the other groups, especially to the control group in the 6-12 weeks age category, considering the shorter follow-up and smaller sample size in this group.

a. RTS,S Clinical Trial Partnership. *The Lancet*, 2015. [dx.doi.org/10.1016/S0140-6736\(15\)60721-8](https://doi.org/10.1016/S0140-6736(15)60721-8)