# 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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**Will RTS,S prevent or delay acquisition of natural immunity, resulting in an increased risk of malaria at older ages?**

Descriptive epidemiology studies have constantly demonstrated that the age of peak incidence of clinical malaria depends on the malaria transmission intensity and occurs earlier in higher transmission areas. This is explained by the acquisition of natural immunity early in life through repeated exposure. It is therefore expected that where malaria control is successful, the decrease in malaria transmission intensity will result in a decrease of the absolute number of malaria cases but with a delay of the peak age of clinical malaria[(a)], and this has been observed in some settings[(b)].

Children who receive a preventive malaria intervention, eg chemoprophylaxis, may not develop natural immunity through exposure to infection. When the intervention is withdrawn these children may have less immunity than children of the same age who did not receive the intervention. In previous Phase II studies conducted in Mozambique[(c)] and Kenya[(d)], the RTS,S malaria vaccine candidate provided clinical benefit up to 4 years following initial vaccination with no indication of an increased incidence of malaria disease in vaccine recipients compared to controls.

In the Phase III efficacy study, following an initial protection we observed a shift of severe malaria to an older age as protection wanes. This shift was seen predominantly in sites with a high level of malaria transmission[(e,f)]. This could be a chance finding. However, it cannot be excluded that this could also be a true increase of the incidence of severe disease in the RTS,S group, resulting from a delay in the acquisition of natural immunity following vaccination. The administration of a booster dose of RTS,S/AS01 prolonged the efficacy of the vaccine and allowed to avoid the shift of severe disease within the time frame of follow-up in the trial (approximately 2 years after the booster dose). This finding suggests that if a decision is made to implement RTS,S/AS01 in an age category similar to that of the older children recruited to this trial, then strong consideration should be given to inclusion of a booster dose, especially in high transmission areas.[(f)]

The overall public health impact of a malaria intervention should be assessed based on the overall disease burden reduction throughout childhood, rather than on the effect at one particular point/period in time. Despite the temporary observation of a higher incidence of severe disease at older age, RTS,S/AS01 vaccination still provided an overall positive effect. Over the entire study period of 3-4 years, for every 1,000 infants or children vaccinated an average of 8 severe malaria cases were prevented after a primary schedule and even more (12 to 19 cases) in those who received a booster.


a. *Doumbia SO et al. Acta Trop. 2012 March ; 121(3): 175–183*

b. *O'Meara WP et al. Lancet 2008; 372: 1555–62*

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

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

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

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