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 estimated public health impact of RTS,S in view of its moderate efficacy?

Due to the significant burden of malaria in sub-Saharan Africa, even a vaccine with moderate efficacy could still provide substantial public health benefit in malaria endemic regions when implemented in addition to existing malaria interventions such as bednets.

The results from the phase III efficacy trial indicate that RTS,S "if used correctly, has the potential to prevent millions of cases of malaria" [(b)]:

- Over 4 years of follow-up , an average of 1774 clinical malaria cases were prevented for every 1000 young children vaccinated with 4 doses of RTS,S in the clinical phase III efficacy trial.The cases averted ranged from 205 to 6565 per 1000 vaccinees, being greater in areas of higher malaria transmission. [(b)]

Cases averted per 1000 children vaccinated (median 48 months follow-up) [(b)]	**3 doses**	+ 4th dose
	n (LL ; UL) *range across sites*	**n** (LL ; UL) *range across sites*
Clinical malaria	**1363** (995 ; 1797) *215 to 4443*	**1774** (1387 ; 2186) *205 to 6565*
Severe malaria	**8** (-9 ; 26)	**19** (4 ; 35)

- Although vaccine efficacy was lower in infants, meaningful public health impact might still be provided in areas with high disease burden. In the phase III study site with highest malaria incidence, over 3000 clinical malaria cases were prevented over 3 years of follow-up for every 1000 infants receiving 4 doses of RTS,S. [(b)]

Cases averted per 1000 infants vaccinated (median 38 months follow-up) [(b)]	**3 doses**	**+ 4th dose**
	n (LL ; UL) *range across sites*	**n** (LL ; UL) *range across sites*
Clinical malaria	**558**(158 ; 926) *-172 to 2178*	**983**(592 ; 1337) *-30 to 3406*
Severe malaria	**8** (-13 ; 28)	**12 (-6 ; 32)**

Modelling predicts that four doses of RTS,S could prevent roughly 484 malaria deaths per 100,000 vaccinated young children over an initial 15-year period when introduced on top of existing control programs. [(c)]

- Model predictions were made based on the final phase 3 efficacy results [(b)] by four different groups. Estimations were generated assuming a vaccination program starting in 2017 across a range of estimated parasite prevalence among 2-to-10 year-olds (*Pf*PR_{2-10}) and access to treatment of 45%. Vaccination was done at the ages of 6, 7.5 and 9 months (90% coverage for 3rd dose) and a 4th dose at age 27 months (72% coverage, i.e., 80% of dose 3). [(c)]
- Over a 15-year period in settings of *Pf*PR_{2-10} of 10-65%, 4 doses of RTS,S would:
    - Avert 484 (189-859) malaria-related deaths per 100,000 vaccinated children
    - Avert 116,480 (31,450-160,410) clinical cases
- Public health impact of RTS,S is projected to be greatest in settings of *Pf*PR_{2-10} ≥ 10%, although positive even at *Pf*PR_{2-10} of 5-10% and reasonably predicted by using the mean *Pf*PR_{2-10} in a country.
    - The impact by prevalence setting can be visualized on Malaria maps through the gsk web platform www.gskmodelsonweb.be/models/66#/models/66
- Other influencing factors on the modelling estimates of overall public health impact were: vaccine efficacy profile, vaccine coverage in real-life settings, changes in insecticide resistance, or anti-malarial resistance, changes in access to treatment.

a. *Madhi S. et al. NEJM 2010; 362: 289-98.*

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

c. *Penny et al, Lancet 2015 ; dx.doi.org/10.1016/S0140-6736(15)00725-4*