

## Technical note on malaria vaccine efficacy values

### Background

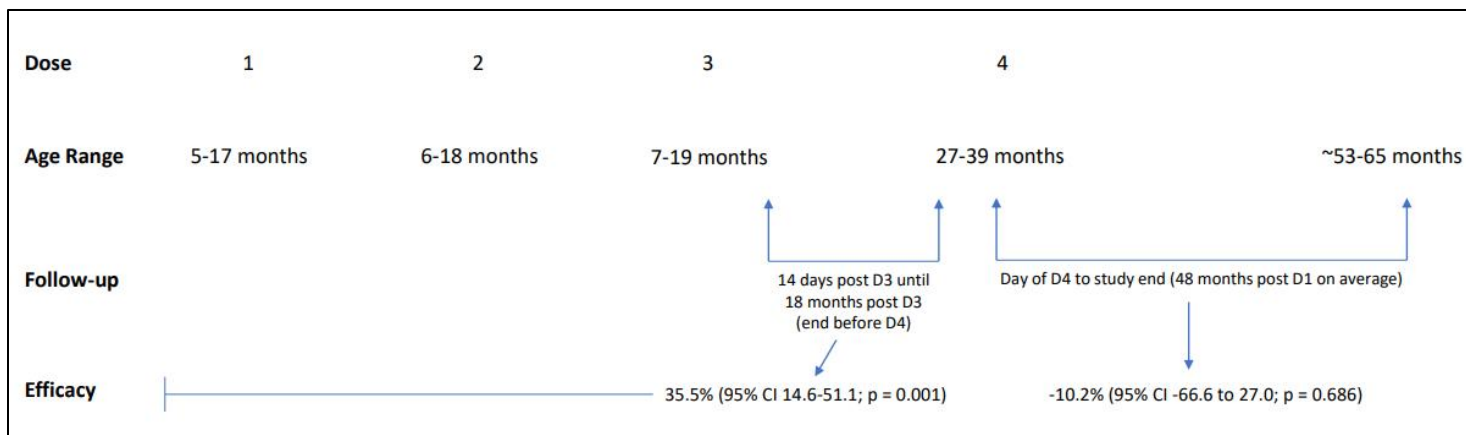
On October 6<sup>th</sup>, 2021, the World Health Organization (WHO) officially recommended the use of the RTS,S/AS01 malaria vaccine in regions with moderate to high *P. falciparum* malaria transmission based on an ongoing pilot program in Ghana, Kenya, and Malawi.<sup>1</sup> Furthermore, the RTS,S Clinical Trials Partnership conducted a phase 3, double-blind, individually randomized, controlled trial between March 27, 2009 and Jan 31, 2014 in seven countries in sub-Saharan Africa with varying levels of malaria transmission.<sup>2</sup> The RTS,S/AS01 vaccine was administered to children aged 5-17 months in a series of four doses. Vaccine efficacy against severe malaria 18 months after the third dose was determined to be 35.5% (95% CI 14.6 to 51.1;  $p = 0.001$ ) in the per-protocol analysis.<sup>2</sup> However, RTS,S/AS01 vaccine efficacy against severe malaria appears to wane over time even after a booster (fourth) dose. Follow up beginning on the day of the booster dose through the end of the study period (48 months post dose one on average) showed vaccine efficacy against severe malaria to be -10.2% (95% CI -66.6 to 27.0;  $p = 0.686$ ).<sup>3</sup>

### Efficacy values in the Lives Saved Tool

Because the Lives Saved Tool (LiST) is focused on modeling the impact health interventions have on mortality, severe malaria was used as the outcome of interest when selecting a vaccine efficacy value for the model. Furthermore, vaccine efficacy values obtained from per-protocol analyses were used instead of intention-to-treat values. Briefly, per-protocol analysis excludes children who received the opposite treatment from what they were assigned at randomization (e.g. assigned to receive the RTS,S/AS01 vaccine but received the control vaccine) or who left the trial prior to completion, while intention-to-treat analysis includes all children regardless of whether they correctly received the assigned vaccine or completed the full dosing schedule. We expect that children in real world vaccination programs will not receive a “control” vaccine when they were supposed to receive the RTS,S/AS01 vaccine. Moreover, LiST outputs are based on the change in the proportion of children who receive three doses of the RTS,S/AS01 vaccine not the number of children who receive one, two, or three doses, so efficacy values that include children who did not completed the trial (intention-to-treat) are less applicable to what LiST attempts to model.

Figure 1 illustrates the RTS,S/AS01 dosing schedule that led to the vaccine efficacy values described above. Children received their first dose between the ages of five and 17 months with subsequent doses at one, two, and 20 months after the first dose.<sup>3</sup> The first follow up period started 14 days after the third dose and ended 18 months later. The second follow up period began on the day of the fourth dose and finished at the end of the study period, resulting in children being followed for, on average, 48.1 months after the first dose.<sup>3</sup>

WHO's recommendation to begin RTS,S/AS01 vaccination at five months of age means 20% of children in LiST's first age band (1-5 months) will be eligible for vaccination. As a result, RTS,S/AS01 vaccine efficacy in this age band is set at 7.1% ( $35.5\% * 0.20 = 7.1\%$ ). Children in the 6-11 and 12-23 month age bands are assumed to receive 35.5% efficacy in accordance with the RTS,S Clinical Trials Partnership results. Vaccine efficacy against severe malaria appears to last until approximately 37 months of age, resulting in 33% of children in LiST's fourth age band (24-59 months) being covered by the vaccine. Therefore, an efficacy value of 11.8% is used in the 24-59 month age band ( $35.5\% * 0.33 = 11.8\%$ ). Table 1 outlines the RTS,S/AS01 vaccine efficacy values for each age band.



**Figure 1.** RTS,S/AS01 dosing schedule, follow-up time, and resulting vaccine efficacy.<sup>3</sup>

**Table 1.** RTS,S/AS01 vaccine efficacy by age group.

	1-5 months	6-11 months	12-23 months	24-59 months
RTS,S/AS01 vaccine efficacy	7.1%	35.5%	35.5%	11.8%

## References

1. World Health Organization. WHO recommends groundbreaking malaria vaccine for children at risk. 2021 Oct. 6; Geneva, Switzerland. <https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk>.
2. RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomized, controlled trial. The Lancet. 2015 July 4; 386(9988) 31-45. doi: 10.1016/S0140-6736(15)60721-8. PMID: 25913272 PMCID: PMC5626001
3. RTS,S Clinical Trials Partnership. Supplementary appendix: Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomized, controlled trial. The Lancet. 2015 July 4; 386(9988) 31-45. doi: 10.1016/S0140-6736(15)60721-8. PMID: 25913272 PMCID: PMC5626001