

Dramatic reductions in malaria cases and deaths continue over five years with seasonal malaria vaccine-drug combination

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The final results of a landmark study published in *The Lancet Infectious Diseases* confirm that the benefits of combining the RTS,S/AS01_E

(RTS,S) malaria vaccine with antimalarial drugs in settings of highly seasonal malaria transmission continue over five years.

The vaccine-drug combination reduced clinical malaria episodes, including cases of severe malaria, and deaths from malaria in [young children](#) by nearly two-thirds compared with either RTS,S vaccination or seasonal malaria chemoprevention (SMC) alone.

The Phase 3 study, coordinated by the London School of Hygiene & Tropical Medicine (LSHTM) with partners Institut des Sciences et Techniques and Institut de Recherche en Sciences de la Santé, Burkina Faso; the Malaria Research and Training Center, University of Sciences, Techniques and Technologies of Bamako, Mali; and PATH, Seattle, Washington, U.S., followed more than 5,000 children over a total of five years. The study also confirmed that the efficacy of RTS,S in preventing malaria in highly seasonal settings was similar, or "non-inferior," to that of SMC.

The findings from five years of follow-up are consistent with those from the first three years, which were published in 2021. Those findings contributed to the World Health Organization's (WHO) decision that year to recommend the RTS,S vaccine for use in settings of moderate-to-high malaria transmission, including its use in areas with highly seasonal malaria or in areas of perennial malaria transmission with seasonal peaks. These new findings confirm the potential of seasonal vaccination to provide a high level of protection in young children over the first five years of life, a period when this protection is needed.

LSHTM's Professor Brian Greenwood, MD, a member of the research team, said, "In addition to the study's findings—which by themselves are remarkable—we can say that children who received the RTS,S-drug combination and also used bed nets likely had greater than 90% protection against malaria episodes during the study. This points to the

importance of ensuring access to multiple malaria prevention tools for reducing the tremendous burden of malaria disease and death in these highly seasonal settings."

Professor Jean-Bosco Ouedraogo, Ph.D., of Institut des Sciences et Techniques, also a member of the research team, said, "It is tremendously exciting to know that our research could benefit the health of millions of children at high risk of malaria in countries like Burkina Faso and Mali. The challenge now is to determine how best to deliver the vaccine-drug combination and to follow these highly protected children as they grow older."

In light of what is already known about the potential for malaria "rebound" following the withdrawal of malaria prevention, children in the study who received SMC and/or the vaccine are being followed for a further two years. This additional follow-up will help to determine how long protection lasts and whether the high level of protection against malaria provided by the combination of SMC and seasonal RTS,S vaccination impaired the acquisition of naturally acquired immunity among the children in the study by reducing the number of infections they received in early life. Currently, SMC is not given to children above the age of 5 years in most countries where it is deployed.

The newly published results come from a two-year extension of the Phase 3 study begun in Burkina Faso and Mali in 2017. The extension began in April 2020, when 5,048 (94%) of the 5,433 children who completed the initial three-year follow-up were re-enrolled.

Over the full five years, protective efficacy of the RTS,S-SMC combination was very similar to that seen in the first three years, with protective efficacy of the combination versus SMC alone being 57.7% and versus RTS,S alone, 59%. The comparable figures for the first three years of the study were 62.8% and 59.6%, respectively. (The protective

efficacy of each intervention alone could not be assessed because all children participating in the study received one or both interventions; there was not a group of children who received neither intervention.)

Compared with SMC alone, the RTS,S-SMC combination reduced by two-thirds hospital admissions for WHO-defined severe malaria (66.8%), malarial anemia (65.9%), blood transfusions (68.1%), and malaria deaths (66.8%).

Professor Alassane Dicko, MD, of the Malaria Research and Training Center and a member of the research team, said, "Our study showed that administering the RTS,S vaccine seasonally every year reduces the burden of malaria drastically in children under the age of 5, who are the most affected by this disease. Rapid implementation of this new additional tool is needed to reduce the huge burden of malaria on children in our countries."

SMC, which involves giving [antimalarial drugs](#) sulfadoxine-pyrimethamine and amodiaquine to young children four or five times during the rainy season when malaria transmission peaks, is highly effective in preventing malaria and was recommended by WHO in 2012 for use in areas with highly seasonal transmission.

Continued testing of a subset of children in the study found that the drugs currently used for SMC remain effective in the study areas. However, the study authors concluded that seasonal vaccination with RTS,S could be a potential solution, if resistance to the drugs increases and no alternatives are available.

The study took advantage of the fact that RTS,S efficacy is highest in the months immediately after vaccination, at about 70%. In this study, the primary course of three vaccine doses, administered one month apart in the run-up to the rainy season, was shown to have similar protective

efficacy against clinical malaria as four courses of SMC. Efficacy of the combined intervention against clinical malaria was higher in the few months after the primary series of vaccination than after the booster doses, but efficacy was seen in each year of the study.

There were no safety issues following multiple annual booster doses of RTS,S, with some children receiving four seasonal booster doses after the initial three-dose primary series.

"These study results come at a critical time," said Mary Hamel, MD, Senior Technical Officer at the WHO Product Development Research Unit and Team Lead for Malaria Vaccines. "Nearly half of childhood deaths from malaria are in children living in areas of highly seasonal transmission. These data show the remarkable reduction in malaria that can be achieved by strategically delivering the vaccine with other effective interventions—and the potential for saving many young lives."

Mark Palmer, DPhil, Director of International Relations at the Medical Research Council, said, "It is exciting to see the potential for a significant reduction in malaria cases and deaths in children under 5 demonstrated by this landmark study. This crucial evidence expands the range of tools available to combat this disease in the future."

"This study's findings should be a source of hope for families in these highly malarious areas," said Ashley Birkett, Ph.D., Global Head of Malaria Vaccines and Biologics at PATH. "But they also present a challenge to regulators, policymakers, and donors: how to ensure that these lifesaving interventions are available and accessible to all who need them. No child should die from malaria or have their potential sapped by repeated malaria illnesses."

Thomas Breuer, MD, Chief Global Health Officer at GSK, said, "Once again, the RTS,S [malaria vaccine](#) is making scientific history. At GSK,

we are excited by these new findings—the result of continued collaboration among scientists across the globe, including Africa, and with organizations such as PATH. We continue to see the potential for this vaccine to help protect children at risk of malaria while also paving the way for future vaccines against malaria. We remain fully committed to the rollout of this important vaccine in Africa."

"We know that seasonal administration of a vaccine poses a challenge to immunization services," said LSHTM's Professor Daniel Chandramohan, Ph.D., a member of the research team. "Not only are additional resources needed to determine how best to deliver vaccines in highly seasonal settings, but we also need to understand the barriers to implementing this approach and whether they can be overcome."

"Around 45 million children were reached with SMC in 2021," said Professor Greenwood. "Yet malaria is still killing tens of thousands of [children](#) each year in areas where SMC is used, and many more are hospitalized. This study points to what is possible when all the available tools are brought to bear, although new and improved tools and approaches are still needed if we are to end [malaria](#) altogether."

More information: Seasonal vaccination with RTS,S/AS01E vaccine with or without seasonal malaria chemoprevention in children up to the age of 5 years in Burkina Faso and Mali: a double-blind, randomised, controlled, phase 3 trial, *The Lancet Infectious Diseases* (2023). [DOI: 10.1016/S1473-3099\(23\)00368-7](https://doi.org/10.1016/S1473-3099(23)00368-7)

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