

## ICAP Journal Club

ICAP's Journal Club is designed to inform ICAP staff and colleagues of the latest scientific literature by providing a succinct summary and critical analysis of important studies, and by discussing the implications of the research on clinical work.

### Article

Chandramohan D, Zongo I, Sagara I, et al. **Seasonal malaria vaccination with or without seasonal malaria chemoprevention**. *N Engl J Med*. 2021;385(11):1005-1017.

<https://www.nejm.org/doi/full/10.1056/NEJMoa2026330>

### Study Summary

This double-blind, randomized controlled trial compared the efficacy of vaccination with the RTS,S/AS01<sub>E</sub> vaccine to chemoprevention for preventing clinical malaria in young children, and evaluated whether a combination of the RTS,S/AS01<sub>E</sub> vaccine and chemoprevention was superior to either intervention alone.

### Study Setting

- Selected districts in Burkina Faso and Mali with high a prevalence of *Plasmodium falciparum* malaria in school-age children.

### Methods

- Children between 5 months and 17 months of age were eligible to participate. Children were excluded if they had an immune deficiency disease or other serious underlying illness, were receiving immunosuppressive therapy, had received a prior malaria vaccine or had a history of adverse reactions to sulfadoxine/pyrimethamine or amodiaquine.
- All households within the trial areas with children who would be eligible on April 1, 2017 were enumerated from February through March 2017.
- Enrolled children were randomly assigned (1:1:1) to receive chemoprevention (chemoprevention-alone group), the RTS,S/AS01<sub>E</sub> vaccine (vaccine-alone group), or chemoprevention plus RTS,S/AS01<sub>E</sub> (combination group).
- All participants were given a long-lasting insecticide-treated bed net (LLITN) at the time of enrollment.
- Children in the vaccine-alone group and the combination group received three doses of RTS,S/AS01<sub>E</sub> in April, May, and June 2017, followed by a fourth and fifth dose in June 2018 and June 2019; children in the chemoprevention-alone group received three doses of inactivated rabies vaccine (Rabipur) in 2017 and a dose of hepatitis A vaccine (Havrix) in 2018 and 2019.

- Children in the chemoprevention-alone group and the combination group received four courses of sulfadoxine–pyrimethamine and amodiaquine at monthly intervals each year; children in the vaccine-alone group received placebos on the same schedule.
- Chemoprevention dosing for children  $\geq 12$  months of age was sulfadoxine 500 mg, pyrimethamine 25 mg, and amodiaquine 150 mg on day 1, with an additional 150 mg of amodiaquine on days 2 and 3; infants  $< 12$  months received half the dose of each medication according to the same schedule.
- Administration of each dose of study medication was directly observed by trial staff.
- The primary outcome was uncomplicated clinical malaria, defined as a measured temperature of  $\geq 37.5^{\circ}\text{C}$  or a history of fever within the previous 48 hours and *P. falciparum* parasitemia (parasite density  $\geq 5000/\text{mm}^3$ ) in children who presented to a trial health facility.
- Pre-specified secondary outcomes were hospital admission with malaria, death from malaria, and malaria parasitemia or anemia at the end of the malaria transmission season.
- Children with suspected malaria were tested with the use of a rapid diagnostic test. Children who were positive were treated with artemether–lumefantrine, and a blood film was obtained for subsequent microscopic examination.
- Each week, 24 randomly selected children in each country were visited at home (8 children per trial group), and a blood film was obtained. Children were also evaluated during a cross-sectional survey conducted 1 month after the last course of chemoprevention at the end of each malaria transmission season to measure hemoglobin level and to obtain a blood film.
- At the end of the 2018 and the 2019 transmission seasons, 200 randomly selected school-age children who were 6 to 12 years of age (and therefore too old to receive chemoprevention), resided in the trial areas, and were in good health were tested for malaria by means of microscopic examination.
- The primary analysis was performed in the modified intention-to-treat population, which included all enrolled children who received a first dose of trial vaccine or placebo in April 2017, and the pre-specified noninferiority margin was set at 1.20.

#### Study Population and Follow-up

- From April-May 2017, a total of 5,920 children received the first dose of the trial vaccine or placebo; 1,965 in the chemoprevention-alone group, 1,988 in the vaccine-alone group, and 1,967 in the combination group.
- By March 31, 2020, 87.3% in the chemoprevention-alone group, 87.2% in the vaccine-alone group, and 88.5% in the combination group had completed follow-up.
- The baseline characteristics and the use of insecticide-treated bed nets were well balanced between groups. In total, 51.8% of the participants were male and 80.2% reported use of bed nets the night before the 2017 census.
- In the first year of the trial, 93.4% of children received all three doses of vaccine; among children who were still in follow-up, 95.1% received a booster dose in year 2 and 94.7% received a booster dose in year 3.

- All four chemoprevention visits were attended by 82.8% of the children in year 1, 84.1% in year 2, and 87.7% in year 3.

#### Primary Efficacy Outcome

- There were 3,825 events of clinical malaria among the participants.
- The incidence of clinical malaria was 278.2 events per 1,000 person-years at risk in the vaccine-alone group and 304.8 events per 1,000 person-years in the chemoprevention-alone group (hazard ratio 0.92; 99% confidence interval [CI] 0.82-1.04), which met the pre-specified criteria for non-inferiority.
- The incidence of clinical malaria in the combination group was 113 events per 1,000 person-years at risk, indicating a protective efficacy of 62.8% (95% CI 58.4-66.8) as compared with chemoprevention alone and an efficacy of 59.6% (95% CI 54.7-64.0) as compared with vaccine alone.

#### Secondary Efficacy Outcomes

- As compared with chemoprevention alone or vaccine alone, the combined intervention provided a high level of protection against hospitalization for malaria, hospitalization for severe malaria, severe malarial anemia, and death from malaria.
- The protective efficacy of the combination as compared with chemoprevention alone was 70.5% (95% CI 41.9-85.0) against hospital admission with severe malaria, 67.9% (95% CI 34.1-84.3) against severe anemia and 72.9% (95% CI 2.91- 92.4) against death from malaria. The protective efficacy of the combination as compared with the vaccine alone against these outcomes was 70.6% (95% CI 42.3- 85.0), 60.6% (95% CI 18.3-81.0) and 75.3% (95% CI 12.5-93.0), respectively.
- The prevalence of malaria parasitemia at weekly surveys was consistently approximately 50% lower in the combination group than in the chemoprevention-alone or vaccine-alone groups.
- At the end of each malaria transmission season, the prevalence of *P. falciparum* parasitemia and anemia (hemoglobin level, <7 g per deciliter) was lower in the combination group than in the two other groups.

#### Safety Outcomes

- Febrile seizures developed in five children, all of whom had received RTS,S/AS01E, the day after vaccination.
- Three of these events occurred after a priming dose, and two occurred after a booster dose. All of these children recovered and had no sequelae.
- No other serious adverse events occurred that were considered related to vaccination.

## Critical Analysis

This double-blind, randomized controlled trial found seasonal vaccination with the RTS,S/AS01<sub>E</sub> malaria vaccine was non-inferior to four annual courses of chemoprevention in protecting young children against uncomplicated clinical malaria over a three-year period. Furthermore, a combination of RTS,S/AS01<sub>E</sub> and chemoprevention was superior to either intervention alone in reducing the incidence of uncomplicated clinical malaria, hospital admissions with severe malaria, and deaths from malaria. No major safety concerns were identified with the vaccine.

The following points should be considered when interpreting the study findings:

- The combination intervention showed substantial efficacy in each year of the trial, however, there was evidence that efficacy was higher in the first year of the trial than in the subsequent two years.
- Chemoprevention alone was more protective than RTS,S/AS01<sub>E</sub> alone during the four months when it was administered, but RTS,S/AS01<sub>E</sub> alone provided protection outside this period, and was thus not inferior over the whole year.
- Children with serious medical conditions, including HIV infection, were excluded from the trial. Therefore, these results cannot speak to the safety and efficacy of the vaccine in these vulnerable groups.
- The results suggest that the drugs currently used for chemoprevention (sulfadoxine–pyrimethamine and amodiaquine) are effective in the trial areas. However, if resistance to these drugs increases without an available alternative chemoprevention regimen, the relative efficacy of seasonal vaccination with RTS,S/AS01<sub>E</sub> could increase.
- Analysis of the primary outcome was performed using a modified intention-to-treat approach, and excluded 14% of participants in the vaccine-alone and combination groups who did not attend the first visit. This may have resulted in a bias in favor of RTS,S/AS01<sub>E</sub>, as a comparable restriction was not applied in the chemoprevention-alone group. However, similar results were obtained in the per-protocol analysis and sensitivity analyses.
- The primary outcome of clinical malaria was ascertained passively when children attended the trial health facilities, which would miss untreated or self-medicated cases and those seeking treatment elsewhere.
- To mitigate the confounding effect of LLITN use, bed nets were distributed to all participants at the time of study enrollment. However, investigators did not measure actual LLITN utilization during the study period, and if this differed by study arm it may have confounded the observed results.

## Implications

This double-blind, randomized controlled trial in Burkina Faso and Mali found the RTS,S/AS01<sub>E</sub> malaria vaccine to be non-inferior to seasonal chemoprevention in young children, and the combination was superior to either intervention alone. These findings suggest that the combination of seasonal chemoprevention with seasonal vaccination is a promising approach for the prevention of malaria in similar contexts, including large areas of Africa with seasonal malaria and where malaria is currently poorly controlled. These findings also support the recent recommendation by the World Health Organization for widespread use of the RTS,S/AS01 malaria vaccine among children in Sub-Saharan Africa and in other regions with moderate to high *P. falciparum* malaria transmission.<sup>1</sup> Operational guidance is needed on how best to integrate this vaccine into a country's vaccination schedule, given the need for at least four doses, which may not align with a child's routine health visits.

*This article synopsis was written by Dr. Cassia Wells with inputs from Dr. Bereket Alemayehu. Share your thoughts on this article or suggest an article for Journal Club by emailing [caw2208@columbia.edu](mailto:caw2208@columbia.edu).*

## References

- 1) World Health Organization; WHO recommends groundbreaking malaria vaccine for children at risk; News Release, October 6<sup>th</sup>, 2021. Available at: <https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk>