Selected Summaries

Vaccination against malaria: A dream too distant?

Olotu A, Fegan G, Wambua J, Nyangweso G, Leach A, Lievens M, Kaslow DC, Njuguna P, Marsh K, Bejon P. (Kenya Medical Research Institute [KEMRI]–Wellcome Trust Programme, Kilifi, Kenya; Ifakara Health Institute, Bagamoyo, Tanzania; the Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom; GlaxoSmithKline Vaccines, Wavre, Belgium; and PATH, Seattle, USA.) Seven-year efficacy of RTS,S/AS01 malaria vaccine among young African children. *N Engl J Med* 2016;**374:** 2519–29.

SUMMARY

In 2007, a study evaluated the efficacy of a candidate vaccine for malaria called RTS,S/AS01. The study was conducted at two places in Africa—Kilifi, Kenya and Korogwe, Tanzania. In the Korogwe arm, the study began in March 2007 and was completed in August 2008. However, in Kilifi, the study was extended thrice: first till November 2008, second till April 2011, and third till November 2014. Thereafter the follow-up was discontinued. The 4-year efficacy results were published in 2013.[1] The 7-year results were the focus of this article by Olotu *et al*.

The study was a double-blind, randomized, controlled phase 2 trial. The study population consisted of children who were 5 to 17 months of age at the time of the first vaccination. The children were randomly assigned to receive three doses of either the RTS,S/AS01 vaccine or a rabies (control) vaccine. The doses were given at baseline, 1 and 2 months.

Transmission of malaria varies dramatically from place to place, referred to in the article as 'fine-scale geographic heterogeneity'. Since prior exposure to the parasite affects immunity, the participants were categorized into high- and low-exposure groups. Exposure was predicted by estimation of the prevalence of malaria infection among children who resided within 1 km radius of each participant. The authors used data from 870 children who were under active surveillance in the same trial area to determine exposure indices.

The participants were followed up both by weekly active surveillance and passive surveillance to identify clinical malaria cases. Blood samples for the assessment of asymptomatic parasitaemia were obtained at 8, 12, 15, 25, 38, 49, 65, 78 and 91 months after vaccination. The primary end-point was clinical malaria caused by *Plasmodium falciparum* (temperature of ≥37.5 °C and *P. falciparum* parasitaemia density of >2500 parasites per cmm). The incidence of malaria was calculated for both groups. Vaccine efficacy was defined as 1 minus the hazard ratio or the incidence-rate ratio, then multiplied by 100; p values were calculated using a Cox proportional-hazards model for first episodes and negative binomial regression for multiple episodes.

Of a total of 447 children recruited, 312 completed all three extensions of follow-up (164 participants in the RTS,S/AS01 group and 148 in the control group). All enrolled children were included in the analysis. The intention-to-treat cohort included all children who had undergone randomization. The per-protocol cohort included children who received three doses of vaccine according to the trial protocol and for whom surveillance data were available from 2 weeks after receipt of the third dose. All participants who underwent randomization received at least one dose of the vaccine.

The characteristics of the RTS,S/AS01 group and the control group were similar at baseline. There were 150 cases of first episodes of clinical malaria among 223 participants in the RTS,S/AS01 group and 157 cases among 224 participants in the control group. Throughout the 7 years, there were 1002 episodes of malaria in the RTS,S/AS01 group and 992 in the control group.

Vaccine efficacy against the first episode of clinical malaria was 27% (95% CI 8.5–41.8; p=0.0006), and against all episodes was 4.4% (95% CI –17.0–21.9; p=0.66). Efficacy was consistently lower in the high-exposure group (–2.4% [95% CI –26.1–16.8] p=0.82) than in the low-exposure one (16.6% [95% CI –24.6–44.2]; p=0.38). It declined from 35.9% (95% CI 8.1–55.3; p=0.02) in the first year to 3.6% (95% CI –29.5–28.2; p=0.81) in the seventh year. Waning of efficacy was more rapid in the high-exposure group than in the low-exposure one.

The prevalence of asymptomatic *P. falciparum* parasitaemia was lower in the RTS,S/AS01 group than in the control group before the fourth year. Thereafter, the prevalence was similar in the two groups. Serious adverse event rates were similar in the two groups (17.9% [95% CI 13.1–23.6] and 25.4% [95% CI 19.9–31.7], respectively). Fifteen patients of severe malaria were identified during follow-up: 5 in the RTS,S/AS01 group and 10 in the control group. All these resolved without long-term sequelae.

The authors concluded that RTS,S/AS01 provided protective efficacy in the first year after vaccination but that the efficacy subsequently waned. Efficacy was close to zero in the fourth year and may have been negative in the fifth year, with a partial rebound in the high-exposure cohort. It was felt that rebound may have occurred because the RTS,S/AS01 vaccine protects against malaria sporozoites but does not induce clinical immunity against blood-stage parasites. This result eroded the benefits that were seen in early years, such that over a period of 7 years, vaccine efficacy was estimated at just 4.4%.

COMMENT

Malaria remains a key health problem in tropical countries. It is an important cause of preventable mortality, especially in children. According to a WHO estimate in 2015, 214 million new cases of malaria and 438 000 malaria deaths were reported worldwide, predominantly in Africa. Most of these deaths—306 000 in 2015—occurred in children under the age of 5, indicating their particular susceptibility to the disease.[2] Disease control efforts largely focus on vector control, early diagnosis and treatment.

Several factors have hindered the development of an effective vaccine. The parasite, a protozoa, has a complicated structure and life cycle as compared to bacteria and viruses. It shows extensive antigenic variation and our understanding of its interaction with the human immune system remains poor.[3] Lack of funding is also an issue. At present, there are more than 20 candidate vaccine-constructs that are being evaluated in phase 1–2 clinical trials.[4]

In a phase 1 trial, Seder *et al.* tested a vaccine called PfSPZ, consisting of live, weakened *P. falciparum* sporozoites, given intravenously for four doses, and found that the protection rate was 55% at the end of 1 year.[5]

The candidate vaccine of this article, RTS,S/AS01, is also known as Mosquirix. It is a vaccine against *P. falciparum*, and offers no protection against other species. It is a hybrid protein particle, formulated in a multicomponent adjuvant.[6] It was developed by Glaxo SmithKline Biologicals, with initial collaboration with the Walter Reed Army Institute of Research, and funding from the PATH Malaria Vaccine Initiative and the

Bill and Melinda Gates Foundation. Despite limited efficacy shown in trials, it was given a favourable opinion by the European Medicines Agency (EMA) in 2015.[7] Also, notwithstanding the results of the 7-year follow-up of this trial, WHO plans to go ahead with its large-scale pilot studies to further assess efficacy and safety of four doses, which is expected to yield results in 3–5 years.

As this study illustrates, although the protection with this vaccine during the initial years appeared to be at least modest, disappointingly, the effect was not sustained over the long term, with vaccine efficacy declining to almost negligible levels. It was also noted that in areas where exposure to the parasite was higher, the vaccine efficacy was lower, and the number of cases actually showed a rebound increase. This seems to defeat the very purpose of the vaccine, i.e. providing protection to those who need it the most. A silver lining appears to be that fewer cases of severe malaria were reported in vaccine recipients as compared to controls. The authors have acknowledged that the sample size was too small to draw any definitive conclusions about the long-term efficacy of the vaccine.

A larger phase 3 trial tested the efficacy of three doses of the vaccine along with a booster dose. Over 4 years of follow-up, efficacy was higher among children who received a fourth dose than among those who did not (36% *v.* 28%). Extended follow-up is currently being obtained which will provide further information on outcomes in year 5 and beyond.[8] This raises the possibility that perhaps periodic boosters might be an option to maintain immunity.

Some questions remain: If three doses do not work by 7 years, how much would an additional fourth dose help? Would additional boosters be required? If so, how many and for how long? Also, is it a good idea to roll out large-scale pilot studies for a vaccine that is well-proven to be only partially efficacious? Rather than focusing on this vaccine which Glaxo SmithKline has been working on for 30 years, perhaps it is high time that other vaccines are given a fair trial.

To sum up, an effective vaccine for malaria remains a mirage for the time being. It is hoped that the future portends better news.

Relevance to the Indian scenario

The predominant species in India is *P. vivax*, which is not targeted by this vaccine. To the best of our knowledge, there is no research under way for development of vaccines against other species of *Plasmodium*. Therefore, even if an effective vaccine targeting the *P. falciparum* species is licensed, the unfavourable cost–benefit ratio would preclude its use in mass immunization programmes in India. Unless further research yields surprises, it is safe to assume that malaria control in India would have to keep its hopes pinned on vector control and treatment.

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