Malaria vaccine fails to work after four years

March 20 2013, by Kerry Sheridan

A new vaccine that has raised hopes of becoming a potent new tool in the battle against malaria seems to stop working in children after four years, according to research published Wednesday.

The vaccine candidate—known as RTS,S—is not yet on the market, but ongoing trials in seven African countries generated hope that it might help slow new malaria cases as drug resistance to the deadly parasite grows.

One child in Africa dies every minute from malaria, a mosquito-borne disease that kills an estimated 655,000 people every year. There is currently no vaccine available that offers full protection against it.

The latest data comes from a phase II follow-up study on 320 children in Kenya which found that in the first year after vaccination, protection against malaria was 43.6 percent, but that dropped to zero by the fourth year.

It also found that the more often a child was exposed to malaria, the less effective the vaccine appeared to be.

The vaccine's efficacy was 45.1 percent in children with below-average exposure to malaria, but just 15.9 percent in children with above-average exposure, said the study, published in the *New England Journal of Medicine*.

"Despite the falling efficacy over time, there is still a clear benefit to the

vaccine candidate," said senior author Phillip Bejon.

"We now need to look at whether offering a vaccine booster can sustain efficacy for longer," added Bejon, a fellow at the KEMRI-Wellcome Trust Research Programme and the Centre for Tropical Medicine, University of Oxford.

Early results from larger, ongoing phase III trials have shown the vaccine cut malaria cases in half during the first year of follow-up in young children, and by about a third in babies.

Mary Anne Rhyne, a US spokeswoman from GlaxoSmithKline, the pharmaceutical company that makes the vaccine, said the Kenya study is "small" and uses data from just one of many trial sites, while larger studies are still under way.

"The Phase III pivotal study, involving 15,460 children, is ongoing and should provide meaningful insights into the vaccine candidate's efficacy in different malaria parasite transmission settings, longer-term efficacy (2.5 years after primary vaccination) and the impact of a booster dose," she told AFP in an email.

"These analyses are expected to be publicly available by the end of 2014."

In the meantime, she said, the vaccine is "still under development and subject to the evaluation of its benefits and risks by the regulatory authorities before being made available."

In November 2012, results from phase III tests on 6,500 infants showed that the RTS,S vaccine only protected about a third of very young babies, compared to success rates of between 47 percent and 55 percent in children between the ages of five and 17 months.

At the time, GSK's chief executive officer Andrew Witty described those results as "a little frustrating."

The RTS,S vaccine candidate trial is the largest of its kind, and is being conducted at 11 sites across seven African countries.

There are several other projects under way with vaccine candidates in clinical trials worldwide.

Separately on Wednesday, a group of international researchers announced progress in studies on mice that could lead to a new malaria vaccine candidate for humans, one that appears not to create drug resistance in the parasites.

"This is one of the first drugs ever to kill the malaria parasite in all three stages of its life cycle," said Dennis Kyle of the University of San Francisco College of Public Health's Global Infectious Diseases Research team.

The drug, called ELQ-300, is being prepared for clinical trials, according to the research published in the journal *Science Translational Medicine*.

More information: Olotu A et al. Four-year efficacy of RTS,S/AS01E and its interaction with malaria exposure. New England Journal of Medicine 2013 [epub ahead of print]. www.nejm.org/doi/full/10.1056/NEJMoa1207564

Press release:

Follow-up study describes declining efficacy of malaria vaccine candidate over 4 years

Long-term follow-up of a phase II study from KEMRI-Wellcome Trust

Research Programme and Oxford University researchers in Kenya shows that the efficacy of a malaria vaccine candidate, RTS,S, wanes over time and varies with exposure to the malaria parasite.

The findings will help to inform which populations are likely to benefit most from the vaccine candidate. They also have important implications for the design of future clinical trials of this and other vaccine candidates and highlight the importance of long-term follow-up studies for assessing vaccine efficacy.

The study involved 447 children in Kilifi, Kenya, who had been part of an earlier phase II trial to assess the safety and efficacy of the vaccine candidate. Of the 447 children, 320 completed four years of follow-up. The analysis, which was published today in the '*New England Journal of Medicine*', was designed to look at how well the vaccine candidate protects against malaria over time.

Initial results from larger ongoing phase III studies showed that the candidate RTS,S vaccine reduced malaria over 12 months of follow-up by approximately half in young children and one-third in infants. The new findings on long-term follow-up of an earlier phase II study reveal that the vaccine efficacy dropped from 43.6 per cent protection against malaria in the first year to zero by the fourth year after vaccination.

The study's senior author, Dr Phillip Bejon (Research Fellow at the KEMRI-Wellcome Trust Research Programme and the Centre for Tropical Medicine, University of Oxford), said: "Despite the falling efficacy over time, there is still a clear benefit to the vaccine candidate. Many of the children will experience multiple episodes of clinical malaria infection, but overall we found that 65 cases of malaria were averted over the four-year period for every 100 children vaccinated. We now need to look at whether offering a vaccine booster can sustain efficacy for longer."

The study also shows that relative vaccine efficacy declines with increasing exposure to malaria, from 45.1 per cent among children with below-average exposure to malaria to 15.9 per cent among children with above-average exposure to malaria. The relative efficacy describes the number of cases of malaria that were avoided by vaccination as a percentage of the total number of cases in that group: because there were many more cases of malaria at higher exposure, the cases averted per 100 children vaccinated actually increased from 62 at below-average exposure to 78 at above-average exposure.

The study's lead author, Dr Ally Olotu, a Wellcome Trust PhD student at the KEMRI-Wellcome Trust Research Programme and Oxford University, explains: "We need to consider whether relative efficacy or absolute number of cases averted is the more informative measure. In any case, these are important findings that will help to inform which populations are likely to benefit most from the vaccine.

"The ongoing phase III study will provide further insights to the vaccine's efficacy in different settings of malaria exposure and includes an assessment of a booster dose to sustain efficacy over time."

Malaria remains an important cause of illness and death among children in sub-Saharan Africa, and there is currently no vaccine that offers complete protection against the disease. RTS,S is the most advanced candidate malaria vaccine and entered phase III clinical trials in Africa in 2009. The vaccine candidate seems to be well tolerated and has an acceptable safety profile, but it remains unclear which sub-groups of children might benefit most and what the duration of efficacy is.

Jimmy Whitworth, Head of International Activities at the Wellcome Trust, said: "This study indicates the durability of protection of a single initial course of this vaccine against malaria, and the variability of protection at different levels of exposure to malaria. These are key

pieces of information required for us to understand how best to use this vaccine and the regimes of boosters that will be required to provide optimum protection."

Latest figures estimate that there are 1.44 billion people living in regions of stable malaria transmission worldwide. Most deaths occur among children living in Africa, where a child dies from malaria every minute.