Malaria vaccine results present infant immunization quandary

Babies receive a battery of vaccines after they're born to protect them against dreaded diseases such as tetanus, whooping cough and polio. Public health officials in the developing world had hoped to soon add a malaria (*Plasmodium falciparum*) vaccine to the childhood immunization schedule to take advantage of the existing vaccine distribution system. However, new results from a trial of the leading candidate—a shot known as RTS,S, or Mosquirix—suggest that the vaccine reduces the risk of malaria by only a third in infants.

Given the low efficacy, some experts are now questioning whether RTS,S would be a useful addition to the childhood vaccination roster. John Lusingu, a malaria researcher at the National Institute for Medical Research in Tanga, Tanzania, and a principal investigator on the trial, points out that children six months and older are most affected by the disease, so it might make sense to administer the vaccine to older children, for whom the vaccine is more protective. But that would probably require an expansion of the routine immunization program to include additional clinic visits, which can be burdensome for health workers and families.

The vaccine's developers, GlaxoSmithKline (GSK) and the PATH Malaria Vaccine Initiative, plan to push on with the phase 3 trial, which is slated to end in 2014. "This is not a mission we should just walk away from," Andrew Witty, chief executive of GSK, said in a press conference on 9 November. The London-based company has spent approximately $300 million on RTS,S to date and expects to invest another $200 million before the project is finished.

The study, published last month in the *New England Journal of Medicine* (doi:10.1056/NEJMoa1208394, 2012), included more than 6,500 infants between 6 and 12 weeks old from across seven African countries. The vaccine reduced the risk of clinical episodes of malaria by 31% in this young cohort, a lower level than that found in children vaccinated between 5 and 17 months for whom the vaccine provided up to 56% protection (*N. Engl. J. Med.* **365** 1863–1875, 2011).

Why the vaccine is less effective in infants than it is in toddlers isn't yet clear, but the research team behind the trial has a number of hypotheses. One complicating factor could be antibodies passed on from the babies' mothers during pregnancy. These maternal antibodies protect infants from disease, but they can also prevent vaccines from eliciting a strong immune response.

Mauro Fermariello / Science Source

Baby blues: Given the latest efficacy data, researchers question the value of vaccinating newborns.

Those same antibodies decay over time, however, so the older group of children would probably have had lower levels of them, says Rick Fairhurst, chief of the malaria pathogenesis and human immunity unit at the US National Institute of Allergy and Infectious Diseases in Rockville, Maryland. The effect could be especially pronounced in areas with the highest burden of malaria. Repeated exposure to the parasite results in higher levels of antibodies in the mothers, which can then be passed on to the children.

Primed for success

Trial investigator Mary Hamel, an epidemiologist at the US Centers for Disease Control and Prevention in Atlanta, offers another possibility. RTS,S uses a hepatitis B surface antigen to act as a carrier protein for a fragment of a cell surface protein found on the sporozoite stage of the malaria parasite. Because the older group of children had been immunized against hepatitis B prior to receiving RTS,S, their immune systems may have been primed to respond better to the vaccine. In contrast, younger kids received RTS,S at the same time as the hepatitis B vaccine, and thus presumably had no such priming advantage.

Natural infections can help enhance immune responses, too. And, as Hamel notes, "the older children had likely already experienced at least one episode of *P. falciparum* malaria before they were vaccinated." Which explanation fits best, however, won't be clear until the research group delves deeper into the data.

Even if the vaccine is approved, it's not yet clear how it should be administered and to whom. "I am very interested in seeing the site-specific data," Hamel says. If the efficacy varies by site, she suggests that RTS,S could be tacked on to the routine vaccine schedule in some areas and administered separately in others.

Valentina Buj, a malaria specialist at UNICEF in New York, says it's premature to start talking about integrating RTS,S into the routine immunization schedule before the study is complete in 2014. She points out that other candidates in the pipeline may prove more effective. The World Health Organization expects to decide whether to recommend the vaccine or not as early as 2015.

If RTS,S reduces hospital admissions, "it's going to save lives," says Eleanor Riley, an immunologist at the London School of Hygiene & Tropical Medicine. "The question is: how many lives and how much is that going to cost?"

Cassandra Willyard