Quarter-century quest for malaria vaccine shows signs of success

The long development of RTS,S, the leading malaria vaccine candidate, has yielded preliminary positive Phase III results, and laid a path for future success.

Alisa Opar

After toiling for 25 years to create a malaria vaccine, scientists have reported the first Phase III promise. Interim results of an ongoing trial of the vaccine candidate RTS,S, manufactured by GlaxoSmithKline (GSK), show it provides children with nearly 50% protection from severe bouts of the disease. While the field awaits further results before being able to assess the vaccine's utility, its development has provided a key stepping stone on the road to malaria vaccine success.

"This is a huge step forward," says Carla Botting, Director of Product Development and Access at the PATH Malaria Vaccine Initiative (MVI), a non-profit that partnered with GSK and others to develop RTS,S — a vaccine that targets sporozoite and liver-stage antigens. "To have a malaria vaccine … make it this far in development is a massive achievement."

The large-scale trial enrolled over 15,000 children — aged either 6–12 weeks or 5–17 months — in seven countries in sub-Saharan Africa. Preliminary results now show that in the older cohort, vaccination reduced the risk of clinical malaria by 56% after 12 months and the risk of severe malaria by 47% (*N. Engl. J. Med.* **365**, 1863–1875; 2011). Despite the optimism over these findings, preliminary results for the younger cohort, an ideal target population because routine vaccinations are already administered at this age, may be less encouraging: vaccine efficacy against severe malaria dropped to 34.8% when both cohorts were analysed together. There are also questions about the durability of RTS,S (its effects appear to wane after about 6 months), uncertainty over its effect on mortality due to infection and concerns about side effects including seizures, fever and meningitis. Detailed results for the younger subjects alone are expected in late 2012, and results on the effects of an 18-month booster shot are expected in 2014.

Until these further results are disclosed, it is unclear whether the vaccine will make it to market. Typically, a vaccine doesn't gain approval unless it is at least 90% effective. But malaria kills around 800,000 people each year, mostly African children, and a less efficacious malaria vaccine could still save many lives. The World Health Organization has therefore called for a first-generation vaccine by 2015 with 50% protective efficacy against severe disease, followed by another with a protective efficacy of more than 80% by 2025.

"I'm hopeful that we will be able to reach this goal or come very close," says Joe Cohen, GSK's Vice President of Research and Development, Emerging Diseases & HIV, who has been working on RTS,S for 25 years.

Adrian Hill, a malaria vaccine researcher at the University of Oxford, UK, is a little more sceptical. "The frustrating thing is that they have a vaccine that's got real biological, measurable and fairly consistent efficacy, but it's just not high enough and doesn't last long enough. My view is that its efficacy isn't high enough yet to persuade funders to deploy RTS,S widely," he says. "In scientific terms," he adds though, "[the trial] is a real achievement."

A vaccine is born

The long effort to make RTS,S dates back to the 1980s. In 1984, researchers first cloned *Plasmodium falciparum*'s circumsporozoite (CS) protein — a cell-surface protein that is expressed by the sporozoite, the parasite stage that invades the liver — and a New York Times headline announced: "Malaria Vaccine Is Near." Led by a team at Walter Reed Army Institute of Research and SmithKline, a predecessor of GSK, which together spearheaded the development of the first CS vaccine, FSV-1, the hope was that a vaccine based on a portion of the CS protein would prevent disease.

Two years later, investigators tested this approach using a synthetic peptide vaccine consisting of a stretch of the CS protein linked to a stretch of a tetracycline-resistant protein delivered with an alum adjuvant. GSK produced the vaccine, and the military researchers as well as a team from the US National Institutes of Health conducted the challenge trial on themselves. "I got the vaccine and I thought that I was going to be protected, because the controls and several of the volunteers came down with malaria and I was still feeling well," says Stephen Hoffman, then head of malaria vaccine development at Naval Medical Research Institute and now Chief Executive of malaria vaccine company Sanaria. "I flew out to California, and in the middle of a presentation developed high fever and uncontrollable shaking chills characteristic of malaria." The trial was a failure.

In 1987, after this attempt, GSK tasked Cohen with heading up the development of the vaccine. After meeting with Hoffman and others, the team decided to try to develop a next-generation vaccine that would induce both antibodies and cell-mediated immunity against the CS protein. So they fused fragments of the CS protein to the hepatitis B surface antigen — which, at high concentrations, forms virus-like particles that drive the production of antibodies — and RTS,S was born. But it was still slow-going. "There were a lot of ups and downs, and a lot of scepticism about whether the CS antigen was the right one, or whether it was possible at all at that time to develop a malaria vaccine," says Cohen. "It took 9 years to get the first really exciting results," he adds.

During the interim, the team progressed slowly but steadily through preclinical studies. They first demonstrated that the fusion antigen induced antibodies and T cell responses in various laboratory animals. By combining RTS,S with different adjuvant systems, which enhance immune response to antigens, they also showed they could enhance these immune responses.

In 1992, GSK and Walter Reed collaborators tested RTS,S in the clinic for

the first time. They evaluated two formulations: one with alum, a widely used adjuvant, the other with GSK's first new adjuvant, alum plus monophosphoryl lipid A (MPLA; a toll-like receptor 4 agonist). The alum formulation failed to offer any protection, and only two out of eight individuals vaccinated with the other formulation were protected after challenge by five bites from infectious mosquitoes. "This was a point where we sat down and wondered whether we should continue or not."

They forged ahead, bolstered by preclinical data suggesting that other adjuvant systems would fare better. In 1996, an AS02 adjuvant formulation (consisting of an oil-in-water emulsion and two immunostimulants: MPL and QS21) finally showed unprecedented efficacy in the clinic, with only one out of seven vaccinated individuals falling ill after a challenge (*N. Engl. J. Med.* **336**, 86–91; 1997). "That was a tremendous boost," says Cohen. To other malaria vaccine developers, it also demonstrated the importance of getting the adjuvant right for the induction of protective immune responses. With clinical data in hand, GSK tested RTS,S in Africa in 1998 for the first time, and it again showed efficacy.

Partnering for success

Having achieved this initial success, GSK — which has spent US$300 million developing RTS,S — needed to find a partner to share the risks and costs of conducting paediatric trials in Africa. Fortunately, the Bill & Melinda Gates Foundation created the MVI in 2001. After a year of negotiations, the two entered into a partnership to develop the vaccine together for African children.

From 2001 to 2009, the partners conducted Phase II trials in children and infants, and found that the vaccine was acceptable, safe, well-tolerated and induced significant efficacy (*N. Engl. J. Med.* **359**, 2521–2532; 2008; *N. Engl. J. Med.* **359**, 2533–2544; 2008). They also developed a paediatric dose of RTS,S and switched to a new adjuvant system, AS01 (which is similar to AS02, except it uses a liquid suspension instead of an oil-in-water emulsion). In 2008, the partners decided to push forward with the huge Phase III trial, which began in May 2009.

"I think that a lot of people had doubts that this kind of trial could be done," says Botting, noting the size and complexity of the study as key hurdles. She credits the partnership with being "instrumental in moving RTS,S forward". African researchers contribute their expertise in the field and their understanding of local communities. Northern partners offer technical expertise, training and support. The MVI brings field expertise, capacity-building, financing and management skills, and GSK has expertise in vaccine development as well as financial resources. To date, the Bill & Melinda Gates Foundation has put $200 million into RTS,S development.

The large size of the trial has opened up several instructive avenues, says Hill. If RTS,S proves to be more effective in the older cohort only, this could generate discussions about giving a vaccine outside of the standard programmes. It could also shed light on interference with other vaccines, he says. "That may be a big issue."

Perhaps equally importantly, the development programme and large Phase III trial for RTS,S has laid down an infrastructure and built up the expertise needed for the clinical development of second-generation vaccines. A number of projects are ongoing, both with and without support from the MVI.

GSK is looking to combine RTS,S with other vaccine candidates. It is collaborating with Dutch biopharmaceutical company Crucell to develop a prime–boost vaccine that will enter clinical trials soon. In preclinical models, priming animals with one dose of adenovirus 35 coding for the CS protein and then boosting with two subsequent doses of RTS,S gives a much better cell-mediated immune response than does RTS,S alone. This vaccine trial will also be the first to incorporate systems biology from the outset. "I believe the systems approach will tell us, at a mechanistic level, how the vaccine is working or not working," says Alan Aderem, Director of the Seattle Biomedical Research Institute, which is overseeing the systems biology efforts. "It should allow us to predict whether a vaccine will work or not, and it should also allow us to further optimize the vaccine so it works more effectively."

Hill, who works on T cell vaccines, believes that multicomponent vaccines that target more than one life-cycle stage are the key. Preclinical studies indicate that combining RTS,S with a T cell vaccine provides a substantial multiplier effect, he says. "Because very few parasites are getting into the liver after treatment with the RTS,S component, it's much easier for the T cell component to clear the last liver cell or two, rather than having to clear the whole liver of parasites." Some such combination approaches have made it into early-stage clinical trials.

Vaccines against the blood-stage — which causes the clinical symptoms of malaria —have also been in the works since the 1990s, but progress has been mixed and slower than with pre-erythrocytics. Most of these candidates are based on the merozoite surface protein 1 and apical membrane antigen 1, are given with an adjuvant and are being tested in preclinical, Phase I and Phase II trials.

The MVI has also recently invested in vaccines that block parasite transmission by targeting the sexual stage of the parasite. These 'community vaccines' don't provide a direct benefit to individuals, but might combat the disease at the population level. "There's beginning to be more interest and investment, and in animal models it looks pretty good," says Hoffman.

Hoffman, meanwhile, takes a whole-parasite approach, based on the discovery in the 1970s that irradiated sporozoites delivered by mosquito bite induced protective efficacy exceeding 90%. At Sanaria, Hoffman's labour-intensive approach involves manually removing the salivary glands of infected and irradiated mosquitoes and then purifying the sporozoites, which are delivered as a vaccine. Although the vaccine did not show efficacy in a first clinical trial, Sanaria suspects the failure may be due to issues with delivery into the skin. Another trial testing intravenous delivery is underway, and a third trial is planned for next year.

Given all the activity, and the pending detailed results from RTS,S, it is too early to say which approaches will be most successful, says Hill. "It would be wrong to give the impression that there are only two or three horses in this race — there are quite a lot of candidates coming along."

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CORRIGENDUM

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The spelling of Stephen Hoffman's name has been corrected online, as his affiliation.