more attention on tackling the mosquitoes that carry the disease and preventing transmission, rather than priming people to fight off the parasite. Hill thinks eradication of malaria is not possible with the tools currently available, and that new vaccines are ultimately necessary. Duffy agrees: "An effort like elimination means you have to bring lots of tools together," he says. "A vaccine can be an important addition."

Vaccines could be useful in the battle to prevent transmission, too. One way to stop the parasite jumping between human and mosquito is to sabotage the parasite's sexual stage. Duffy's team has developed a transmission-blocking vaccine that targets the sexual forms that are taken up by mosquitoes when they ingest human blood cells. In an initial field trial of this type of vaccine, conducted in Mali in 2018, it proved safe[8]. Next, Duffy is planning to report the results of a trial of a vaccine that combines Pfs230, a protein on the outside of the parasite gamete, with GlaxoSmithKline's adjuvant ASO1, which is included in the RTS,S vaccine to boost T-cell response. A major challenge with these transmission-blocking vaccines, however, will be developing the methods to measure any reduction in malaria transmission in the field, and to prove that the vaccines work.

Hill doubts that a stand-alone transmission-blocking vaccine will ever emerge, but can see it being part of a multi-component vaccine. A combination vaccine that includes a transmission blocker could be more effective and practical.

The need for a malaria vaccine is not diminishing, and researchers are optimistic. "We can see the top of the mountain now," says Kappe of his team's work. Although scientists might not agree on the best approach to take, they can see progress being made – not least the wide distribution of the RTS,S vaccine. "Our best products will be combined in different ways," says Duffy. "RTS,S has found a very specific role to reduce clinical malaria in children." It might not be perfect, Hill says, but malaria is such a horrendous problem that even a partially effective vaccine could make a big difference.

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Q&A

Jeffrey Bethony: Taking on worms

OLIVIA ANDERSON/GW SCHOOL OF MEDICINE AND HEALTH SCIENCES

About two billion of the world's poorest people are infected with parasitic worms. Treatments are available, but Jeffrey Bethony, a microbiologist at George Washington University in Washington DC, explains why only vaccines can eradicate infection.

Why is it more difficult to develop a vaccine for parasites than for many viruses?
Parasites go through a series of life stages and occupy several different niches in the body. They've also developed clever mechanisms to evade the immune system. So parasitic infections are the ultimate challenge.

Which diseases caused by parasitic worms do we most need a vaccine for?
Schistosomiasis results in the greatest disease burden, especially in sub-Saharan Africa and Brazil. There is an effective treatment, praziquantel, but without a vaccine we can't prevent reinfection, so it has proved impossible to eliminate the parasite in low-income countries. And more than 500 million people are infected with hookworms, which can impair physical and mental development.

What progress are you making on a schistosomiasis vaccine?
We are developing a candidate vaccine based on proteins found on the outer surface of the worms. We're currently running a phase II trial in Uganda, funded by the US Department of Defense, that targets a fragment of such a protein on the worm *Schistosoma mansoni*. A group at Leiden University Medical Centre in the Netherlands is working on a controlled human infection model, or CHIM, for schistosomiasis. This approach allows researchers to give people an experimental vaccine and then challenge them with a dose of pathogen. This would allow us to use fewer volunteers and reduce the costs of trials.

What vaccine strategies are you developing against hookworms?
We have developed two subunit vaccines, each containing a protein given with an immune stimulant. One protein degrades haem, a component of the blood protein haemoglobin. Haem is potentially toxic, and antibodies against the degradation protein reduce the worm's ability to eliminate haem from its blood meals. The other protein prevents hookworms from breaking down haemoglobin for consumption. We have done separate phase I trials of our two vaccines in the United States, Brazil and Gabon, and have just received funding to test both proteins using a controlled human infection model in endemic areas of Brazil. We then plan to test the simultaneous delivery of both proteins in a single vaccine.

So a CHIM study involves injecting healthy people with parasites?
Yes. We borrowed the idea from malaria researchers. I immunize people against hookworms by administering the proteins in the subunit vaccines, and then challenge the volunteers with hookworms. If the vaccines don't work, we can get rid of the infection with drugs. If we had to wait for people to get infected, studies would take longer and cost more; CHIM studies accelerate vaccine development.

Isn't it tricky to get people to volunteer to be infected with a parasitic worm?
We have no problem getting volunteers. There are lots of people who think that hookworms, because they can modulate the immune system, can be therapeutic for coeliac disease, Crohn's disease or irritable bowel syndrome. That strategy is being trialled by other researchers now. We suspect that's why some people volunteer.

Do you have any problems getting funding?
People who need a vaccine against parasitic worms can't afford to pay hundreds of dollars for it. So there's not lots of money spilling around. Malaria is better funded than disease caused by parasitic worms – it's considered more important. Malaria researchers are usually one or two steps ahead of us. But success with a malaria vaccine would help all of us. If they can do it, so can we.

By Anthony King
This interview has been edited for length and clarity.