THE END OF THE BEGINNING

After decades of work, a pioneering malaria vaccine may soon reach the final phase of clinical trials. In the first of two features on efforts against malaria, **Brendan Maher** reports on a vaccine that is far from perfect — but which may provide new direction and save thousands of lives.

In 1987 Rip Ballou taped an ice-cream carton to his arm. The young US Army doctor was doing his bit for science; inside the carton five hungry mosquitoes set about doing theirs. It's an uncomfortable situation, Ballou remembers with a grimace, to have a bunch of the insects "just whaling away on your arm"; all the more so when you know that they have been carefully infected with malaria parasites, and soon you will be too.

Ballou and five colleagues at Walter Reed Army Institute of Research (WRAIR) in Silver Spring Maryland were testing a vaccine candidate, FSV-1. They'd first been injected with it a year earlier; now it was time for any immunity they might have developed as a result to be 'challenged'. Nine days after the mosquitoes had their meals, the first unvaccinated control tested positive for parasites and was given drugs to clear his system. The second control and three vaccinated volunteers followed suit in short order, apparently no more resistant.

On the eleventh day another of the six volunteers fell ill — the tremors struck Stephen Hoffman, a WRAIR colleague in the Navy as he was giving a lecture in San Diego. On the twelfth day, while at a party, Ballou started to feel out of sorts. Not sure if it was the home-brewed beer he'd been drinking or parasites ravaging his red blood cells, he had his wife drive home. Soon he was cycling between chills and fevers and experiencing headaches of unprecedented intensity. "I have never been so sick in my life," he says. "It gave me an extremely healthy respect for this disease." Five of them had succumbed.

But the sixth vaccinee, Daniel Gordon, was still healthy more than four weeks later. For the first time a simple vaccine had protected someone from malaria[1].

That first glimmer of hope grew into an extensive collaboration between WRAIR and the drug company GlaxoSmithKline (GSK) that has turned a descendant of the FSV-1 vaccine, the oddly named RTS,S, into the world's 'most advanced' malaria vaccine. Most advanced means that phase III clinical trials, the final step before licensing the drug, could start by this September. If they go well the vaccine could be licensed and in use by 2011.

To get this far speaks of determination, imagination and perseverance — qualities Ballou and his colleagues, like so many researchers into tropical medicine, show in abundance. It also speaks of something rarer in the field: a lot of money. All told, GSK and partners will have spent upwards of US$500 million by the end of the next set of trials. "We were convinced that if we develop the malaria vaccine it will be hard for society to refuse to pay for it," explains Jean Stéphenne, president and general manager of GSK Biologicals, the unit that works on the vaccine at its facility in Rixensart, Belgium.

And in recent years this conviction has begun to look warranted. Private donors and governments are funnelling hundreds of millions of dollars into projects such as the GAVI Alliance, which provides access to immunizations in the developing world; there is increasing pressure for countries to promise 'advanced market commitment', the setting aside of funds today to buy vaccines when they become available tomorrow.

> **"I have never been so sick in my life. It gave me an extremely healthy respect for this disease."**
> — Rip Ballou

But if RTS,S is the first vaccine to be so bought, it will still fall short of the traditional goals for vaccines. It has improved since its meagre one-in-six showing in that first 1987 challenge, but not that much. RTS,S will offer at best partial protection, maybe 30%, against infection; some indicators predict it might diminish levels of severe malaria by as much as 50%. That may be enough to give infants and small children a better chance of surviving the scourge while they're most vulnerable. But it is a long way from the last word.

Military origins

Malaria research has long been of interest to armies and navies fighting wars in hot wet climes. It was while embroiled in Vietnam that the US military began funding work at New York University on irradiated parasites, which turned out both to be non-infectious and to provide immunity in lab animals. The work culminated in a landmark 1973 paper describing long-lasting protective immunity in humans inoculated with irradiated sporozoites[2] — the form of the parasite that travels from the insects' salivary gland to the victim's liver.

Irradiated sporozoites were not, however, seen as a practical way forward, because their production required live mosquitoes and the use of human blood (Hoffman is now revisiting that conclusion at Sanaria, a company that he has founded in Rockville, Maryland). Instead, researchers looked for what it was about the sporozoites that gave protection, and how the new technologies of genetic engineering might mass produce it.

In the early 1980s antibodies against the sporozoites were used by researchers at the National Institutes of Health and WRAIR to identify the 'circumsporozoite' protein (CSP) and clone the relevant gene[3]. Working with WRAIR, the labs of what was then SmithKline Beckman in Philadelphia, Pennsylvania, zeroed in on a repeating pattern in the protein that seemed to be a major target of antibodies. This fragment, grown from genes cloned into bacteria, went on to become the main ingredient in FSV-1.

In the coming years, Ballou and the SmithKline researchers in Philadelphia tested several variations on the theme. But SmithKline had been moving most of its vaccine development efforts to Rixensart, where they had recently acquired a small but dynamic laboratory, Recherche et Industrie Thérapeutiques. Joe Cohen, who took over the project in Rixensart at the same time as Ballou and his colleagues were infecting themselves, had new plans for the CSP.

Faced with turning the repeating fragment from the protein into a real vaccine, Cohen decided to use lessons that the company had learned from its successful development of a recombinant hepatitis B vaccine, Engerix-B. That vaccine consisted of a surface antigen protein from hepatitis grown in yeast; at high enough concentrations that protein spontaneously forms virus-like particles that have a greater effect on the antibody-making parts of the immune system than loose proteins could. Fusing the repeat region from the CSP to the hepatitis surface antigen protein, Cohen hoped, would make similar particles festooned with the CSP fragments and thus able to provoke the production of antibodies targeted at the sporozoites.

Given a widespread suspicion that antibodies wouldn't be enough to elicit immunity, Cohen

went on to add a fragment from the tail end of the CSP that was thought likely to interest the other arm of the immune system — the arm that prompts T cells to attack infected cells. The resultant "double whammy", as Cohen calls it, was a gene for a protein containing the antibody-inducing repeat (R), the portion recognized by T cell white blood cells (T) and the hepatitis B surface antigen (S).

With all these additions, though, the surface antigen protein lost its knack for self assembly. Through a lot of fine tuning, Cohen finally hit on a way to regain it: one part RTS to four parts plain old S. RTS,S was born.

The vaccine factory

Cohen has shaggy grey hair and an endearing politeness. When showing visitors around the Rixensart facilities where RTS,S was developed, he holds the door for all those he has in tow, necessitating an awkward dance as he takes up the lead again.

Although Ballou and others wax eloquent about the part he played in inventing RTS,S (the patent is in his name), Cohen shrugs the praise off, insisting it was a team effort. But the pride with which he opens a nondescript door in a nondescript building on GSK's Rixensart campus and ushers visitors into the production facilities is unmistakeable. Knee-high windows along one side of a long hallway look out over a fermentation room where yeast colonies from Petri dishes are scaled up to fill 1,600-litre vats, tended by technicians clad in clean-room paper suits. Through a second set of windows opposite, more technicians tend the bank of computers that monitor fermentation. They're in testing now, but Cohen says that once running at regular capacity, this facility could produce tens of millions of RTS,S doses per year. Already, there is more than enough capacity to provide the doses needed for the 16,000 infants he and his colleagues want to recruit into the imminent phase III trials, which will take place across 10 research sites in 7 African countries.

It's just one indication of how quickly the project is moving. Twenty kilometres away, in Brussels, investigators from all over Africa are arriving at a moderately swanky Sheraton right near the Grand Place — people such as Salim Abdulla of Tanzania, who oversees the Ifakara Health Research and Development Centre, a research study site in Bagamoyo, and currently chairs the Clinical Trials Partnership Committee, the formal group of study-site leaders that meets once a year. His cackling laugh rings out repeatedly despite the 30 hours he spent travelling here and the knowledge that the next two days will be intense. High on the agenda is how the different study sites that might take part in phase III trials define severe malaria, a measure

P. COLLINS/WRAIR

WRAIR

C. CAHILL/GLAXOSMITHKLINE BIOLOGICALS

Rip Ballou giving himself malaria in 1987 (above), and today (right), with the vaccine that failed to protect him in a lucite block on his desk.

that has been difficult to standardize. "They go to the same school but they don't agree," Abdulla says. In the lobby, talk centres on the state of affairs at the two sites in Kenya, where violence has been spreading after a disputed election.

Getting from a well designed virus-like particle to international politics and hundred-million-dollar trials was a demanding business. The first requirement was to find a way to get the biggest immunological bang possible for the RTS,S buck — which is to say choosing the right adjuvants. Adjuvants are, in the oft-quoted words of Yale immunologist Charles Janeway, the vaccine makers' "dirty little secret". Ranging from inorganic chemicals such as aluminium hydroxide to fragments of bacterial cell wall, adjuvants boost the immune system's response to the vaccine they accompany, although only recently have researchers begun to understand why. In the 1980s one of the arguments that Stéphenne used to convince SmithKline to invest heavily in Rixensart was that more sophisticated adjuvant formulations would lift hard-to-develop vaccines to the next level of efficacy. The malaria effort, aiming at something no other vaccine had ever achieved — immunity against a complex parasite — was in part an adjuvant stalking horse.

In 1990 the first human challenge trials of RTS,S showed that adjuvants were crucial; with one adjuvant preparation the vaccine was worthless, but with another it protected two out of eight subjects — with a hint of the sought-after T-cell response. "People were excited," says Gray Heppner, a major in Ballou's department at the time. Heppner, now a colonel at WRAIR, has an encyclopaedic knowledge of the army's malaria programmes and an enthusiasm for sharing that knowledge.

Heppner cooked up a protocol to look for responses in Rhesus macaques, and once the difficulties of assessing the monkeys' responses to skin tests in a dimly lit monkey house were sorted out, he had a winner — an oil-in-water emulsion with monophosphoryl lipid A (MPL) and QS21, an extract from the Chilean soapbark tree *Quillaja saponaria*. In 1996 the first human trial with this 'AS02' adjuvant provided protection for an impressive six-out-of-seven individuals[4]. "That was a huge a-ha moment for us," says Ballou.

As with much of the celebration around RTS,S, though, there was sombre dénouement. Six months after the first challenge, five volunteers who had been protected by RTS,S/AS02 took up their ice-cream containers again. This time all but one fell ill[5]. This pattern has, in general, held ever since; the vaccine's protection falls off quite steeply with time.

> **"I knew there and then that this was going to be a vaccine against malaria."**
> — Joe Cohen

Nevertheless, the results were deemed good enough to take into the field. In the summer of 1998, 250 men in the Gambia received three doses of either RTS,S/AS02 or a rabies vaccine and were followed up for 15 weeks. The unblinding, in which the differences — if any — between control and test group are revealed, took place the next year in Rixensart. These unblindings are long-drawn-out processes. Statisticians who know what the data show describe every aspect of the study — compliance rates, randomization, adverse events, immunogenicity and more — to the researchers who actually carried out the work but, because of the blinded structure of the study, didn't know what was going on. Sitting in the audience, Ballou was anxious.

The results were difficult to interpret. During the surveillance period 81 of 131 men who had been given the RTS,S/AS02 vaccine exhibited measurable levels of parasite in their blood. In the control group 80 out of 119 tested positive[6]. That's 62% against 67%, which is not much of a margin. "People really felt that this was way too low to be important," says Heppner. "But Dr Ballou said 'Wait a minute. Look, it works well for the first portion of the trial'." Indeed, during the first nine weeks of surveillance, the vaccine posted an impressive 70% efficacy, but that had tailed off to zero in the remaining six weeks. "It took some additional investigation and analysis by the statistician there to put that into context of what was happening," says Ballou. They were dealing with adults of different ages, many of whom had had malaria many times over and had a certain level of natural immunity to the diease. Further confounding things was that as individuals became infected, the pool of people from whom cases could be measured was shrinking.

Booster benefit

SmithKline, WRAIR and their collaborators in the Gambia quickly made a decision to follow up with a booster dose for a portion of the men the next summer. That follow-up provided strong signals that the vaccine was acting in two ways; it was protecting against infection, and it was also weakening the symptoms in cases where the infection nevertheless took hold. SmithKline decided that a vaccine that could protect people in these ways when they were most vulnerable could save lives. And the most vulnerable are the young: children under five are thought to account for 75% of malaria mortality in Africa.

So SmithKline decided to step down the age of the next trial participants to infancy; if it hadn't, Ballou says, the project would have died. But the company felt that at this stage, it needed help: Ballou remembers Stéphenne telling him and Cohen that to move forward they would need a partner with more money. Ballou wrote a proposal to the William H. Gates Foundation asking for $25 million to help assume some of the risk that SmithKline was taking. In the end the Gates foundation gave $50 million to establish the Malaria Vaccination Initiative (MVI) through PATH, a non-profit organization based in Seattle, Washington. Ballou was asked to lead it, but instead took a job with Washington DC biotechnology

firm MedImmune working on other vaccines, and Regina Rabinovitch, who had managed a network of vaccine initiatives at the National Institutes of Health, became the leader.

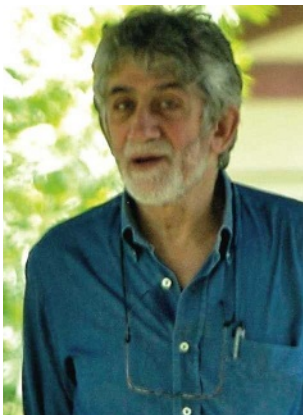
With MVI on board, what was by now GSK began to collaborate with Pedro Alonso, a researcher at Barcelona Centre for International Health Research in Spain, who had developed a field research site in Saude de Manhiça, Mozambique, in 1996. In addition to building health and research facilities, making such a site ready requires outreach to thousands of people in surrounding communities, training staff and developing reliable logistics, such as the 'cold chains' required to keep vaccines viable on their way to recipients. Alonso's site would be the setting for the biggest RTS,S trial so far, a study called Malaria 026 that eventually enrolled an unprecedented 2,022 children between the ages of 1 and 5 to test RTS,S/AS02. Melinda Moree, who succeeded Rabinovitch at the head of MVI, says that the study's tremendous scale was undertaken to make it definitive. It would make or break RTS,S.

When Ballou rejoined the effort in 2003, having left MedImmune to join the GSK team in Rixensart, Malaria 026 was just ramping up and the mood, he says, was very positive. The unblinding was held in Maputo, the capital of Mozambique, on 9 August. For Ballou, Cohen and other veterans, the lengthy ritual was a gratifying one. In one cohort of 1,600 children, infection in the vaccine group was 37% lower. What's more, the vaccine seemed to reduce severe malaria infections by 65% (although that number would come down with further follow-up data)[7]. Cohen says that the news left "A moment of silence that is very difficult to describe ... I knew there and then that this was going to be a vaccine against malaria."

If the investigators were elated, MVI policy-makers were a little less so. "We had sort of our go criteria and our no-go criteria. Then there was this whole area called the grey zone. We were hoping the results wouldn't be in the grey zone," says Moree. But they were. "So there was some amount of disappointment." Even so, Moree put more Gates Foundation money into the MVI project for further trials. "I'd make that call again without hesitation," she says.

Several smaller phase II studies ensued, including Malaria 038, a Manhiça trial looking at safety and efficacy in infants vaccinated at 10 weeks, 14 weeks, and 18 weeks of age. Its results were published in October 2007. The vaccine was safe and seemed again to have efficacy on the order of 65% in the first 3 months and 35% in the first 6 (ref. 8). Across the continent, operations have expanded to encompass several more research sites, all in preparation for the big show, a clinical phase III trial enrolling 16,000 children. MVI has $107 million earmarked for the phase III trials, says Barbara Savarese, a senior programme director there, and intends "to spend every dime of it". The investment is on a par with practically any modern vaccine initiative, says Ballou (who is in the process of moving again, this time to the Gates Foundation).

"A vaccine with 50% efficacy against severe malaria gives us a chance to save 1,000 to 1,500 lives daily."
— Christian Loucq



C. CAHILL/GLAXOSMITHKLINE BIOLOGICALS

Joe Cohen tailored the genes necessary for the RTS,S vaccine.

But doubts persist. In a commentary that accompanied Malaria 038's results in *The Lancet*, Judith Epstein of the US Military Malaria Vaccine Program took issue with the degree to which the RTS,S trials rely on what is known as time-to-event analysis rather than the overall number of cases in the two groups[9]. Although such analysis is appropriate, she says, on its own it may not communicate the whole picture to the people who would ultimately use the vaccine. Hoffman is more critical. "It's not as if it's inappropriate to evaluate a vaccine based on this time-to-event analysis. But the point is, what's the biological meaning of that type of an analysis, and the answer is, we don't know." Without knowing what exactly is going on, how can researchers explain to potential vaccinees what they should expect?

Better than nothing

Dyann Wirth of the Harvard School of Public Health, who is considering a collaboration with RTS,S trial investigators, offers an explanation of what might be going on that draws on analogy to a previous intervention. "The sporozoite vaccine is like the effect of the bed net. It doesn't completely eliminate infection but it does reduce the onset of disease. And the interpretation of that could be that fewer sporozoites get through and establish infection." It is possible that these infecting sporozoites are, in a way, extending the work of the

SOME MALARIA VACCINES IN RECENT OR CURRENT DEVELOPMENT

Stage of infection targeted	Vaccine	Antigen	Phase	Location	Developer
Pre-erythrocytic (targets sporozoite cells, or the liver cells they infect)	RTS,S with AS01/AS02	Circumsporozoite protein (CSP)	Ib/IIb	Multiple African sites	GlaxoSmithKline
	Fowlpox (FP) 9/modified vaccina virus Ankara (MVA), ME-TRAP	Multi-epitope thrombospondin-related adhesive protein (ME-TRAP)	IIb	Kenya	University of Oxford
	Simian adenovirus/MVA	ME-TRAP	Ia/Ib	United Kingdom	University of Oxford
	Liver-stage antigen (LSA) 1/AS02	LSA-1	Ia/IIa	United States	Walter Reed Army Institute of Research (WRAIR)
	Human adenovirus serotype 35 (AdHu35)	CSP	Ia	United States	Crucell
Blood stage (targets merozoite cells that infect human erythrocytes)	Falciparum malaria protein (FMP) 1/AS02	$MSP1_{42}$	Ib/IIb	Kenya/Mali	WRAIR
	Apical membrane antigen (AMA) 1/AS02	AMA1	Ia/IIa	United States	WRAIR
	Merozoite surface protein (MSP) 1_{42}/Alum bi-allelic	MSP1	Ia	United States	National Institutes of Health (NIH)
	AMA1 C1/Alum + CpG	AMA	Ia/Ib	United States/Mali	NIH
	$pfAMA1\text{-}FVO_{[25\text{-}545]}$	AMA1	Ia/Ib	Netherlands/Mali	Biomedical Primate Research Centre
	GMZ2	Glutamate-rich protein/MSP3	Ia	Germany	Statens Serum Institute
	PfCP2.9	$AMA1/MSP1_{19}$	Ia	China	Shanghai Wanxing
	MSP3-Long synthetic peptide	MSP3	Ib	Tanzania	Pasteur Institute
Multi-stage (targets multiple stages of the parasite)	FP9/MVA polyprotein	Six antigens	IIa	United Kingdom	University of Oxford
	PEV3a	AMA1/CSP	IIa	United Kingdom	Pevion
	Adenovirus 5	AMA1/CSP	I/IIa	United States	US Navy

A. V.S. HILL

vaccine. A child may be inoculated with sporozoites by hungry mosquitoes dozens of times. If the vaccine means fewer of those inoculations lead to disease, even for a little while, the children may be able to build more of their own natural immunity before the vaccine's effects dissipate. They'll still get malaria — but not as debilitatingly.

This line of argument offers some grounds for optimism. Clinical trials of insecticide-treated sleeping nets in the 1980s and 1990s posted modest, sometimes conflicting reductions in clinical malaria. But some areas with expanded programmes have now reported 50% or better reductions in child mortality (see page 1047). Malaria control is already a multi-factorial undertaking, with spraying, drugs and bed nets playing what seem often to be reinforcing roles. Even a partially effective vaccine could be another useful component to the strategy. It could even, conceivably, be the one that tips it over onto a trajectory leading to the eradication of the disease — the Gates Foundation's long-term goal.

The Malaria Vaccine Technology Roadmap put together in 2006 by a group from the malaria-vaccine community shows how partially effective vaccines are now playing a part in thinking on the disease. The group's goal for 2025 was a vaccine that provided four years of protection from clinical disease to 80% of users — the sort of target that traditional vaccines aim for, although not a very stringent one. But as a nearer-term goal it saw real advantages in a vaccine offering 50% protection from severe disease for a year. If indications of RTS,S's efficacy against severe malaria hold up, it might deliver that, which would be no small thing. "If tomorrow we can propose a vaccine in Africa that is going to have 50% efficacy against severe malaria," says Christian Loucq, the current director of the MVI, "we have a chance to save 1,000 to 1,500 lives daily."

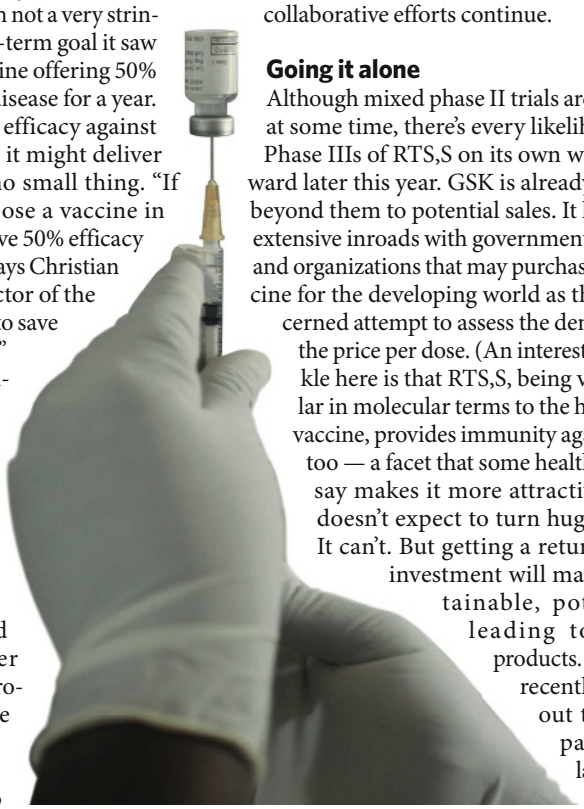
J.-M. MAAS/DARBY COMMUNICATIONS

Adrian Hill at the University of Oxford's Jenner Institute, UK, isn't impressed, though. He is concerned with the reporting from Alonso's group on a second cohort in the Malaria 026 trial. In a 400-subject cohort at a second site with much higher transmission rates, the proportion protected at the end of 6 months seems to be just 11%. Moreover, the data showed no difference in clinical malaria. The investigators on the study maintain that clinical malaria was not a primary endpoint for that part of the study, which was designed to measure the time to the first infection. But Hill still wonders how a phase III roll out will look: "Will it be like cohort 1 or cohort 2?"

Hill's doubts about the vaccine bolster a more general frustration with what he sees as GSK's go-it-alone approach, "unconnected to the other 12 or 15 groups developing vaccines". (see table, page 1045) He and others want different vaccines to be combined with RTS,S in Phase II testing, suspecting efficacy might be greatly enhanced. Heppner, for example, says that results of studies he and his colleagues have carried out on macaques indicate that combining an adenovirus-based vaccine made by the Netherlands biotech company CruCell with RTS,S would offer much better effects[10]: "My hope is that a way can be found to evaluate this clinically just as we've done for earlier improvements of RTS,S." Ballou says that although progress in studying this combination has been stalled for "various business reasons", several collaborative efforts continue.

J.-M. MAAS/DARBY COMMUNICATIONS

Salim Abdulla wants new vaccines to be able to build on the advances of RTS,S.



Going it alone

Although mixed phase II trials are possible at some time, there's every likelihood that Phase IIIs of RTS,S on its own will go forward later this year. GSK is already looking beyond them to potential sales. It has made extensive inroads with government agencies and organizations that may purchase the vaccine for the developing world as those concerned attempt to assess the demand and the price per dose. (An interesting wrinkle here is that RTS,S, being very similar in molecular terms to the hepatitis B vaccine, provides immunity against that, too — a facet that some health officials say makes it more attractive.) GSK doesn't expect to turn huge profits. It can't. But getting a return on the investment will make it sustainable, potentially leading to better products. Bill Gates recently singled out the company's collaborative efforts as a model example of "creative capitalism".

Meanwhile, the partnership has been building infrastructure and good will in Africa. At the meeting of site investigators in Brussels, there was a buzz of excitement about the coming trials. Abdulla is one of the many African doctors who will be seeing the RTS,S project through to its completion, some 25 years after Ballou first had a carton of mosquitoes taped to his arm. Abdulla projects a chipper but world-weary wisdom. His laugh comes easily when describing the maddening attitudes of some local politicians or when he is asked how many times he has had malaria himself and realizes he doesn't know — in the dozens at least. He doesn't worry about the results of phase III. And he doesn't worry that mothers in Africa will feel a false sense of security about their vaccinated children, as Epstein's article suggested[9]. They're more savvy than that. They know that all the various approaches are only partially effective, and that progress means using the right combination.

With luck, Phase III trials will show that RTS,S might be part of that combination. What matters most to Abdulla, though, is that even if it isn't, the infrastructure for research is maintained, so that if after all its hard work GSK has to pull out, there is still a trials pipeline down which future candidates may flow. Whatever the phase IIIs of RTS,S show, there will be volunteers such as Ballou taping ice-cream cartons of mosquitoes to their arms for years to come in the expectation of a short, sharp introduction to one of the world's worst killers. And there will be researchers such as Abdulla, for whom repeated infection is a way of life, eager to take the fruits of those volunteers' labours. Creating a lasting link between them may offer as much lasting benefit as any single vaccine. ■

Brendan Maher is a features editor at *Nature*.

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See Editorial, page 1030, and online at www.nature.com/news/specials/malaria/index.html.