

STATEMENT ABOUT HUMAN CHALLENGE STUDY IN MALARIA BY KEMRI-WELLCOME TRUST

About controlled human infection models

Human infection models, also called human challenge studies, involve deliberately exposing consenting volunteers to infectious substances – bacteria, parasites and viruses. They allow researchers to understand how the body's immune system responds to an infection, and how infection could be treated or prevented.

They have been used in research for almost 300 years, but recently there has been an increase in these studies being conducted especially where disease is mostly known to occur.

Why human challenge is so important

Human infection models involve complex ethical and logistical deliberations, but they also offer significant benefits. They can be used to investigate various things, such as:

- Testing how effective a vaccine is against a specific pathogen – e.g. typhoid
- Helping to identify targets for new vaccines, by allowing researchers to understand how the body mounts a protective immune response – e.g. malaria
- Testing new treatments, for example anti-influenza drugs
- Studying diseases for which no suitable animal model exists, e.g. dengue

More than 20 challenge models are currently in use. Most of them have been carried out in Europe and the US, involving populations with a different genetic background and disease history to those living in the countries where vaccines and treatments are most needed. The human infection models have now been expanded to more countries in Africa and Asia, where the infections are more common, with the eventual goal of developing vaccines that are more effective in these populations.

In the year 2009, a malaria vaccine called RTS,S AS01E was tested here in Kilifi County as part of a larger study. The results have shown that this vaccine was promising but not all children are protected from developing malaria and as of yet we do not have a licensed vaccine.

We still do not understand the immune response to malaria and how we can develop a vaccine that works for all children. This challenge will help us understand the immune response to malaria and may help in the development of a better malaria vaccine.

Malaria model in Kilifi, Kenya

KEMRI-Wellcome, based in Kenya, established a controlled human infection model for malaria in Nairobi, initially in 2013 and more recently in Kilifi with 200 participants drawn from (Junju, Pingilikani and Ngerenya), Nairobi and Kisumu (Ahero).

What they're trying to find out

We know from previous work that repeated infection with malaria results in increased immunity to the malaria parasites, but the biological processes that drive this immunity are not completely understood.

This model allows the research team to study natural immunity to malaria in the Kenyan population to help them understand which antibody responses are most protective against the parasite. The ultimate goal is to enable them to develop a next-generation malaria vaccine that targets the blood stage of the parasite's life cycle which could lead to an 'RTS,S plus' vaccine.

Making a malaria vaccine is complex

The malaria parasite has around 5000 genes, around 200 of which are reasonable candidates for vaccine development against the blood stages of infection. But, making 1 vaccine from 1 gene and testing it can take several million dollars and many years, before determining whether it works.

The KEMRI-Wellcome team have found already that some participants in the malaria challenge, living in malaria-endemic regions, are completely parasite negative after challenge – the parasites just don't replicate in their bodies. These people are super-immune. Super immunity is linked with higher exposure to malaria in the past.

If scientists could replicate the responses leading to this immunity, in theory they could develop an effective vaccine.

How did the study work

On each round, 40 to 60 healthy adults, who had given informed consent, were voluntarily infected with *Plasmodium falciparum* malaria parasites. This was done after carefully checking that these adults were healthy and had an understanding of the study. They were then closely monitored with regular blood tests (PCR) to measure how much malaria they had in their bodies. During this time they remain free to leave the study at any time if they wish.

Participants were treated at an early stage with the recommended antimalarial drugs used for treatment of malaria in Kenya before they reach a certain threshold of parasites. Some had a few symptoms when treated, but none had any severe symptoms. They spent the duration of a maximum of 24 days in accommodation at a local University (Pwani) who are partners in the study. This was done to monitor with them for any signs and symptoms of malaria.

In addition to understanding about malaria, there was a social science and ethics component alongside spearheaded by a team of social scientists at KEMRI that were studying the ethics and participant experience. This was important as any findings from this study would feed back to improve the conduct of the study in the future.

Why were the participants monitored as in-patients?

We can't do the same study in the field (real-life setting) because there are too many variables - whether participants use bed nets or not, if they've taken anti-malarials, if they are bitten by mosquitoes regularly or not at all. Doing a challenge, allows the experiment to be more controlled. Therefore, keeping them in an in-patient facility not only helps to circumvent these variables but also allows for monitoring (twice daily) for any signs and symptoms of malaria.

All of the primary laboratory analysis are being carried out in Kenya, making this an important resource for African scientists, and the resource will also be made available for international collaborations to other groups to learn the maximum amount from the study.

Were the participants compensated

Yes, the participants were compensated for the time they spent at the in-patient facility. The amount compensated was arrived at by considering what they would earn on a daily basis were they engaged in their daily earning activities.

Is the study safe

This study, like all others, has been reviewed by ethics committees here in Kilifi, 2 national committees in Nairobi, and other committees from the study sponsors. These committees check the scientific methods and ensure that the rights, safety and wellbeing of participants are respected throughout the study.