Weaponization of Mosquitos? The Malaria Vaccine's Success Story Hides Legitimate Concerns

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It has been a good year for vaccines. Remarkably effective inoculations were engineered, tested, and rolled out to rein in the COVID-19 pandemic which has killed over 4.8 million people, and on October 6 the World Health Organization (WHO) officially recommended a "groundbreaking malaria vaccine for children at risk." It's hard to wrap our heads around the numbers that make up the fabric of mass infectious illnesses like malaria. In 2019, the number of cases of malaria all over the world wasestimated at 229 million. That's a little over the total population of Pakistan, the fifth most populous country on Earth. For that same year, deaths from malaria added up to 409,000. Two-thirds of those deaths were in children under the age of five.

The announcement by the WHO that a vaccine against malaria, more than thirty years in the making, could finally be recommended was greeted with joy in the media. But our vaccine efficacy expectations, raised aloft by the COVID-19 vaccines' stunning results, need to be tampered down in this case. And while anti-vaccination activists claim, wrongly, that the approved RNA vaccines are "experimental" and are administered to people without their informed consent, the way in which the malaria vaccine's implementation was pilot-tested in three African countries has raised the ethical questions of what constitutes research and whether or not proper consent was indeed secured in those children.

A protean adversary

If the crash course the public received in 2020 about how a respiratory virus infects the body was a beginner's class in infectious diseases, malaria is the advanced lesson.

A coronavirus spitting out its genetic guts inside our cells so that their replication machinery will make more copies of it is plain sailing compared to the complex, shape-shifting life cycle of malaria, a disease that wrangles at least three different organisms. First, there's the infected human. Then, there's the female mosquito, which could be any one of 41 species under the larger umbrella known as *Anopheles*. Finally, and most interesting of all, there's the vector, the go-between, the shapeshifter itself. It's a microscopic, single-celled parasite called *Plasmodium* whose adaptable existence has forced exotic nomenclature from the pens of scientists, words to describe its life stages like "merozoites" and "schizont."

Put simply, the mosquito bites you and its saliva delivers the *Plasmodium* parasite inside your body. For the first week or two, the malaria parasite enters the liver stage of its existence: it replicates itself asexually inside the human liver. Its numbers grow. Eventually, it infects new red blood cells, and thus begins the blood stage and with it the symptoms of malaria.

For the uncomplicated form of the disease, these include the non-specific symptoms we associate with the flu, like fever, headache, chills, and body aches. For the severe form of malaria, this tiny parasite can cause acute injury of the lungs and kidneys, coma, and birth complications with long-term consequences. The parasite continues to make copies of itself asexually inside the red blood cells until the cells burst and the parasites look for new cells to infect. Some of the *Plasmodium* parasites turn into the equivalent of immature sperm and eggs, sexual cells known scientifically as gametes. When you get bitten by another mosquito, these immature gametes get scooped up and the parasite's life cycle continues inside its new mosquito host. The "sperm" and "egg" mature, meet-cute, and lead to new infectious versions of the parasite ready to travel from the mosquito's long proboscis and into a fresh human host.

To complicate matters, *Plasmodium* is not just one thing. It includes six species of parasites that are known to give humans malaria, the most famous of which is *Plasmodium falciparum*, responsible for the vast majority of malaria deaths. But other species—specifically *P. vivax* and *P. ovale*—have the superpower to lay dormant in the form of hypnozoites, which can awaken and cause a relapse of the infection months or years later.

This ability the malaria parasite has to change over the course of its life cycle—a good word for that being "protean," after the mythological Greek god Proteus who would assume different shapes—has really vexed researchers.

Developing a vaccine against a coronavirus is relatively easy, but against this? Which form of the parasite should even be displayed as the crown jewel of a vaccine?

The asexual form that couch-surfs in our liver?

The one that spreads in the blood?

The immature gametes? The mosquito stage?

Should we use the full parasite or a simple protein from it? Given that different forms of the parasite can express different proteins, selecting one such protein for the vaccine also spoils us for choice, unless we should choose two or three proteins together to cover more bases. Different strategies were used by scientists over decades, and while a small number of vaccines managed to make it to a phase II trial in humans, their efficacy was judged "modest" and the immunity they granted was not sustained.

Finally, a large clinical trial in thousands of children and infants yielded encouraging results in 2015 for a specific malaria vaccine that targeted the liver stage of the parasite's life cycle. The vaccine is commonly called RTS,S (an initialism for a shockingly long descriptor), with Mosquirix as its trade name. Whether or not it will be a safe and effective "game-changer" requires a closer look at the results of its testing and how the testing itself was conducted.

"A serious breach of international ethics standards"

Mosquirix prevents 4 in 10 cases of malaria. In terms of efficacy, we have certainly seen better, with two doses of the MMR vaccine being 97% effective against measles and 88% effective against mumps. Even the COVID-19 vaccines had higher efficacies in their clinical trials. When compared to the WHO's goal of having licensed malaria vaccines with efficacies of at least 75% by the year 2030, Mosquirix clearly doesn't check the box.

But given the enormity of the problem, preventing 4 in 10 cases of malaria is still an impressive achievement, especially given that Mosquirix is the only vaccine of a crop of 25 to successfully make it through all three phases of human testing.

This vaccine could save the lives of tens of thousands of children each year. However, as the results of the Mosquirix clinical trials came to light, a number of key questions lingered. Would a four-dose regimen of the vaccine be feasible in the real world of sub-Saharan Africa, where most people are affected by malaria?

Would vaccine recipients assume they were fully protected and dismiss other protective

measures, like insecticide-treated bed nets?

Given the complexities of malaria, the potential for reinfection, and the relatively short length of the phase III trial, would the vaccine really prevent deaths in the long run?

A seven-year follow-up in children who participated in the phase II trial of Mosquirix revealed that the efficacy of the vaccine had gone down over time. There was a rebound effect later on in areas particularly prone to malaria. And more disturbingly, in the biggest trial of the vaccine, three safety signals were picked up: there was a ten times higher rate of meningitis, a higher chance of cerebral malaria, and a doubling of deaths from all causes in girls who had received the vaccine and not the placebo. Were these effects real or chance artefacts?

To answer these questions, the WHO launched a pilot evaluation of the vaccine roll-out in Malawi, Ghana, and Kenya, and this is where we find what has been described as "a serious breach of international ethics standards."

This pilot was registered withClinicalTrials.gov. Its master protocol clearly calls it a "study" and it contains many sections dedicated to "research questions" and "research methods." Indeed, areas within these countries were randomized to either receive the vaccine or not. This is why there was outrage in the scientific community when it was revealed that the WHO had not used informed consent during this pilot study.

Informed consent is when a patient is properly informed about the potential risks, benefits, and alternatives of an intervention and, being of sound mind, can decide to go forward with it or not. Ever since the Nazis' sickening experiments, informed consent has become enshrined in medical ethics.

But in the case of the Mosquirix pilot study, the WHO denied that it was a research activity and stated it had used "implied consent," meaning that the children who received the vaccine and their parents or guardians were not informed that they were taking part in a study.

What emerged out of an investigation by the *British Medical Journal* is that the WHO said it had sent training material to country partners about the potential risks, although the association with an increased risk of deaths among girls seen in the clinical trial was not mentioned in the training material. The vaccine deployment was handled by the countries as part of routine vaccinations. It is this protean roll-out—appearing clearly as a risk assessment research project to some people and as a routine vaccination campaign to others—that the WHO used to recently endorse the wider use of Mosquirix, to much media acclaim.

When interviewed by German radio station *Deutschlandfunk*, Professor Charles Weijer, who co-wrote the ethical rules on the kind of randomized design the WHO used for their pilot study and which were adapted in collaboration with the WHO, declared that the WHO was violating the very rules it had co-authored. This waiver of informed consent looks to Weijer like there is one standard for research in wealthier countries and a different standard for research done in poorer countries. "It looks like colonial science to me," he told the interviewer.

But what about the potential risks of the Mosquirix vaccine detected in the clinical trial?

Were they seen in the pilot roll-out?

According to the WHO, it is now clear that there is no link between the vaccine and these original concerns, but the lack of follow-up at an individual level, the low vaccine coverage, and the short duration of this pilot study (which, to be fair, is still on-going) mean that the actual effect of the vaccine on female mortality, real or not, may have been missed, according to a 2020 analysis by Dr. Christine Benn of the University of Southern Denmark and colleagues. These safety signals, for meningitis, cerebral malaria, and deaths from all causes in girls, have to be sufficiently addressed. A petition, which now has close to 35,000 signatures, is calling for the WHO to be more transparent about its pilot evaluation and to answer the ethical questions that have been raised.

Trust

What a mess. The fight against malaria has been plagued by difficulties. *Plasmodium* is a slippery beast to successfully sketch out for the "Wanted" poster that is a vaccine. It owns many fake moustaches. Mosquirix began testing in 1987, the year that saw the release of *Good Morning, Vietnam* and the first *Lethal Weapon*movie. It has reportedly cost over USD 750 million, a substantial bill that was mostly settled by GlaxoSmithKline and the Gates Foundation. Its efficacy is not great but it can't be dismissed, especially considering the magnitude of the problem. Other interventions exist to prevent or treat malaria, but none are perfect. Bed nets are affordable, but in 2016, only a little over half of people at risk for malaria in sub-Saharan Africa were sleeping under one. Not everyone wants to spend the whole night under a net and, as a WHO spokesperson explained, the nets don't stop mosquitos by day. Treatment with the drug artemisinin, which led to the 2015 Nobel Prize in Physiology or Medicine, has saved millions of lives, but the emergence of drug resistance in Southeast Asia is sounding the alarm. A vaccine, even if it does not prevent every case of malaria, would be a useful part of the armamentarium.

But doubts remain, in my mind, about Mosquirix's safety. It is worth pointing out that travellers to Africa will, by and large, not be eligible for Mosquirix, as the WHO has recommended its use only in children at the moment. This vaccine is meant for the children who live in countries where malaria is widespread. There are, of course, other vaccines in the works, like R21/MM which was recently tested in a phase II clinical trial with 450 children and found to have an efficacy of up to 77%. We will have to see if it and others can clear the hurdle of making it through a phase III trial.

It is high time Africa got a safe and effective vaccine against malaria, but ethical standards and transparency cannot be sacrificed. A vaccine's protection does not simply come from its building blocks. It also comes from trust.

Note: To any reader genuinely curious as to what Mosquirix's generic name, RTS,S/AS01E, stands for, this article unfurls it as "the central repeat region (R) and T-cell epitopes (T) of *P. falciparum* circumsporozoite protein carried by the hepatitis B surface antigen (HBsAg, S), and co-expressed within *Saccharomyces cerevisiae* with unfused copies of HBsAg(S)/adjuvant system 01E." Worth infinite points in Scrabble.

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