ISSN: 3048-8397

Bio Vet Innovator Magazine
(Fueling The Future of Science…)
Volume 3 (Issue 8) AUGUST 2026

OPEN ACCESS | World Mosquito Day – 20th August 2026 | Popular Article

From Cattle to Children: How Veterinary Science Could Help Shape the Next Malaria Vaccine

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DOI: https://doi.org/10.5281/zenodo.22011614

Received: August 16, 2026
Published: August 18, 2026

Abstract:

Every year, malaria reminds us that some of humanity's oldest diseases can remain among its most difficult scientific challenges. The disease is caused by *Plasmodium* parasites and transmitted by infected mosquitoes. Children in malaria-endemic regions are particularly vulnerable, and the burden remains greatest in Africa. In 2024 alone, the World Health Organization estimated about 282 million malaria cases and 610,000 deaths worldwide, with African children accounting for a large proportion of the deaths. The parasite infects cattle; it is transmitted by ticks. *Theileria parva* causes East Coast fever, a serious tick-borne disease of cattle in parts of Africa. At first glance, the disease appears to have little connection with malaria. But *Theileria* and *Plasmodium* belong to the same broad group of parasites known as apicomplexans. They share important biological characteristics, including aspects of their intracellular lifestyles and complex life cycles. For veterinary researchers, *Theileria* is therefore much more than a cattle pathogen. It provides a useful model for understanding how the immune system can recognize and control an intracellular parasite. The cattle research suggests that cell-mediated immunity deserves greater attention as part of the search for durable protection against apicomplexan parasites.

Introduction:

For decades, scientists have searched for a vaccine capable of stopping malaria before the parasite can cause serious disease. That search finally produced a historic breakthrough. In 2021, the World Health Organization (WHO) recommended RTS, S/AS01, the first malaria vaccine for widespread use in children in areas with moderate-to-high transmission. Two years later, WHO recommended a second vaccine, R21/Matrix-M. These vaccines have changed the landscape of malaria prevention. But they are not the end

of the story. They are, perhaps, the beginning of a more ambitious question: Can we develop malaria vaccines that are more powerful, longer-lasting and capable of helping communities move closer to malaria elimination? Surprisingly, some clues may come from an unlikely place—not only from human malaria research, but also from veterinary science and the study of a devastating disease of cattle.

Why is Malaria so Difficult to Vaccinate Against?

One reason malaria has challenged vaccine researchers for so long is the extraordinary complexity of the parasite. Unlike many viruses and bacteria, *Plasmodium* does not remain in one form inside its host. During its life cycle, the parasite passes through different stages involving the mosquito, the liver and the blood. This creates several possible targets for vaccination—but it also creates a problem. A vaccine designed to attack one stage may not adequately protect against another. The two currently recommended vaccines, RTS, S/AS01 and R21/Matrix-M, primarily target the circumsporozoite protein (CSP), which is present on the parasite during its pre-erythrocytic stage, before it establishes infection in red blood cells. These vaccines therefore attempt to stop the parasite early in its journey. However, their protection is incomplete and can decrease with time. In clinical studies, protection can be improved with additional doses, including a fourth dose. The current vaccines therefore represent an important advance, but scientists continue to search for vaccines that provide stronger and more durable protection.

RTS, S and R21: A Major Step Forward

The story of modern malaria vaccination changed dramatically with RTS, S/AS01, commonly known by its trade name Mosquirix. WHO's recommendation in 2021 followed years of clinical research and a large pilot programme in Ghana, Kenya and Malawi. The programme demonstrated that the vaccine could be delivered through routine childhood immunization systems and was associated with reductions in malaria illness and severe disease. The pilot evaluation also reported a 13% reduction in mortality among children eligible for vaccination.

R21/Matrix-M subsequently became the second WHO-recommended malaria vaccine. In a Phase 3 trial, R21 showed 75% efficacy at sites with seasonal malaria transmission and 68% at sites with perennial transmission during the study period reported in the source article. These vaccines have therefore given malaria-endemic countries a new tool.

Learning from the Parasite's Genes:

Another lesson comes from modern genomics and transcriptomics. Parasites do not express every gene at the same level throughout their life cycle. Different stages require different biological machinery. By examining which genes are switched on or off at particular stages, researchers can begin to identify proteins that could serve as vaccine targets. Research on *Theileria* is using genomic and transcriptomic approaches to identify candidate antigens systematically rather than relying entirely on trial and error. Similar approaches are increasingly important in malaria research.

The Next Generation of Malaria Vaccines:

The future of malaria vaccination is unlikely to depend on a single vaccine platform. Researchers are exploring several different strategies.

1. **Whole-sporozoite vaccines:**

   Instead of presenting the immune system with only one parasite protein, whole-sporozoite approaches expose the immune system to a much broader range of parasite components. Studies using attenuated sporozoites have demonstrated substantial protection in experimental settings. New approaches are being developed to allow the parasite to undergo limited development in the liver without progressing to disease, potentially giving the immune system a longer period of stimulation.

2. **mRNA malaria vaccines:**

   The success of mRNA technology during the COVID-19 pandemic has also encouraged researchers to explore the same platform for malaria. mRNA technology offers an interesting advantage: a vaccine can potentially encode several parasite antigens rather than focusing on only one. Early malaria candidates are being developed against CSP as well as conserved regions of proteins expressed during liver-stage infection. This could eventually help researchers design vaccines capable of attacking the parasite at more than one point in its life cycle.

3. **Multi-stage vaccines:**

   Another strategy is to combine antigens from different stages of the parasite. The researchers are investigating combinations that pair a pre-erythrocytic vaccine such as R21 with a blood-stage antigen such as RH5. The idea is straightforward: if the parasite manages to escape the first immune barrier, another immune response could meet it later.

From One Vaccine to A Toolbox:

The future of malaria control may not be defined by the discovery of one perfect vaccine. Instead, it may involve a toolbox of vaccines, each designed to perform a different task.

One vaccine might stop the parasite before it reaches the liver. Another might strengthen immunity against the blood stage. A third might prevent the parasite from developing inside the mosquito, and new platforms such as mRNA technology might allow researchers to combine several targets in a single vaccine.

This combination is particularly important because malaria parasites continue to evolve, drug resistance threatens treatment options, and environmental and climatic changes can alter patterns of transmission. The need for better vaccines therefore remains urgent.

A Lesson That Crosses Species:

The history of medicine is full of discoveries that began in unexpected places. A disease of cattle may reveal something about a human pathogen. A parasite studied by veterinary scientists may teach

immunologists how to stimulate stronger T-cell responses. A technology developed for one disease may become the platform for a vaccine against another. Malaria vaccine research is now entering such a period of convergence. RTS, S and R21 have demonstrated that malaria vaccination can work and can save lives.

Conclusion:

Theileria research shows how strong T-cell responses can contribute to protection against an intracellular apicomplexan parasite. Genomic and transcriptomic studies show how parasite biology can be mined systematically for new vaccine targets. Work on low-cost vaccine platforms also highlights the importance of developing vaccines that are practical for resource-limited regions. These lessons could complement, rather than replace, conventional malaria vaccine research.

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