TARGET MALARIA

A Vector Control Research Alliance

Together, we can end malaria

We are developing an innovative approach to stop malaria transmission

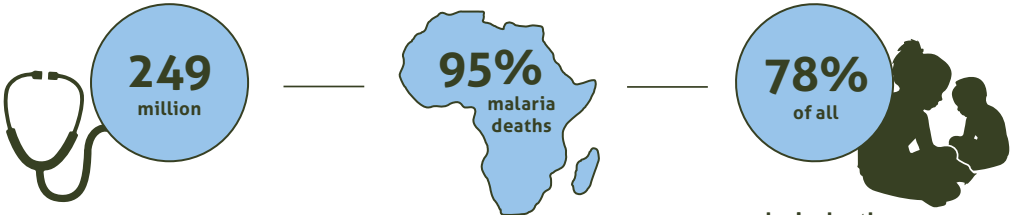
Target Malaria is a not-for-profit international research consortium that aims to develop and share novel genetic technologies for malaria control. We want to help save millions of lives from malaria.

Every year, malaria kills half a million people and infects over 200 million people; a third of the world is at risk of contracting this disease transmitted by mosquitoes. The majority of the victims are children under the age of five living in Africa.

At Target Malaria, we believe that we can find solutions to prevent this disease so that it stops destroying lives, families, economies, and countries.

We are researching genetic technologies to find new approaches to control malaria, focusing on reducing the number of mosquitoes that transmit the parasite.

Current interventions, such as drug treatments, bed nets and insecticide spraying, have helped to lower the burden of malaria but have not been able to eradicate the disease in many countries.



cases of malaria occurred worldwide

occur in Africa

malaria deaths are among children

World Malaria Report 2023[1]

According to the World Malaria Report 2023[1] published by the World Health Organisation (WHO), since 2015, progress in reducing malaria around the world has stalled and cases have even increased since the Covid pandemic. WHO warns that the global response to malaria has reached a "crossroads": if new tools are not found, key targets of WHO's global malaria strategy will be missed[2].

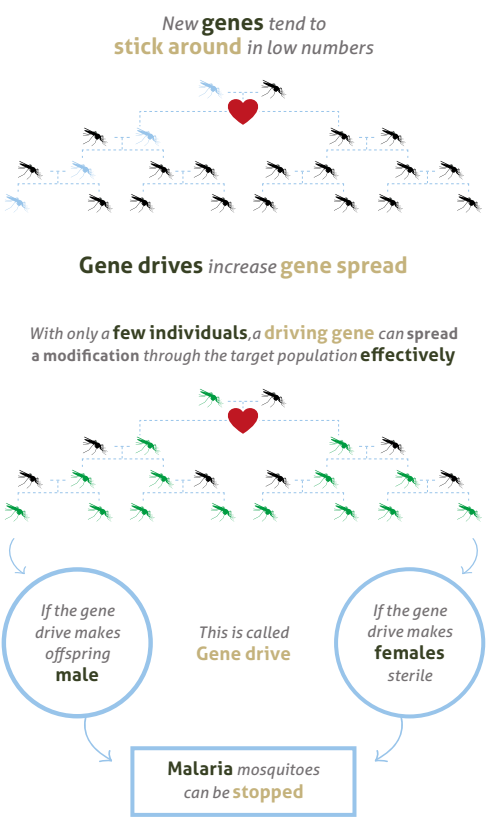
To end this disease, Target Malaria aims to bring new tools to complement existing methods and address current challenges.

Our work

Target Malaria's vision is a world free of malaria. To support this vision, we are developing genetically modified mosquitoes that can be released into a target population to reduce the number of mosquitoes that can transmit the disease. This novel approach would complement existing methods for malaria control. Our aim is to co-develop and share our innovative genetic technologies.

We are adapting a natural genetic mechanism called **gene drive**, to spread a genetic modification in malaria mosquitoes that would affect the mosquitoes' ability to reproduce.
Gene drive is a process that allows the biased inheritance of certain genes from one generation to another, until the gene reaches a frequency where it starts to impact mosquito reproductive ability. Gene drive technologies hold the promise of being a self-sustaining and cost-effective method to reduce the population of malaria mosquitoes.

Our gene drive approaches affect the reproduction of *Anopheles gambiae* mosquitoes, by targeting genes involved in the ability of mosquitoes to mate, lay eggs or reproduce, making them sterile. If most of the female mosquitoes in a given population become sterile or dominated by male mosquitoes, because of the modification, the population will reduce in size to numbers so low that malaria is not transmitted any longer. The technology we are developing allows such modifications to spread through the targeted mosquito population, starting from a release of a small number of modified individuals.



By reducing the population of malaria mosquitoes, we aim to reduce the transmission of the disease.

The use of gene drive is compelling because the modified mosquitoes can be established relatively quickly throughout the target population and would then be maintained over time, effectively making this approach "self-sustaining".

This would make the control of the malaria mosquito population relatively cost-effective to implement because it can cover wide, remote and rural areas with limited need for repeated releases, since the mosquitoes do the work of controlling transmission themselves.

While there are more than 3,500 species of mosquito worldwide and 837 in Africa, only three very closely related species are mostly responsible for transmitting the disease: *Anopheles gambiae*, *Anopheles coluzzii* and *Anopheles arabiensis*. Our technology specifically targets these *Anopheles* species and so should not affect other types of mosquitoes or insects in the surrounding environment.

Target Malaria's work is structured around three key pillars:

Science

Our science teams in Africa, Europe and North America seek to achieve excellence, creating a path for responsible research in the development of genetic technologies. In order to succeed, our research requires the participation of many experts, as no single institution has the knowledge or research environment necessary to succeed alone. The sustainability of our research and the effectiveness of our tools depend on sharing knowledge and investing in partnerships across disciplines and among institutions.

Stakeholder engagement

Throughout each phase, we carry out stakeholder engagement activities to ensure that communities participating or directly affected by the research can make an informed decision about project activities and that these decisions are recorded. The project uses ethically designed engagement best practices to empower these communities to make the most informed decisions about the project's work and its activities. Our engagement goes beyond what is required by law because we see engagement as a process of co-development that helps us improve our research. As our work progresses, we have reached out to an increasing number of national, regional and global stakeholders to inform and consult with them on our development pathway, and to improve our working processes and the technology we aim to develop.

Regulatory affairs

Our project's ability to move through each evaluation phase is subject to national regulatory and ethical approvals. We are committed to abide by international guidelines and to conduct our work only when we have appropriate authorisations from the regulatory authorities in all the countries where we work. Safety is of paramount importance to the project. External scientific advice and independent external risk assessment are being sought for each phase and stage of the research. The project fully complies with international and national legislation and respects existing and emerging guidance relevant to the use of genetic technologies.

Our step-by-step development pathway

Target Malaria is progressing through several phases of iterative research to enable its stakeholders and national authorities in the countries concerned to gain understanding of this new field of research and its potential.

Each of our development stages builds on lessons learnt from previous ones, from the recommendations made by several expert[3] groups and from progress shared among the countries and teams.

Our various strains of genetically modified mosquitoes

Sterile Male
(Non Gene Drive)

Male Bias
(Non Gene Drive)

Gene drive

Non gene drive sterile male

Our development pathway started with a non gene drive genetically modified sterile male mosquito as proof of principle in the laboratory in 2008. The males were genetically modified to be sterile, so they could not have any progeny. This was not intended to be a viable tool for controlling malaria but it was an important step to gain knowledge, start a dialogue with stakeholders and provide a strain of mosquitoes that we could use to evaluate our process, procedures and preparedness. The first release of the sterile male mosquitoes took place in Burkina Faso in July 2019.

Non gene drive male bias

Another step in our phased development pathway has been the development of a mosquito that could successfully mate and produce offspring, but in which the genetic modification would only persist for a few seasons before disappearing. The effect of the genetic modification is to cause a bias in the sex ratio of offspring, leading to more male than female offspring (male mosquitoes do not bite and therefore do not transmit malaria).

Gene drive mosquitoes

Our ultimate goal is a new vector control tool for malaria that can complement existing tools. To achieve this goal, we are developing gene drive mosquito strains, which carry a modification able to reduce the target mosquito population's ability to reproduce. This would help to decrease the population of the malaria vector, the *Anopheles* mosquitoes, and therefore result in a reduction in the number of malaria infections in Africa.

Our research is still at the laboratory stage, and even though results so far have been promising[4], we still have a long way ahead of us before gene drive mosquitoes could be imported and released in Africa. Our models and experiments in laboratory settings (small and large cages) indicate the potential to significantly reduce the numbers of *Anopheles gambiae* mosquitoes, and therefore the transmission of malaria, within a timeframe of years.

Our consortium

7 institutions with over 200 experts

- **CDC Foundation**, USA
- **Imperial College London** – ICL, UK
- **Institut de Recherche en Sciences de la Santé** – IRSS, Burkina Faso
- **Polo d'Innovazione di Genomica, Genetica e Biologia** – PoloGGB (Innovation hub for genomics, genetics and biology), Italy
- **Uganda Virus Research Institute**, Uganda
- **University of Ghana**, Ghana
- **University of Oxford**, UK

The financing

Target Malaria receives core funding from the Bill & Melinda Gates Foundation and from Open Philanthropy. Some individual labs also received additional funding from a variety of sources to support their work, including the Department for Food Environment and Rural Affairs-DEFRA (UK), the European Commission, the MRC Centre for Global Infectious Disease Analysis (UK), the National Institutes of Health-NIH (USA), the Uganda National Council for Science and Technology-UNCST, Ugandan Ministry of Health, the Wellcome Trust (UK), and the World Bank.

To learn more about our work visit our website: **targetmalaria.org**

TARGET MALARIA

A Vector Control Research Alliance

1 World Health Organization (WHO) World Malaria Report 2023. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023

2 World Health Organization (WHO) Position Statement Evaluation of genetically modified mosquitoes for the control of vector-borne diseases - 2020. https://www.who.int/publications/i/item/9789240013155

World Health Organization (WHO) Benefits, future scenarios and feasibility. Executive summary, WHO Strategic Advisory Group on Malaria Eradication - 2019 https://www.who.int/publications/i/item/WHO-CDS-GMP-2019.10

Feachem, R., Chen, I, Akbari, O. et al. Malaria eradication within a generation: ambitious, achievable, and necessary. The Lancet Commissions Volume 394, ISSUE 10203, P1056-1112 (2019). https://doi.org/10.1016/S0140-6736(19)31139-0 https://www.thelancet.com/commissions/malaria-eradication

World Health Organization (WHO) Vector Control Advisory Group, Fifth Meeting - 2017. http://apps.who.int/iris/bitstream/handle/10665/255824/WHO-HTM-NTD-VEM-2017.02-eng.pdf;jsessionid=2E6C156B21FBFC7C1C42ACB251E6DCD8?sequence=1

World Health Organization (WHO) Global Technical Strategy for Malaria 2016-2030 – 2015. http://apps.who.int/iris/bitstream/handle/10665/176712/9789241564991_eng.pdf?sequence=1

The African Union's report on "Gene Drives for malaria control and elimination in Africa". https://www.nepad.org/publication/gene-drives-malaria-control-and-elimination-africa

3 2014 World Health Organisation (WHO) Guidance framework for testing of genetically modified mosquitoes, the 2016 National Academies of Sciences, Engineering and Medicine report Gene Drives on the Horizon and most recently, the 2018 Pathway to Implementation of Gene Drive Mosquitoes as a Potential Biocontrol Tool for Elimination of Malaria in Sub-Saharan Africa: Recommendations of a Scientific Working Group

4 Kyrou, K., Hammond, A., Galizi, R. et al. A CRISPR–Cas9 gene drive targeting *doublesex* causes complete population suppression in caged *Anopheles gambiae* mosquitoes. Nat Biotechnol 36, 1062–1066 (2018). https://doi.org/10.1038/nbt.4245

Simoni, A., Hammond, A.M., Beaghton, A.K. et al. A male-biased sex-distorter gene drive for the human malaria vector *Anopheles gambiae*. Nat Biotechnol 38, 1054–1060 (2020). https://doi.org/10.1038/s41587-020-0508-1