New research published in Science highlights potential of a naturally occurring bacterium to help eradicate malaria

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BY GSK

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- GSK scientists have discovered a strain of Delftia tsuruhatensis bacterium, named Tres Cantos 1 (TC1), that inhibits P. falciparum malaria parasites in mosquitoes

- Discovery led to a collaboration with Johns Hopkins Malaria Research Institute on studies which show bacteria drastically reduces malaria parasite burden in the mosquito, potentially reducing transmission to humans significantly

- TC1 was effective in both An. stephensi and An. gambiae mosquitoes and also inhibits P. berghei malaria parasites, suggesting potential against all malaria parasites affecting humans

- TC1 is naturally occurring in different ecosystems suggesting potential for safe release into the environment and is not transmitted to humans by mosquitoes

- Several characteristics of TC1 suggest low potential for either mosquitoes or the malaria parasite to develop resistance

Research published in Science today shows that a naturally occurring bacterium discovered by GSK scientists – Delftia tsuruhatensis Tres Cantos 1 (TC1) – could be the basis for new anti-malarial interventions. Studies done in collaboration at the Johns Hopkins Malaria Research Institute at Johns Hopkins Bloomberg School of Public Health show that the bacterium can significantly reduce the malaria parasite load in both the mosquito midgut and salivary glands indicating the potential of TC1 to inhibit transmission of the parasite to humans via the mosquito.

The potentially ground-breaking research, which also includes data from preliminary semi-field studies conducted with Institut de Recherche en Sciences de la Santé (IRSS) in a contained 'MosquitoSphere' facility in Burkina Faso suggest that laboratory findings could be successfully translated to the field for malaria control.

Thomas Breuer, Chief Global Health Officer, GSK, said:

> This new discovery is the result of our ongoing commitment to malaria innovation at GSK, adding to the first ever vaccine against malaria, and the first ever radical cure for P. vivax malaria. An additional tool, Delftia tsuruhatensis Tres Cantos 1 (TC1), as an entirely novel approach for malaria control, has potential to further reduce the huge burden of malaria in endemic countries and is more evidence that through deploying a range of prevention approaches, we may be able to finally eradicate this terrible disease.

The discovery of the TC1 bacterium was made by scientists at GSK's Global Health Medicines R&D site in Tres Cantos, Spain, working on next generation malaria medicines. They observed that mosquitoes from an An. stephensi colony in their insectary were no longer able to sustain P. falciparum infection – the most prevalent and fatal type of malaria in Africa, as well as other parts of the world. Experiments confirmed that a particular strain of Delftia tsuruhatensis, which has been named TC1, was responsible for the loss of infectivity.

Researchers from GSK, Johns Hopkins Malaria Research Institute and Fundación MEDINA then found that TC1 secretes very small quantities of a molecule, harmane, that inhibits early stages of P. falciparum development in the mosquito midgut. Importantly, mosquitoes exposed to either the TC1 bacterium or very low concentrations of harmane showed a significant reduction in the form of the Plasmodium parasite which is transmitted to humans by the bite of a mosquito. Once in the midgut, the bacterium stably populates the mosquito gut and P. falciparum inhibition lasted for more than 16 days and potentially for the entire mosquito lifespan.

Delftia tsuruhatensis is a naturally occurring bacterium which is already widely distributed in different ecosystems (fresh and marine water, soil and plants) suggesting potential for safe release into the

environment. Mosquitoes do not release the bacterium with their saliva when feeding, suggesting it is not transmitted to humans.

TC1 was effective in An. stephensi and An. gambiae mosquitoes which are the main vectors of malaria in the Indo-Iranian region and Africa. TC1 was also shown to inhibit two types of malaria parasite – P. falciparum which is the most prevalent type of malaria in Africa and the rodent malaria parasite, P. berghei. These results suggest it has potential to inhibit the development of all malaria parasites which affect humans (P. vivax, P. ovale and P. malariae in addition to P. falciparum).

Several characteristics of TC1 suggest there is low potential for either mosquitoes or the malaria parasite to develop resistance. It does not impact the fitness or reproductive ability of the mosquito avoiding the selection of resistant mosquitoes. By targeting the parasite in the mosquito instead of in humans, parasite numbers are much smaller, so the chances of the parasite developing resistance are greatly reduced.

Today's data demonstrates the potential for TC1 to be used in field settings using low-cost technologies, indicating that TC1-based products could be used as an entirely novel approach for malaria control, adding to the toolbox of interventions needed to get ahead of the disease. A GSK led extensive semi-field study is currently underway with partners at IRSS in Burkina Faso and additional studies on efficacy, manufacturability and safety are currently underway.

Dr Abdoulaye Diabaté, Director of Medical Entomology and Parasitology, IRSS, said: "Malaria is a major public health threat that kills millions of children and profoundly restricts socioeconomic development in Africa. Discoveries such as TC1 bacterium hold huge potential for Africa. We hope to provide a viable solution that can be readily adopted in field settings to control and prevent malaria transmission which could have a profound impact on public health, ultimately helping to save the lives of millions of children and fostering sustainable development in malaria endemic regions."

GSK will continue to pursue this ground-breaking research while engaging with global health institutions and partners to identify the most effective and sustainable approach for development and mobilisation if successful.

In conducting this research programme, in addition to the Johns Hopkins Malaria Research Institute, GSK also worked with scientists from Fundación MEDINA, Institut de Recherche en Sciences de la Santé (IRSS) and used mathematical modelling done in conjunction with scientists from Imperial College London. The Innovative Vector Control Consortium (IVCC) provided technical guidance for the development of potential TC1-based tools.

Potential deployment of TC1

Investigations have found three potential active ingredients (the live bacterium, cell-free supernatant and harmane) which could be incorporated into different mosquito-targeted products for malaria control. Each of these have unique features which allow for deployment to mosquitoes via different routes of administration: all three can be administered to mosquitoes orally, and the supernatant and harmane can also be taken up through contact via the mosquito exoskeleton. This suggests there could be multiple ways to administer these active ingredients for malaria control.

Malaria continues to be a major health threat in many parts of the world with nearly half of the world's population at risk of contracting the disease. In 2021, there were an estimated 247 million cases of malaria and over 619,000 deaths, the majority of whom were children under the age of 5 living in Africa. Progress against this devastating disease has stalled since the pandemic, with an additional 13 million cases and 63,000 more deaths in 2020 and 2021. The warming climate is predicted to expand the areas where malaria spreads and increase the length of the malaria transmission season in many places. Extreme weather events like flooding, which are becoming increasingly frequent, also lead to surges in malaria infections.,, With mosquitoes becoming increasingly resistant to insecticides and the malaria parasite developing resistance to medicines, novel interventions are urgently needed to get ahead of the disease.

GSK is a global biopharma company with a purpose to unite science, technology, and talent to get ahead of disease together. Find out more at gsk.com/company.

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The 2022 report of the Lancet Countdown on health and climate change: health at the mercy of fossil fuels - The Lancet

Malaria and dengue predicted to affect billions more people if global warming continues uncurbed | LSHTM

Felled by a Warming World: Will Malaria Be the Next Pandemic? - Opinion - The Global Fund to Fight AIDS, Tuberculosis and Malaria

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