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Tropical medicine researchers show malaria prophylaxis is effective when the timing is right

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Over 100 million travelers from temperate regions visit malaria-risk areas every year. Some 30,000 become infected with the pathogen Plasmodium falciparum, which is spread by the Anopheles mosquito. Malaria takes its deadly toll on the local population also; especially on high-risk groups such as children and pregnant women. There are various drugs available which can prevent malaria. But some can have serious side effects; others must be taken every day to be effective. Forgetting to take the anti-malaria tablets is currently the biggest risk factor for travelers when it comes to contracting the disease. Researchers headed by Professor Peter Kremsner and Dr. Benjamin Mordmüller at the Institute of Tropical Medicine of the University of Tübingen and the German Center for Infection Research (DZIF) have run the first clinical trials on a new agent, DSM265. In a study supported by MMV (Medicines for Malaria Venture) and the DZIF, healthy volunteers were infected with malaria parasites after taking the new active substance; DSM265 demonstrated a good prophylactic effect. The study has been published in the medical journal *The Lancet Infectious Diseases*.

Preventive drugs must meet high standards of efficacy, safety, and tolerance. "They are taken by healthy persons who, due to living outside malaria-endemic regions, have no acquired immunity to the disease," explains the manuscript's first author, dr. Mihály Sulyok of the Institute of Tropical Medicine and the DZIF. DSM265 is the furthest developed agent in a new generation of malaria medications; researchers say it has

the potential to effectively prevent the disease. DSM265 is taken orally and inhibits dihydroorotate dehydrogenase, an enzyme in the metabolic chain leading to the production of pyrimidines. Pyrimidine forms the basis of important DNA building-blocks – which carry genetic information. The researchers are exploiting this, the malaria parasite's Achilles' heel. Unlike many other organisms, the malaria pathogen depends on production of its own pyrimidines. Its replication first in the human liver and then in the blood can be stopped using Plasmodium-specific blockers of this process. "Theoretically DSM265 can stop an infection by Plasmodium straight after the mosquito bite," says Professor Kremsner.

In the trial, 21 healthy volunteers who had never had malaria were given either a single dose of DSM265, placebo, or an already established drug for malaria prevention. It was a double-blind experiment, which means neither the study participants nor the investigators knew which participant was in which group. One or seven days after taking DSM265 all the participants were infected with malaria parasites and treated with a highly effective drug immediately when first parasites appear in the blood. "As was expected, all volunteers in the placebo group developed malaria. The participants who took DSM265 one day previously were fully protected against the disease," Dr. Mordmüller explains. "Taking it seven days prior to infection was only partially efficacious, but there are ways to improve that, for instance by increasing the dose." Safety and tolerability of DSM265 was very good. "We need to do a lot more studies yet. But this first clinical trial has been very promising," says dr. Sulyok. Now the development of DSM265 as a malaria prophylaxis effective in the long term can go ahead.

More information: Mihály Sulyok et al. DSM265 forPlasmodium falciparumchemoprophylaxis: a randomised, double blinded, phase 1 trial with controlled human malaria infection, *The Lancet Infectious Diseases* (2017). DOI: 10.1016/S1473-3099(17)30139-1