Ivermectin treatment in humans for reducing malaria transmission

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Malaria still kills millions. Researchers are excited by a new intervention: giving people a drug which kills mosquitoes that bite them. Incredibly, this is a reality, as the drug ivermectin, widely used for the

control of parasite infections such as lymphatic filariasis and onchocerciasis, appears to do this. With some mosquitoes now resistant to the insecticides used in treated bed nets, this is a potentially important new control measure.

LSTM's Dr. Rebecca Thomas and Dr. Joseph Okebe, together with Dr. de Souza from the Noguchi Memorial Institute for Medical Research (NMIMR), University of Ghana, first examined the experimental evidence that giving the drug to people kills the mosquitoes that bite them.

All included studies showed large effects of ivermectin on mosquito mortality. They then went on to seek studies that evaluated whether this made a difference in malaria transmission and the amount of malaria in people living in malarial areas. They found only one study has been published to date. When published in 2019, there was quite a lot of press coverage stating ivermectin reduced malaria in children based on original report of this trial.

Unfortunately, although this paper was published in *The Lancet*, the statistical methods used in the analysis were not standard and did not adjust adequately for clustering, so the effect may have been overestimated.

After the researchers who did the original study kindly supplied the data, the London School of Hygiene and Tropical Medicine's Dr. Clémence Leyrat, expert in issues of small samples and non-compliance in cluster-randomized trials, and Dr. John Bradley, expert in cluster-randomized trials, reanalysed the data and are part of the Cochrane review author team.

Dr. Leyrat and Dr. Bradley said: "To date there has been one small pilot trial of ivermectin. The statistical analysis of the trial was unsuitable, and

the original publication overstated the amount of evidence it provided. With this reanalysis we show that the trial did not produce strong evidence that mass administration of ivermectin is useful in preventing malaria, leaving the question of its efficacy open. Fortunately, there are some larger trials in progress which will provide further evidence."

The one included study enrolled eight villages in Burkina Faso, which were randomly assigned to receive ivermectin or a control. All villages received ivermectin, as part of the scheduled control of lymphatic filariasis. In addition, the treatment villages received five more doses of ivermectin, once every three weeks. The effect of ivermectin on malaria was measured in children younger than five years of age. In these children, the treatment did not show a notable difference in the presence of malaria between the treatment and control groups. Following the review of the data from this study, the team summarized that they were uncertain whether community administration of ivermectin influenced malaria transmission.

Dr. de Souza from the NMIMR said, "There may be varied reasons for the observed lack of evidence. However, challenges to the use of ivermectin could be the duration of the reproductive cycle in mosquitoes , the mosquito behaviour, and the incubation period of malaria parasites in the mosquito. While the conditions for laboratory experiments are carefully controlled, there may be wide variations in the natural environment. As such, a short-term increase in mosquito mortality alone through ivermectin administration could slightly reduce the risk of malaria transmission but may not be sufficient for a sustained impact. Given the ivermectin half-life in the blood, maintaininga high enough ivermectin concentration over several days and weeks to kill any blood feeding, infective, mosquito will be key"

Senior author Dr. Joseph Okebe agreed: "Unfortunately, it is currently not possible to say if treating an entire community with ivermectin

reduces malaria. However, several research studies are in progress and, as such, we anticipate they will provide more answers to this important question in the future."

More information: et al, Ivermectin treatment in humans for reducing malaria transmission, *Cochrane Database of Systematic Reviews* (2021). DOI: 10.1002/14651858.CD013117.pub2

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