Advancing the repurposing of ivermectin for malaria

A Crump, TDR, WHO/Science Photo Library

Published Online
March 13, 2019
http://dx.doi.org/10.1016/S0140-6736(18)32613-8

See Online/Articles
http://dx.doi.org/10.1016/S0140-6736(18)32321-3

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There is ever-increasing anticipation for the potential of mass drug administration of endectocides (also known as systemic insecticides) to reduce malaria transmission, with ivermectin emerging as the most likely first-in-class endectocide.[1] More than half of the 46 papers published on this subject in the past decade appeared in the past 2 years. 23 projects are registered in the MESA Track database, of which seven are active today; and, more importantly, trial mapping by the Malaria Ivermectin Roadmap[2] shows that abundant new evidence on the topic will be available by 2020.

Why is there so much interest in repurposing ivermectin? After achieving remarkable advances from 2000 to 2015, the global fight against malaria has stalled.[3] Beyond funding and access gaps, residual transmission—driven by mosquito behavioural adaptations that allow avoidance of home-based insecticides—has become a key liability for vector control, and challenges achievement of the global goals set forth by WHO.[4]

Ivermectin lays the path for a whole new concept: drug-based vector control.[5,6] Ivermectin, or indeed any effective endectocide, could be administered to eligible members of the at-risk community as a complementary tool for vector control. It could be administered alone or in combination with partner drugs to allow for integrated management of malaria or neglected tropical diseases, directly responding to residual transmission by targeting malaria and some lymphatic filariasis vectors, regardless of their feeding behaviour. [7,8]

In *The Lancet*, Brian Foy and colleagues[9] report the results of the RIMDAMAL trial, which enrolled participants from eight village clusters in a high-transmission area in southwestern Burkina Faso. Eligible village residents in the control and intervention groups received a single 150–200 µg/kg dose of ivermectin plus 400 mg of albendazole, but those in the intervention group received five additional 3-weekly doses of ivermectin alone, with mass drug administration coverage of 70–75% across the 18-week intervention period. The active case detection cohort comprised children aged 5 years or younger who were living in these villages. These children were visited three times every 2 weeks by a nurse who tested them for malaria, assessed symptoms, and provided treatment, if needed, allowing for monitoring of malaria incidence in this key age group. The primary outcome was cumulative malaria incidence (adjusted for sex and clustering), which was reduced in the intervention group (648 episodes among 327 children; 2·00 episodes per child) compared with the control group (647 episodes among 263 children; 2·49 episodes per child; risk ratio 0·81 [95% CI 0·72–0·90]; risk difference −0·49 [−0·79 to −0·21], p=0·0009).

Although the sample size was small and the regimen chosen for this trial (six doses over an 18-week period) might not have been optimal for implementation, these results provide the first evidence of an effect of mass ivermectin administration that goes beyond mosquito mortality, showing a measurable reduction in malaria incidence in children aged 5 years or younger, thereby demonstrating the concept of community effects. This trial continues to build the evidence base and, thus, increase interest in the repurposing of an existing drug that could help bridge to a more effective malaria strategy at a time when malaria progress is threatened, as shown by the increase in cases globally.

Ongoing or soon-to-start trials will assess the efficacy and safety of the new malaria indication of ivermectin with two different dosing regimens: either three consecutive daily doses of 300 µg/kg, as identified by the IVERMAL dose-ranging study,[10] which showed a good compromise between safety and the effects on mosquitoes; or a single-dose regimen of 400 µg/kg, currently used for control of lymphatic filariasis. Pharmacokinetic and modelling data support the evaluation of both regimens for the malaria indication. Ivermectin will be tested either alone or in combination with other drug-based strategies against malaria, delivered as seasonal malaria chemoprophylaxis or community mass drug administration.

Beyond the generation of evidence regarding safety and efficacy of ivermectin, the crucial next steps are determination of the best distribution approaches, identification of synergies in alliance with neglected tropical disease programmes, and ensuring a supply of the drug for campaigns at an affordable cost. Interested manufacturers must ultimately have their products prequalified by WHO to allow for the use of multilateral funds in the procurement process. The new malaria indication of ivermectin, combined with appropriate

demand forecasting, could incentivise investment by manufacturers of generics.

Foy and colleagues' work[9] is an important step for a promising, preventive intervention for malaria. The development of this new tool will require clear epidemiological (ie, human disease) impact and coordination with the neglected tropical diseases community,[11] but the ultimate results could help us to get back on track to meet the global malaria goals.

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CC and NRR have co-authored three papers on this general topic with two of the Article's authors, Brian Foy and Hannah Slater, both of whom are participants in the Malaria Ivermectin Roadmap, which we are leading.

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