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First molecular diagnostics for insecticide resistance in sandflies

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A study led by LSTM identifies a potent molecular mechanism for insecticide resistance in the world's most medically-important sandfly species and develops DNA-diagnostics for monitoring future impact on visceral leishmaniasis control and elimination programs.

Leishmaniasis is a group of several related neglected tropical diseases which are all transmitted by the bite of sandflies. Of these, visceral leishmaniasis (VL) is the most severe, with very high fatality if untreated and great impact in rural areas of Brazil, East Africa, and especially the Indian subcontinent. In a paper published in the journal *PLOS NTDs*, researchers from the Department of Vector Biology of LSTM (UK) and the Rajendra Memorial Research Institute (RMRI, India) identify DNA polymorphisms causing two knockdown resistance (kdr) mutations in the pyrethroid and DDT target site gene of the sandfly Phlebotomus argentipes, the sole vector of VL in India.

LSTM's Dr Bruno Gomes, the lead author of the paper said: "Mutations in this gene are widely linked with insecticide resistance in mosquitoes and other insects but this is the first record in sandflies. The two mutations, which are identical to those found in Anopheles and Culex mosquitoes in Africa, co-exist in this species of sandfly in Bihar state, the primary Indian VL focus, and strongly predict survival to DDT and pyrethroids. Phlebotomine sandflies are very difficult to rear in a laboratory setting, which makes assessment of insecticide resistance using bioassays far more challenging than in mosquitoes, and places a premium on DNA resistance markers which can be applied to any

specimen, even those dead and poorly preserved."

For decades, indoor residual spraying (IRS) targeting sandflies with DDT has been the main control tool in the region and is likely to have selected for the - now widespread - DDT resistance via the kdr mutations detected. Indeed, higher frequencies of these mutations are seen in the parts of Bihar which is subject to more IRS. Pyrethroids are now being implemented as an alternative in Bihar but because both insecticides attack the same target, the same mutations also compromise the lethality of pyrethroids, at least at lower doses.

Dr David Weetman, the paper's senior author commented: "Unlike for DDT, pyrethroid resistance affecting sandfly control has not yet been detected in India, however this would be a huge challenge for VL control and must be avoided. Ensuring insecticide is sprayed at the correct dose, which has been a focus of LSTM work for several years in Bihar, becomes even more crucial now that sandflies have a demonstrated genetic resistance mechanism. Sensitive and specific, kdr markers will provide an easily-applied, early-warning diagnostic system to predict oncoming problems. Nevertheless, it is crucial that new methods of control, including further alternative insecticides are trialled against VL-transmitting sandflies as an urgent priority, which forms the next step of LSTM and RMRI's research programme."

More information: Bruno Gomes et al. Knockdown resistance mutations predict DDT resistance and pyrethroid tolerance in the visceral leishmaniasis vector Phlebotomus argentipes, *PLOS Neglected Tropical Diseases* (2017). DOI: 10.1371/journal.pntd.0005504

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