

Drug-resistant *Leishmania donovani* with a higher fitness - could our medicines boost pathogens?

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Background: *Leishmania (Leishmania) donovani* is a protozoan parasite that causes visceral leishmaniasis (VL) in the Indian subcontinent and is transmitted between hosts by sand flies. For decades, pentavalent antimonials (SSG) have been the mainstay in the treatment of VL but SSG-resistant parasites affected its efficacy, contributing to up to 65% SSG-treatment failure in the Indian subcontinent. SSG acts among others through the effector mechanisms of the macrophage, the host cell of *Leishmania. L. donovani* that acquired resistance to SSG might therefore have also acquired a higher tolerance to the immune system of the host of which the host cell is the last link. This would benefit SSG-resistant (SSG-R) *L. donovani* above SSG-sensitive (SSG-S) *L. donovani*, even in absence of the drug.

Methods: This study aimed to evaluate the fitness of SSG-R *L. donovani* to help assessing SSG's legacy for the efficacy of other drugs and the control of VL in general. In order to do this, several life stages of the parasite were mimicked in the lab so that the *in vitro* and *in vivo* survival capacity of SSG-S and SSG-R *L. donovani* could be compared. The transmission of *L. donovani* was also translated into a mathematical model.

Results: A mathematical model showed that the prevalence of SSG-resistance in Bihar could not be explained without assuming a higher fitness of SSG-R parasites. *In vitro*, SSG-R strains showed a greater capacity to generate infectious forms which likely contributed to the observed higher *in vitro* and *in vivo* infection and survival skills of SSG-R *L. donovani* compared to SSG-S *L. donovani*. Field studies also revealed a high prevalence of SSG-R parasites in natural populations of India despite the low SSG pressure nowadays.

Conclusion: SSG-R *L. donovani* does not seem to display the fitness cost that is usually associated with natural drug resistance. On the contrary, our findings suggest that SSG-R *L. donovani* have an increased fitness and might be harder to eliminate than their SSG-S counterparts.

Keywords: drug resistance, fitness cost, virulence, visceral leishmaniasis, pentavalent antimonials