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Invermectin Response "*Byonchocerca Volvulus*" and Genetic Studies: A Short Retrospective Analysis.

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Onchocerca volvulus (nematode worm) is the causal agent of human onchocerciasis, also known as "river blindness". This designation for onchocerciasis is due to the vector (blackflies) breeding in fast flowing rivers or streams close to remote villages located near fertile land where people rely on agriculture. In [1] the World Health Organization (WHO) has presented a good document on onchocerciasis considering all aspects. From this document we emphasize: (i) *O. volvulus* is transmitted to humans though exposure to repeated bites of infected blackflies of the genus *Simulium* (Diptera: Simulidae); (ii) symptoms include severe itching, disfiguring skin conditions, and visual impairment, including permanent blindness.

In our studies on onchocerciasis [2,3] carried out in Guinea- Bissau, we have found several infected individuals presented nodules in subcutaneous tissue (some several centimeters in diameter and visible externally as rounded elevations of the skin) and skin changes in the body were observed, including depigmentation of the skin (leopard skin), and ocular changes including blindness; (iii) more than 99% of infected people live in 31 African countries. The disease also exits in some foci in Latin America and Yemen; (iv) the Global Burden of Diseases Study estimated in 2017 that there were 20.9 million prevalent *O. volvulus* infections worldwide, 14.6 million of the infected people had skin disease and 1.15 million had vision loss; (v) community directed treatment with ivermectin is the core strategy to eliminate onchocerciasis in Africa, in the Americas the strategy is biannual large- scale treatment with ivermectin; (vi) four countries have been verified by WHO as free of onchocerciasis after successfully implementing elimination activities for decades: Colombia, Ecuador, Mexico and Guatemala; (vii) by the end of 2017, three additional countries had stopped mass drug administration and completed three years of post-treatment surveillance in at least one transmission area: Bolivarian Republic of Venezuela , Uganda, and Sudan; (viii) 1.8 million people live in areas that no longer require mass drug administration for onchocerciasis.

Taking these findings into consideration, we can conclude that onchocerciasis is an important public health problem and that ivermectin has been used in mass treatment of this disease.
Our objective is to raise an alert for the genetic implications on the emergence and potential spread of sup-optimal responses. For this, we have a good and recent article [4] when the authors showed that "mass drug administration is likely to exert selection pressure on parasites, and phenotypic and genetic changes in several O. volvulus populations from Cameroon and Ghana (exposed to more than a decade of regular ivermectin treatment). This has raised the concern that sub-optimal responders (SOR) to ivermectin's anti-fecundity effect are becoming more frequent and may spread. On the other hand, those authors, in their conclusions/significance argue that "ivermectin response is a polygenically determined quantitative trait whereby identical or related molecular pathways, but not necessarily individual genes, are likely to determine the extent of ivermectin response in different parasite populations. Furthermore, we propose that genetic drift rather than genetic selection of

SOR is the underlying driver of population differentiation, which has significant implications for the emergence and potential spread of SOR within and between these parasite populations".

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