LETTER TO THE EDITOR

Response to: ‘Nodding syndrome, many questions remain but we can prevent it by eliminating onchocerciasis’

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We thank Dr Gumisiriza et al. (in press) for their interest in our review (Olum et al., 2020), and for drawing attention to their two subsequently published 2020 studies exploring the association of onchocerciasis elimination with the incidence of epilepsy in general and nodding syndrome in particular (Gumisiriza et al., 2020a, b). They conducted epilepsy surveys in northern and in western Uganda and compared their results with historical surveys, respectively, from 2012 and in 1994 (during which interval, community-directed ivermectin treatment and ground larviciding programmes had been completed). In both areas, there was a clear fall in nodding syndrome incidence. Colebunders and colleagues have also now identified nodding syndrome in many other onchocerciasis endemic areas, including Cameroon, the Democratic Republic of Congo and Liberia. The authors draw cause-and-effect conclusions from these and other observations linking epilepsy to onchocerciasis (Colebunders et al., 2017).

These observations are certainly consistent with causality, though the authors stress the absence of a convincing mechanistic explanation: certainly, few if any of Koch’s postulates have been met. As we indicated in our review (Olum et al., 2020), no trace of the organism has been found in CSF or brain autopsy studies (excluding the possibility that the organism might be cultured from CNS tissue). Colebunders and others have very recently added to this literature, showing that even in individuals with epilepsy (not nodding syndrome) and active skin onchocercal infection, neither microfilariae nor parasite DNA were detected in any of the CSF samples by light microscopy or polymerase chain reaction, and no zebrafish injected with the CSF developed seizures (Hotterbeekx et al., 2020). In none of the large animal, non-human primate or rodent experimental onchocerciasis models has epilepsy been reported—and so the fourth postulate, re-isolation, also cannot be met.

An alternative, post-infectious autoimmune relationship to onchocerciasis has (again as we summarized) been suggested by the finding of leiomodin-1 antibodies the sera and CSF of nodding syndrome patients (Johnson et al., 2017)—but only half of nodding syndrome cases appear to have autoantibodies, while a third of healthy controls have the same putatively highly neurotoxic autoantibodies; and autopsy studies do not show the inflammatory changes seen in antibody-mediated encephalitis.

Colebunders and colleagues also emphasize in their studies that, during the interval between surveys (5 years in one study, 34 years in the other), many other changes affecting the population studied will have occurred. The authors successfully controlled for several of these, but others will have included general improvements in public health, the final resolution of internal civil and military conflicts, and the introduction of successful AIDS prevention and treatments, to name but a few. Additionally, widely administered ivermectin will have had therapeutic effects on a significant number of infectious agents other than onchocercal species, as a consequence of its additional antimalarial, antibacterial and antiviral effects (Omura and Crump, 2014) (which are now claimed to
include a putative anti-COVID-19 effect (Chaccour et al., 2020). Indeed, ivermectin also appears to have anti-seizure activity (Mayer and Horton, 1991). Additionally, nodding syndrome has been observed in areas of Uganda not identified as endemic for onchocerciasis.

That said, any deficiency in absolute proof of a causal link to nodding syndrome by no means proves the absence of a link; and we entirely agree with Gumisiriza, Vieri and Colebunders that onchocerciasis remains a widespread, serious and highly treatable condition. We also agree that further research is necessary and important—and we agree in particular that the need for more studies ‘does not justify inaction while communities and individuals remain seriously affected by this condition’ (Colebunders et al., 2019).

Although ivermectin is in fact by no means entirely free of significant adverse effects (Boussinesq et al., 2003), onchocerciasis elimination programmes do work and should remain a global health priority.

Data availability
Data sharing is not applicable to this article as no new data were created or analysed.

Competing interests
The authors report no competing interests.

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