Tackling onchocerciasis-associated epilepsy

New evidence and recommendations for policymakers

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Preventing devastating ‘river epilepsy’

Onchocerciasis, also known as ‘river blindness’, is an eye and skin disease that causes severe discomfort and can lead to permanent blindness. Onchocerciasis affects 19.1 million people worldwide, nearly all in Africa[1]. It is increasingly recognised that onchocerciasis is also associated with high rates of epilepsy (onchocerciasis-associated epilepsy or ‘river epilepsy’). Nodding syndrome and Nakalanga syndrome are two forms of ‘river epilepsy’ that can lead to severe disability and early death. ‘River epilepsy’ is a highly neglected and stigmatised condition. A community-based programme in Western Equatoria State, South Sudan, aims to protect children from developing onchocerciasis and associated epilepsy, and improve the care of persons with epilepsy.

Key findings

- Onchocerciasis-associated epilepsy (OAE), or ‘river epilepsy’, is a leading cause of mortality in areas with high ongoing onchocerciasis transmission. Nearly all people with OAE die before the age of 30 years.
- OAE is seriously impacting the social and economic development of affected areas. A high prevalence of OAE is linked with severe socio-economic consequences and poverty, while children with epilepsy drop out or are excluded from school.
- There are large epilepsy diagnosis and treatment gaps in the study settings.
- **The interventions were effective, demonstrating that OAE is preventable and treatable**. In Maridi, the implementation of a bi-annual CDTI programme and community-based “Slash and Clear” vector control method resulted in an **89.2% reduction in epilepsy incidence.** Blackfly biting rates reduced by 99%. Improvement of epilepsy treatment and care resulted in **over 90% of treated people reporting reduced seizures and increased quality of life**.
- However, while coverage of ivermectin increased from 40.8% to 56.6%, the 80% coverage required for onchocerciasis elimination was not achieved, indicating that CDTI alone is not enough. A multi-pronged approach is needed, with strong community engagement.

Recommendations

- Successful interventions should be scaled up in South Sudan. CDTI coverage and distribution frequency should be increased, prioritising children aged 5−15 years. Effectiveness of CDTI distribution would be enhanced by involving community leaders and community drug distributors (CDDs), and ensuring adequate supervision of CDDs.
- Treatment, care provision and awareness of epilepsy in OAE-affected areas must be stepped up, with attention to improving access to education for children with epilepsy.
- **OAE is preventable.** Donors, humanitarian actors and governments must increase global awareness and resource mobilisation to strengthen onchocerciasis elimination and epilepsy treatment in endemic regions, and develop holistic cross-government responses.
- Further research is needed to inform and support elimination efforts in low-resource settings.

About this briefing

This briefing is based on findings from the study *"Evaluation of a community-based comprehensive epilepsy prevention and treatment programme in onchocerciasis-endemic villages in South Sudan",* led by Principal Investigators from Amref Heath Africa and the Ministry of Health, South Sudan. This research project was funded by Elrha's Research for Health in Humanitarian Crises (R2HC) programme. A full list of partners and acknowledgements are provided on page 11.

Contents

Background and policy context

Onchocerciasis, also known as 'river blindness', is an eye and skin disease that causes severe discomfort and can lead to permanent blindness. Onchocerciasis is caused by the parasitic worm *Onchocerca volvulus* and occurs when an infected blackfly (Figure 1) bites a human and introduces larvae onto the skin, where they enter through the bite wound. These larvae develop into adult worms which can live in the body for approximately 15 years. Symptoms of infection include severe itching, disfiguring skin conditions and visual impairment, which may lead to permanent blindness.

Global burden: Onchocerciasis and its related morbidities constitute a major public health problem and a barrier to socio-economic development, particularly in Africa. According to recent data from the WHO, over 240 million people worldwide were estimated at risk of contracting onchocerciasis in 2020 and therefore required chemotherapy against *O. volvulus* infection.

How onchocerciasis is transmitted

Onchocerciasis is caused by infection with the worm *Onchocerca volvulus*. *O. volvulus* is spread by the bites of infected blackflies (*Simulium* spp.) that breed in fast-flowing water. The three study sites in Western Equatoria State, South Sudan, all contain rivers where blackflies breed.

Child with 'river blindness'

Figure 1: Blackfly

In 2015, the Global Burden of Disease study estimated a total of 990,000 (95% CI: 0.45–1.72) disability-adjusted life years (DALYs) — meaning the number of years lost due to ill-health, disability or early death — attributable to onchocerciasis in sub-Saharan Africa[2]. This number was calculated based on the prevalence of onchocerciasis skin and eye disease but would considerably increase if epilepsy was also considered a co-morbidity of onchocerciasis, as evidence increasingly supports.

Policy responses: In 2021, WHO launched the 2021–2030 road map for Neglected Tropical Diseases (NTDs)[3]. This road map stressed the importance of 1) Stronger accountability—shifting from process to impact indicators and accelerating programmatic action, 2) Intensified cross-cutting approaches, and 3) Stronger country ownership, improved roles of stakeholders, and clearer roles and responsibilities to deliver on 2030 targets. In this road map, the target is to increase the number of countries with interruption of onchocerciasis transmission from 4 in 2020 to 12 in 2030, and to stop mass drug administration (MDA) of ivermectin in at least one onchocerciasis-focus area from 9 to more than 34 countries[3].

To reach this ambitious goal, current onchocerciasis elimination programmes will need to be stepped up: studies have indicated that annual ivermectin treatment alone is not sufficient to interrupt onchocerciasis transmission.[4] Other innovative and cost-effective solutions are needed.

Links between onchocerciasis and epilepsy

The link between onchocerciasis and epilepsy, including Nodding syndrome and Nakalanga syndrome, is increasingly recognised by experts. It is known that onchocerciasis is associated with epilepsy (OAE), and how to prevent it;[5] though the pathogenesis (process by which OAE develops) is still not well understood. A high prevalence of epilepsy, including cases of Nodding syndrome and Nakalanga syndrome, has been reported in all areas with high onchocerciasis transmission where this has been investigated[5,6]. In these areas, either the onchocerciasis elimination programme was working sub-optimally (low community-directed treatment with ivermectin (CDTI) coverage) or there was no programme at all[6].

Onchocerciasis-associated epilepsy (OAE): 'River Epilepsy'

A type of epilepsy that appears in onchocerciasis-endemic regions in previously healthy children between the ages of 3−18 years without any obvious cause. The most debilitating forms of OAE are nodding syndrome and Nakalanga syndrome. **Nodding syndrome** is a neurologic condition characterised by repetitive seizures and dropping forward of the head, often associated with other types of seizures. **Nakalanga syndrome** is characterized by stunting, delayed or absent secondary sexual development and skeletal deformities and epilepsy. **Both conditions are irreversible and progress towards premature death if not treated.**

OAE, a preventable disease: In the last 20 years, countries with sufficient resources and adequate health systems have successfully eliminated onchocerciasis-induced blindness through annual CDTI. However, so far, epilepsy has not been considered internationally to be associated with onchocerciasis. Despite new evidence indicating that bi-annual CDTI combined with vector control can prevent children developing OAE, there has as yet been no global programme established. OAE is a major public health problem in many onchocerciasis-endemic areas in sub-Saharan Africa where onchocerciasis elimination programmes are not working optimally, often due to poverty, conflict or weak health systems**.**

In South Sudan, onchocerciasis is endemic in nearly half the country (49%) [7]. The national onchocerciasis elimination programme was interrupted for several years due to security problems, scarce resources and a weak healthcare system. A modelling study suggested there may be up to 400,000 cases of OAE[2] in Africa. Several recent studies in Uganda[8,9], Cameroon[10], Tanzania (Mmbando *et al.,* unpublished) have shown that interventions against onchocerciasis (CDTI with vector control but also CDTI alone) reduced the incidence of OAE, including nodding syndrome. This study in South Sudan adds to the growing evidence that **we must tackle onchocerciasis to reduce epilepsy.**

"We need to strengthen our onchocerciasis elimination strategies through increasing the distribution of ivermectin, together with the vector control work. We have just seen results in Maridi. If we scale up across South Sudan, we will be able to interrupt transmission of onchocerciasis and end epilepsy/nodding syndrome cases."

Mr Yak Yak Bol, Director of Neglected Tropical Diseases, South Sudan Ministry of Health

About the study

Evaluating a multi-pronged approach: The aim of the study was to evaluate a community-based prevention programme to decrease the onchocerciasis disease burden in South Sudan and improve epilepsy treatment and care. The interventions combined and evaluated in Maridi were: 1) CDTI distribution with bi-annual community directed treatment; 2) 'Slash and Clear' vector control method for eliminating blackflies; and 3) a community-based epilepsy treatment programme. The study took place in Maridi, Mundri and Mvolo Counties, three onchocerciasis endemic areas in Western Equatoria State in South Sudan, with Mundri and Mvolo Counties acting as the control sites. The study took place from 2018 to 2022.

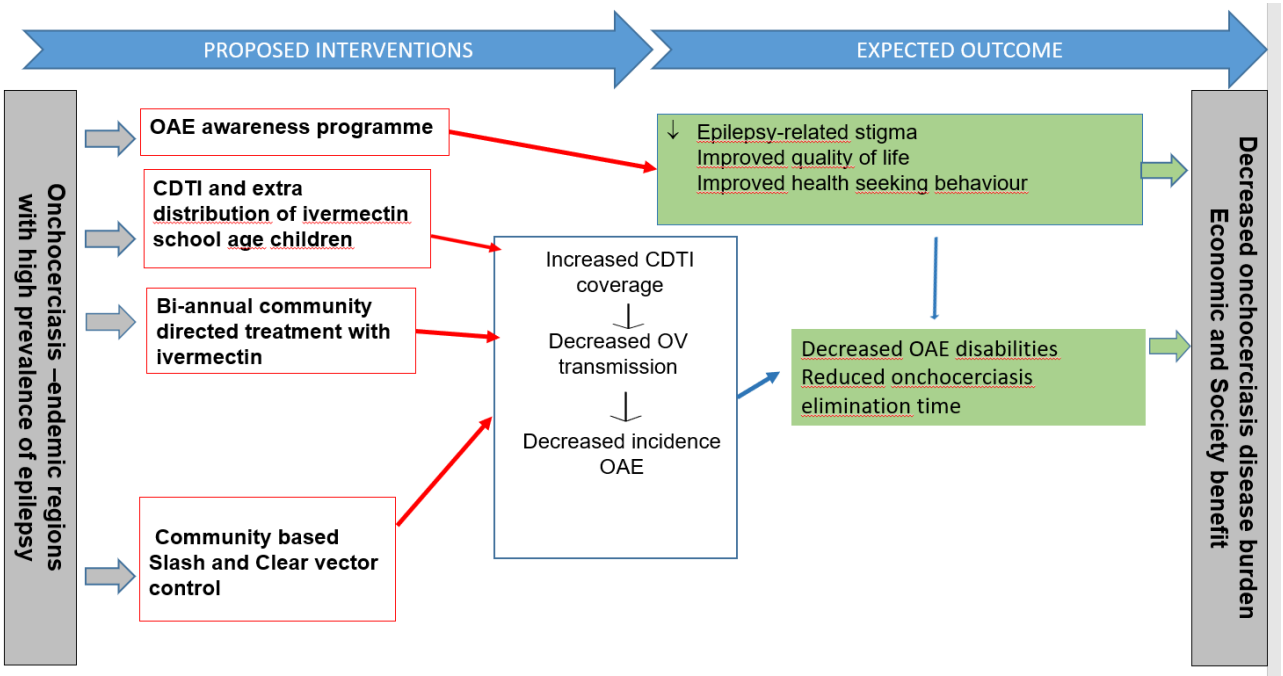

Figure 2: Interventions and expected outcomes

Summary of methods: To determine the effect of onchocerciasis elimination efforts on epilepsy prevalence and incidence, baseline and follow up surveys of house-to house epilepsy were conducted in selected villages in the three study sites. Onchocerciasis prevalence was determined by examining skin snips microscopically for the presence of *O. volvulus* parasites. Level of onchocerciasis transmission was measured by determining the presence of antibodies to *O. volvulus* in blood using the onchocerciasis Ov16 Rapid Diagnostic Test (RDT) in children aged 6–9 years. The effect of the "Slash and Clear" intervention on eliminating blackflies was determined by measuring and monitoring blackfly biting rates. Epilepsy treatment was evaluated by assessing the number of new persons diagnosed with epilepsy, the number of persons treated with epilepsy, the frequency of seizures, treatment adherence, loss to follow up, and epilepsy-related mortality.

Learning from the evidence: Key findings

The scale of the challenge

The prevalence and burden are high in all three counties. In Maridi, at baseline, an epilepsy prevalence of 4.4% was documented[11]; 84.9% of persons with epilepsy (PWE) and 50% of healthy controls had active onchocerciasis infection. Epilepsy was by far the main cause of death, responsible for 17% of deaths. The village closest to the Maridi dam, the main blackfly breeding site, was found to have exceptionally high prevalence and transmission, as well as high blackfly biting rates. This pattern was repeated in Mundri and Mvolo.

Epilepsy is a key cause of morbidity and mortality in the three counties. About 80% of PWE presented with the criteria of onchocerciasis-associated epilepsy (OAE)[12]. The highest prevalence of onchocerciasis-associated morbidities, including epilepsy, is found among households living close to blackfly breeding sites. In such households, often more than one child is affected by epilepsy[13]. Several children with nodding syndrome and other forms of epilepsy may be found in one family[13,14]. Epilepsy is one of the main causes of mortality in the high epilepsy prevalence villages at the study sites, and nearly all people with epilepsy die before the age of 30 years[13,14].

An **extensive gap in epilepsy diagnosis and treatment** was found in all study sites at the start of the programme. For example, in Mvolo, 20% of the PWE had never been treated with anti-seizure medication and 14.4% presented with burn lesions because they had fallen into a fire during seizures[13]. The diagnosis of epilepsy is often delayed; therefore, treatment with anti-seizure medication is started late, leading to the progressive intellectual deterioration from recurrent seizures.

Less than half the population were taking available ivermectin prior to interventions. In **Maridi,** with annual CDTI, only 40.8% of the population took ivermectin in 2018. In **Mundri,** with annual CDTI, only 46.9% of the population took ivermectin in 2021. In **Mvolo** with annual CDTI, only 41.9% took ivermectin in 2019.

Wider social and economic impacts of OAE

Poverty, stigma, and misperceptions: A high prevalence of OAE is associated with severe psycho-social consequences and increased poverty. For example, 8.7% of PWE in Mvolo were reported to present with severe behavioural problems[13], and in Mundri, 4.8% of PWE were severely disabled, unable to walk or attend to their own bodily needs without assistance[14]. The result is that family members need to take care of them and are therefore restricted from working.

The household clustering of persons with epilepsy has led communities and local healthcare workers to wrongly believe epilepsy is contagious and transmissible by direct contact, increasing the stigma. Children with epilepsy are not allowed to sleep with other children under a bed net or eat out of the same plate[15]. There are also serious educational impacts: untreated children with epilepsy are prevented from going to school or may

drop out due to the stigma and fear of transmission, as well as repetitive seizures and progressive intellectual impairment[16].

Community members and local healthcare workers in affected villages are often not informed about onchocerciasis as the likely cause of the high prevalence of epilepsy in their villages[15]. This leads to uncertainty, fear, and misconceptions and contributes to the stigma towards persons with epilepsy[15]. This disease is therefore impacting children and youth in these areas, the next generation of South Sudanese and the hope of the older generation for their country's economic development.

Effectiveness of the interventions

Coverage of CDTI increased: From the start of the project, where coverage was low, in **Maridi**, the coverage increased from 40.8% in 2018 to 56.6% after **biannual CDTI** was implemented, while it did not increase in the control counties Mundri and Mvolo. While the increased coverage in Maridi was significant, it remains below the required 80% to reach onchocerciasis elimination. During meetings with local communities and stakeholders, including the Ministry of Health, recommendations were proposed to improve CDTI coverage and these are reflected in this brief.

Significant impact on epilepsy incidence and nodding syndrome: In **Maridi**, the implementation of biannual CDTI and the community-based "Slash and Clear" vector control method achieved **an 88.9% decrease in epilepsy incidence.** The incidence of nodding syndrome decreased in a similar proportion. Analysis in Mvolo is ongoing to determine the final reduction, but early indications are of a significant decrease (see Figure 3).

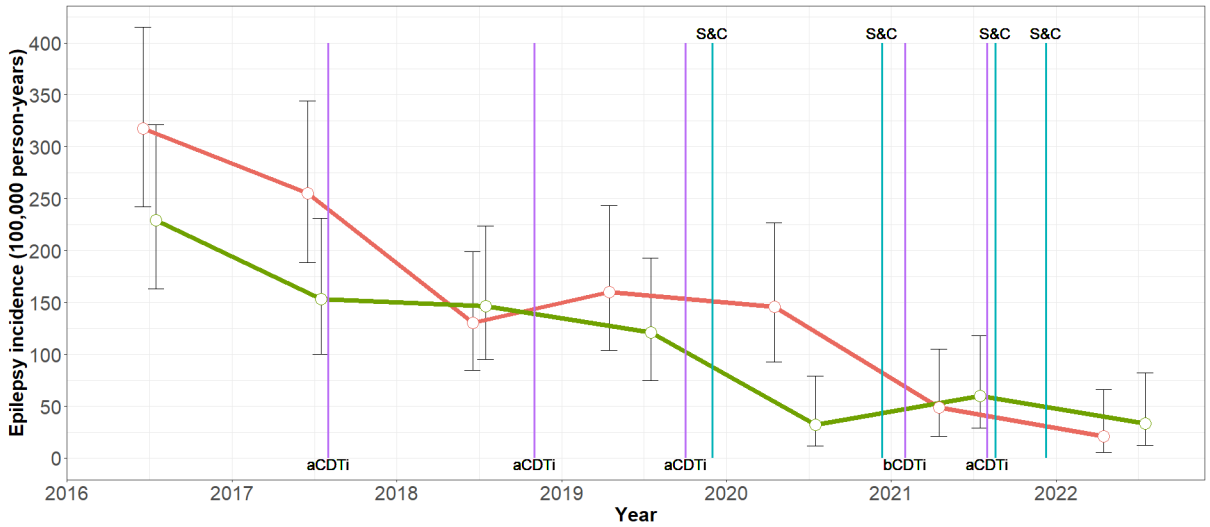

Figure 3: The incidence of epilepsy per year in Maridi (red) decreased after annual CDTI (aCDTI), biannual CDTI (bCDTI) and vector control (S&C). The incidence of epilepsy per year in Mvolo (green) also decreased after annual CDTI (aCDTI).

Improved care and quality of life—the epilepsy treatment centres: Three epilepsy treatment centres were established in the study settings where anti-epileptic treatment was provided free of charge. Epilepsy treatment guidelines were established, and healthcare workers were trained to diagnose and treat epilepsy.

More than 3,500 persons with epilepsy are currently being treated in the greater Maridi and Mundri areas, more than four times the number being treated at the start of the project. Nearly all (94%) persons with epilepsy attending the treatment centres had a decrease in the frequency of seizures, while 91% reported an improvement in their quality of life. A pilot school re-entry programme was initiated, and 120 children could return to school.

'Slash and Clear' vector control at Maridi dam

Impacts of vector control on blackfly biting rates: In Maridi County, the "**Slash and Clear**" intervention which focused on removing vegetation to stop blackflies breeding at the Maridi dam. Biting rates decreased by over 99% after implementing the first round of "Slash and Clear", except for a spike in biting rates in January 2020 shortly after the first "Slash and Clear", likely due to remaining mature larvae and pupae missed from scraping the concrete dam spillway. This reduction in blackfly biting rates was sustained when the "Slash and Clear" intervention was performed twice a year in 2021 (Figure 4).[15,20]

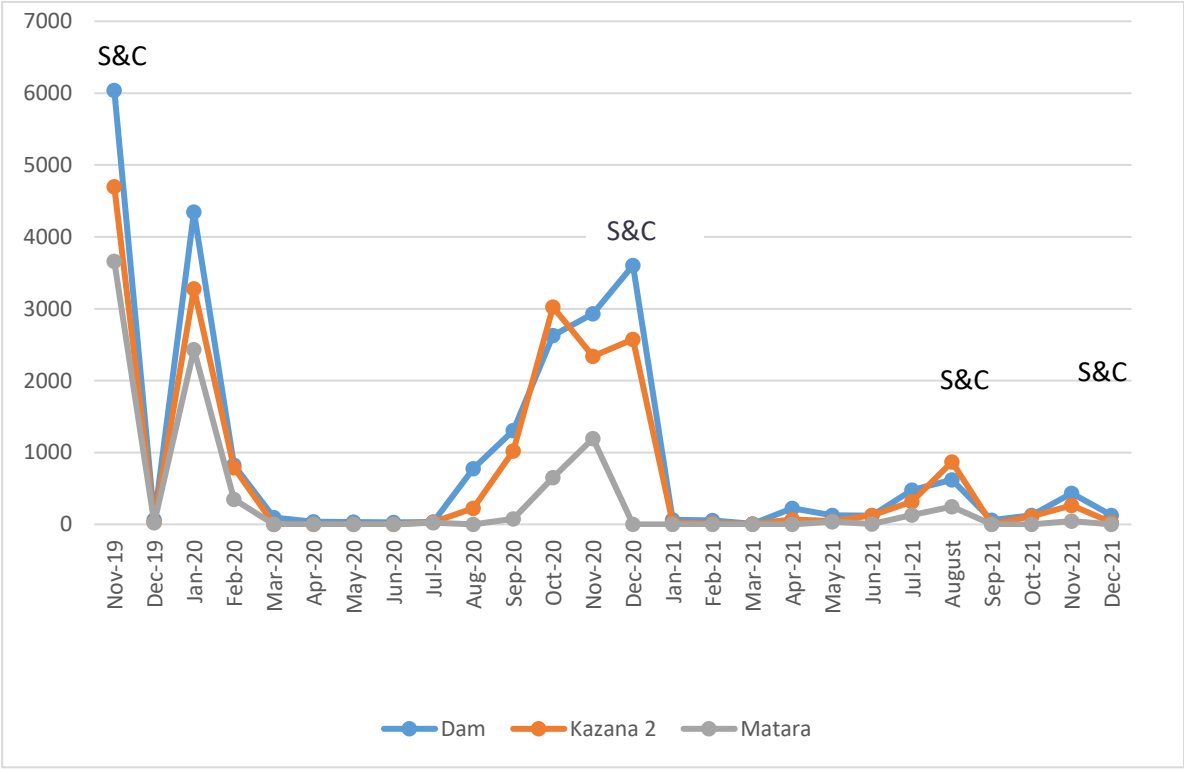

Figure 4. The "Slash and Clear" (S&C) vector control intervention drastically reduced blackfly biting rates. 'Kazana' is the village next to the dam. Matara is a village 3.5 km downstream from the dam.

Recommendations for policymakers

Results demonstrate that a targeted, multi-pronged approach to tackling OAE is effective

- The interventions that were successful in Maridi should be scaled up throughout South Sudan and could be considered in other onchocerciasis endemic regions in Africa.
- CDTI coverage should be increased in all the study sites. This could be achieved by increasing the ivermectin distribution time, increasing the involvement of local community leaders, using community-directed distributors (CDDs) chosen by the communities, and improving CDD supervision.
- Bi-annual CDTI is preferred, but if too costly, extra distribution of ivermectin should be considered among children aged 5−15 years who are most at risk for OAE, at school or at other distribution points, six months after every CDTI.

CDTI alone is not enough. Onchocerciasis elimination programmes should incorporate additional interventions and recognise the wider impacts of OAE on communities

- The community-based "Slash and Clear" vector control method is a simple, inexpensive community-based vector control approach that could accelerate the elimination of onchocerciasis. It should be incorporated, preferably twice a year, as a vector control intervention in onchocerciasis elimination programmes.
- Community engagement is key for both epilepsy and onchocerciasis management. Epilepsy needs to be demystified and stigma and discrimination reduced through OAE awareness programmes. Local leaders should be engaged to increase the coverage of CDTI.
- The negative impacts of OAE are significant for communities. Treatment, care provision and awareness of epilepsy in OAE-affected areas require urgent attention and greater investments within existing health system funding programmes in South Sudan, as does improving access to education for children with epilepsy and reducing care costs.
- A holistic cross-government approach is needed to address OAE's negative impacts on health, education and family livelihoods.

International support and more resource and expertise is needed

- OAE is preventable. It must be recognised by international donors and public health actors as a major public health problem in many remote areas of sub-Saharan Africa and action should be stepped up to prevent children, their families and communities from contracting this devastating disease.
- International efforts must be focused on tackling preventable death, disabilities and the wider negative impacts of OAE in South Sudan and other countries affected.
- OAE should be included in the calculation of the burden of disease caused by onchocerciasis. This could help mobilise additional resources for onchocerciasis disease elimination, treatment and care.
- More research is urgently needed to: map the onchocerciasis disease burden in sub-Saharan Africa; map the blackfly breeding sites in areas of high transmission; identify ways to strengthen onchocerciasis elimination programmes in settings where resources are limited; and obtain further information on how OAE develops.

References

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; 396(10258): 1204-22.
2. Vinkeles Melchers NVS, Mollenkopf S, Colebunders R, et al. Burden of onchocerciasis-associated epilepsy: first estimates and research priorities. *Infect Dis Poverty* 2018; 7(1): 101.
3. World Health Organisation DoNTD. Ending the neglect to attain the sustainable development goals: a road map for neglected tropical diseases 2021–2030. WHO/UCN/NTD/2020.01. 2021. 2021.
4. Dadzie Y, Neira M, Hopkins D. Final report of the Conference on the eradicability of Onchocerciasis. *Filaria J* 2003; 2(1): 2.
5. Colebunders R, Siewe Fodjo JN, Hopkins A, et al. From river blindness to river epilepsy: Implications for onchocerciasis elimination programmes. *PLoS Negl Trop Dis* 2019; 13(7): e0007407.
6. Colebunders R, Njamnshi AK, Menon S, et al. Onchocerca volvulus and epilepsy: A comprehensive review using the Bradford Hill criteria for causation. *PLoS Negl Trop Dis* 2021; 15(1): e0008965.
7. Abd-Elfarag G, Logora MY, Carter JY, et al. The effect of bi-annual community-directed treatment with ivermectin on the incidence of epilepsy in onchocerciasis endemic villages in South Sudan: a study protocol. *Infect Dis Poverty* 2018; 7(1): 112.
8. Gumisiriza N, Mubiru F, Siewe Fodjo JN, et al. Prevalence and incidence of nodding syndrome and other forms of epilepsy in onchocerciasis-endemic areas in northern Uganda after the implementation of onchocerciasis control measures. *Infect Dis Poverty* 2020; 9(1): 12.
9. Gumisiriza N, Kaiser C, Asaba G, et al. Changes in epilepsy burden after onchocerciasis elimination in a hyperendemic focus of western Uganda: a comparison of two population-based, cross-sectional studies. *Lancet Infect Dis* 2020; 20(11): 1315-23.
10. Siewe Fodjo JN, Tatah G, Tabah EN, et al. Epidemiology of onchocerciasis-associated epilepsy in the Mbam and Sanaga river valleys of Cameroon: impact of more than 13 years of ivermectin. *Infect Dis Poverty* 2018; 7(1): 114.
11. Colebunders R, J YC, Olore PC, et al. High prevalence of onchocerciasis-associated epilepsy in villages in Maridi County, Republic of South Sudan: A community-based survey. *Seizure* 2018; 63: 93-101.
12. Colebunders R, Abd-Elfarag G, Carter JY, et al. Clinical characteristics of onchocerciasis-associated epilepsy in villages in Maridi County, Republic of South Sudan. *Seizure* 2018; 62: 108-15.
13. Raimon S, Dusabimana A, Abd-Elfarag G, et al. High Prevalence of Epilepsy in an Onchocerciasis-Endemic Area in Mvolo County, South Sudan: A Door-To-Door Survey. *Pathogens* 2021; 10(5).
14. Jada SR, Dusabimana A, Abd-Elfarag G, et al. The Prevalence of Onchocerciasis-Associated Epilepsy in Mundri West and East Counties, South Sudan: A Door-to-Door Survey. *Pathogens* 2022; 11(4).
15. Jada SR, Tionga MS, Siewe Fodjo JN, Carter JY, Logora MY, Colebunders R. Community perception of epilepsy and its treatment in onchocerciasis-endemic villages of Maridi county, western equatoria state, South Sudan. *Epilepsy Behav* 2022; 127: 108537.
16. Jada SR, Siewe Fodjo JN, Abd-Elfarag G, et al. Epilepsy-related stigma and cost in two onchocerciasis-endemic areas in South Sudan: A pilot descriptive study. *Seizure* 2020; 81: 151-6.

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