Effect of onchocerciasis elimination measures on the incidence of epilepsy in Maridi, South Sudan: a 3-year longitudinal, prospective, population-based study

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Summary

Background High onchocerciasis transmission predisposes endemic communities to a high epilepsy burden. The 4·4% epilepsy prevalence documented in 2018 in Maridi, South Sudan, prompted the strengthening of onchocerciasis elimination measures. Community-directed treatment with ivermectin was implemented annually in 2017, 2018, and 2019, interrupted in 2020, and re-implemented biannually in 2021. We aimed to assess the effect of these interventions, along with slash and clear vector control on the incidence of epilepsy, including nodding syndrome.

Methods In this longitudinal, prospective, population-based study, we did a two-stage house-to-house epilepsy survey before (May 10–30, 2018) and after (March 9–19, 2022) the strengthening of onchocerciasis elimination interventions in South Sudan. Strengthening also included the implementation of a community-based slash and clear vector control method that we initiated in 2019 at the Maridi dam (the main blackfly breeding site). Eight sites were surveyed near the Maridi dam and inclusion required residence in one of these sites. All household residents were first screened by community workers, followed by confirmation of the epilepsy diagnosis by trained clinicians. The primary outcome was epilepsy incidence, including nodding syndrome, which was assessed via self-reported new-onset epilepsy in the previous 4 years of each survey, confirmed by clinician assessment.

Findings The preintervention survey included 17 652 people of whom 736 had epilepsy (315 female and 421 male), and the post-intervention survey included 14 402 people of whom 586 had epilepsy (275 female and 311 male). When biannual community-directed treatment with ivermectin was initiated in 2021, the intervention's coverage rose by 15·7% (95% CI 14·6–16·8); although only 56·6% of the population took ivermectin in 2021. Between 2018 and 2022, epilepsy incidence decreased from 348·8 (307·2–395·8) to 41·7 (22·6–75·0) per 100 000 person-years. Similarly, the incidence of nodding syndrome decreased from 154·7 (127·6–187·3) to 10·4 (2·7–33·2) per 100 000 person-years. The identified risk factors for epilepsy were: living closer to the Maridi dam, being aged between 6 and 40 years, not taking ivermectin, and being male.

Interpretation In onchocerciasis-endemic areas with high epilepsy prevalence, strengthening onchocerciasis elimination interventions can decrease the incidence of epilepsy, including nodding syndrome. Additional efforts are needed to increase community-directed treatment with ivermectin coverage and sustain blackfly control in Maridi.

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Introduction

Onchocerciasis is a neglected tropical disease primarily found in Africa, caused by the filarial nematode *Onchocerca volvulus* and transmitted through bites of infectious blackflies (*Simulium* spp).[1] Annual or biannual community-directed treatment with ivermectin is the cornerstone intervention for the elimination of onchocerciasis.[2] Epidemiological studies have documented high prevalence and incidence of epilepsy in onchocerciasis-endemic areas with suboptimal onchocerciasis elimination programmes and high ongoing *O volvulus* transmission.[3,4] Most people with epilepsy in these areas meet the criteria of onchocerciasis-associated epilepsy.[5–7] Onchocerciasis-associated epilepsy usually appears in previously healthy children between the ages of 3 years and 18 years, with a peak onset at 8–11 years.[8] Onchocerciasis-associated epilepsy comprises a broad spectrum of seizures including generalised tonic-clonic, absence, and nodding seizures (as part of the nodding syndrome). Some onchocerciasis-associated epilepsy cases can also have stunting with delayed puberty (ie, Nakalanga syndrome).[8]

Onchocerciasis is endemic in all ten states of South Sudan, placing nearly half of the population (49%) at risk of contracting the disease.[9] Maridi County is an onchocerciasis-endemic area in South Sudan,[10] with an estimated population of 115 717 in 2020.[11] The region is

Research in context

Evidence before this study

Many epidemiological studies have investigated the association between onchocerciasis and epilepsy (including nodding and Nakalanga syndromes) since 2017. We searched PubMed, Scopus, and ScienceDirect using the search terms "epilepsy", "nodding syndrome", and "onchocerciasis" for articles published in English, French, and Spanish between Jan 1, 1938, and Dec 31, 2022. Two prospective studies in Cameroon showed a temporal relationship with an increased risk of developing epilepsy based on the intensity of *Onchocerca volvulus* infection during childhood. A case definition of onchocerciasis-associated epilepsy for epidemiological studies has been proposed in the literature. A retrospective population-based study in western Uganda suggested that this form of epilepsy disappeared when onchocerciasis was eliminated from the area. Another retrospective study in an onchocerciasis-endemic area in northern Uganda indicated that the incidence of epilepsy decreased, and the incidence of nodding syndrome ceased after the introduction of biannual community-directed treatment with ivermectin and ground larviciding of rapidly flowing rivers with blackfly breeding sites. A slash and clear vector control method was shown to be successful in reducing biting rates in northern Uganda.

Added value of this study

For the first time using a prospective design, our study confirms the results of previous retrospective studies, which found that strengthening onchocerciasis elimination efforts decreases the incidence of epilepsy, including nodding syndrome. Therefore, our study verifies the solid epidemiological link between onchocerciasis and epilepsy. Our study also showed that the community-based slash and clear vector control method effectively decreased blackfly biting rates and potentially contributed to a decline in onchocerciasis transmission in Maridi.

Implications of all the available evidence

Onchocerciasis-associated epilepsy should be considered as part of the onchocerciasis disease burden. Onchocerciasis elimination efforts should be strengthened in onchocerciasis-endemic regions, particularly where the prevalence of epilepsy is high. The slash and clear method should be further evaluated as a potential low-cost, sustainable vector control method in other ecological environments.

flat, open savannah with moderate rainfall for half the year[12] and the main livelihood activities include farming and animal husbandry (mainly cattle, goats, and sheep; no pigs are kept in these sites). The absence of pigs in the area excludes neurocysticercosis as a cause of epilepsy in Maridi.[7] In 2019, the Maridi dam spillway (built across the Maridi River) was identified as the only blackfly breeding site in the area, with biting rates of 202 flies per person per hour.[13] Previous studies in this area have documented both high onchocerciasis transmission (Ov16 antibody seroprevalence of 19·8% among children aged 3–6 years and 33·3% among children aged 7–9 years) and high epilepsy prevalence (ie, 4·4%).[7] Infection rates with *O volvulus* were also high in Maridi: 84·9% (270 of 318) people with epilepsy and 50·0% (17 of 34) people without epilepsy were skin-snip positive.[14] Routine community-directed treatment with ivermectin had been instituted annually in South Sudan since the early 2000s but was interrupted for several years because of insecurity, before being reintroduced in 2017 with very low coverage (ie, 40·8%).[7] Treatment was then increased to biannually in 2021 (February and August). No community-directed treatment with ivermectin was done in 2020 due to the COVID-19 pandemic.

See Online for appendix

So far, the data suggesting that onchocerciasis-associated epilepsy, including nodding syndrome, could be prevented by strengthening onchocerciasis elimination programmes have been obtained through retrospective studies.[15,16] In northern Uganda, a nodding syndrome epidemic was halted after biannual community-directed treatment with ivermectin (ie, every 6 months) and vector control (using larvicides) were introduced.[15] Drawing from the Ugandan intervention, we implemented biannual community-directed treatment with ivermectin with vector control activities, and prospectively investigated the effect of these interventions on the incidence of epilepsy, including nodding syndrome, in eight selected areas in Maridi County, South Sudan. We also explored potential risk factors for epilepsy in the study population.

Methods

Study design

In this longitudinal, prospective, population-based study,[17] surveys were done to establish epilepsy prevalence before and after the onchocerciasis elimination programme in Maridi was strengthened. We did epilepsy surveys before (May 10–30, 2018; survey 1) and after (March 9–19, 2022 ; survey 2) in eight study areas in Maridi County which were organised into two groups according to their proximity to the Maridi dam: first-line sites (ie, Kazana-2, Kazana-1, Hai-Matara, and Kwanga) and second-line sites (ie, Hai-Gabat, Hai-Tarawa, Mudubai, and Nagbaka; appendix p 2). The detailed research procedures have been reported previously.[7,18]

Ethics approval was obtained from the Ministry of Health of South Sudan (MOH/ERB 3/2018) and the University of Antwerp, Belgium (B300201940004).

Participants

All individuals residing in the eight study areas at the time of the surveys were eligible to participate. Considering the door-to-door approach of our study, we opted for a convenience sample size consisting of all

residents in the selected study areas. Informed consent was obtained from all participants, parents, or caregivers, and assent was obtained from children aged 7–17 years. All personal information was encoded and treated confidentially. Blackfly collectors also provided written informed consent and were treated with ivermectin before the human landing catch technique activities.

Procedures

Using a door-to-door approach, research assistants administered a first questionnaire in 2018 (appendix p 3) to participating households to obtain sociodemographic information of the residents, and their history of ivermectin intake during the preceding year of community-directed treatment programme, and to identify suspected cases of epilepsy using a validated screening tool adapted from Diagana and colleagues (appendix p 3).[19] The epilepsy screening questions were translated from English to Arabic by the local team members during group discussions, back-translated into English to ensure no loss of meaning, and pilot-tested in ten households within the study area. Questions were delivered orally. Gender data were self-reported via the questionnaire with the options of male or female (appendix p 3).

All suspected epilepsy cases (ie, those who answered yes to at least one of the screening questions) were referred to a clinician (clinical officer or medical doctor) trained to diagnose epilepsy. The clinician took a detailed medical history, did a clinical (including neurological) examination, and then confirmed or rejected the epilepsy diagnosis (appendix p 4). We adopted the International League Against Epilepsy definition of epilepsy: the occurrence of two or more unprovoked seizures at least one day (ie, >24 h) apart.[20] A person with epilepsy needed to be on anti-seizure medication or to have presented with seizures within the last 5 years. The following elements were also assessed in confirmed people with epilepsy: age of epilepsy onset (ie, first seizures), presence of onchocerciasis-associated skin lesions, cognitive impairment (not oriented in place, time, or person), anti-seizure medication intake, and degree of disability using the modified Rankin Scale with scores ranging from 0 (ie, no disability) to 5 (ie, severe disability).[21] The year of new onset epilepsy was defined as the age of the person with epilepsy and their age at the first onset of seizures. Case definitions for onchocerciasis-associated epilepsy[22] and probable nodding syndrome[23] are provided in the appendix (p 11). The second survey, done in 2022 (survey 2), used the same approach of house-to-house epilepsy screening and epilepsy case confirmation by a clinician at the same eight sites as the initial survey (survey 1).

Research assistants collected data on paper forms, while the clinicians used an e-questionnaire (appendix p 4) implemented in the Open Data Kit software on tablet computers. Participating households were subgrouped into native (ie, household head residing at least 20 years in the village) versus immigrant households (ie, household head residing <20 years in the village). The first survey was supervised in the field by RC and JYC and the second by SRJ.

In 2019, the research team introduced vector control at the Maridi dam, using the community-based slash and clear method.[13] Fast-flowing water overflows the dam spillway, providing a conducive environment for blackfly breeding (appendix p 12). Community volunteers were trained to remove the algae and vegetation (which served as substrates for blackfly breeding) from the dam spillway and throw it on the riverbanks to dry. This slash and clear intervention in Maridi required four trained volunteers working for 4 days for each slash and clear; which were implemented on Dec 6, 2019, Dec 10, 2020, Aug 18, 2021, Dec 8, 2021, and Aug 26, 2022 (video).

See Online for video

Three blackfly-catching sites were established at the Maridi dam (20 m from the dam), Kazana-2 (600 m from the dam), and Hai-Matara (3·5 km from the dam, downstream on the Maridi River). Two blackfly catchers worked alternate hours at each catching site to assess biting density via the human landing catch technique.[24] The human landing catch technique was done for 7 consecutive days before the first slash and clear. Subsequently, the technique was done on a weekly basis for 26 months (November, 2019, to December, 2021), and later repeated in November, 2022. The blackfly monthly biting rate was calculated as recommended by Walsh and colleagues.[24] Data on the monthly total precipitation and the average temperature in Maridi was also gathered historically (ie, 2019–20) and prospectively (ie, 2021).[12] The effect of the first two rounds of the slash and clear on the blackfly biting rates in Maridi has been previously published.[25]

The primary outcome was to calculate and compare the incidence of new-onset epilepsy, including prevalence of nodding syndrome, within the 4 years preceding each survey. Incidence was identified based on the self-reported onset of the first seizures. New-onset epilepsy cases were grouped into three periods: (1) before implementation of onchocerciasis measures, (2) during implementation of annual community-directed treatment with ivermectin, and (3) during implementation of biannual community-directed treatment with ivermectin and with the potential effect of slash and clear. We also measured the seroprevalence of *O volvulus* in December, 2019, and March, 2023, via Ov16 antibody testing in randomly selected children aged 3 years (born after slash and clear implementation) in the study sites, using the SD Bioline rapid diagnostic test.

Statistical analysis

It was hypothesised that the crude incidence of new-onset epilepsy in the Maridi study area would exceed 175·0 per 100 000 person-years before strengthening onchocerciasis control interventions and 100·0 cases per

100 000 person-years after strengthening onchocerciasis control interventions person-years.[26] Based on previous findings in an onchocerciasis-endemic area in northern Uganda[15] and the operational challenges of achieving optimal community-directed treatment with ivermectin coverage in South Sudan, the interventions were anticipated to reduce the incidence of epilepsy by at least 75%. To achieve a statistical power of 80% with a significance level of 5% and two-sided testing, each incidence period was required to contain at least 17 442 person-years.

Data were described with median (IQR) for continuous variables and frequencies and percentages for categorical variables. We used χ^2 tests to compare group differences for categorical variables and Mann-Whitney U tests for continuous variables. All 95% CIs were calculated using Wilson Score Intervals with Yate's continuity.[27] The prevalence of epilepsy and probable nodding syndrome were calculated by dividing the number of clinically confirmed epilepsy cases by the number of individuals screened and reporting per 1000 people screened. The incidence of epilepsy and probable nodding syndrome were estimated by dividing the number of new-onset cases by the summed person-years of the population at risk for each period: pre-control (May, 2013, to May, 2017), under annual community-directed treatment with ivermectin (May, 2017, to March, 2020), and under biannual community-directed treatment with ivermectin and the potential effect of the slash and clear (March, 2020, to March, 2022). We assumed a stable population at risk during the 4 years preceding each survey (2013–17 for survey 1, and 2018–22 for survey 2). The epilepsy incidence calculated from the 2018 survey (2013–18) was adjusted by rake weighting to match the proportion of people screened from first-line and second-line sites in the 2022 survey to allow direct comparisons. The weighting formula is provided in the appendix (p 13).

Community-directed treatment with ivermectin coverage was obtained by dividing the number of individuals who took ivermectin in 2017 and 2021 by the overall population recorded during the surveys. A multivariable logistic regression analysis was done to identify risk factors for epilepsy. Variables previously reported as epilepsy risk factors in Maridi,[7] and those with p<0·05 at the univariable level were included in the final regression model.

	2018	2022	p value
Female	315/736 (42·8%)	275/586 (46·9%)	0·12
Male	421/736 (57·2%)	311/586 (53·1%)	0·15
Age	18·0 (15·0–20·0)	20·0 (16·0–22·0)	<0·0001
Generalised tonic-clonic seizures	511/736 (69·4%)	457/586 (78·0%)	0·0006
Probable nodding syndrome	335/736 (45·5%)	185/586 (31·6%)	<0·0001
Age at onset of seizures*	10·0 (6·0–14·0)	10·0 (7·0–12·0)	0·53
Meeting criteria for onchocerciasis-associated epilepsy	414/486 (85·2%)	457/586 (78·0%)	0·0034
Blindness in one or both eyes	11/633 (1·7%)	10/360 (2·8%)	0·39
Onchocerciasis skin lesions†	81/633 (12·8%)	60/360 (16·7%)	0·11
Nakalanga features‡	102/633 (16·1%)	52/351 (14·8%)	0·66
No significant disability (modified Rankin score of 0–1)	474/736 (64·4%)	474/586 (80·9%)	<0·0001
Slight to moderate disability (modified Rankin score of 2–3)	236/736 (32·1%)	100/586 (17·1%)	<0·0001
Moderately severe to severe disability (modified Rankin score of 4–5)	26/736 (3·5%)	12/586 (2·1%)	0·15
Cognitive impairment	135/633 (21·3%)	34/351 (9·7%)	<0·0001
Treated with anti-seizure medication	378/736 (51·4%)	531/583 (91·1%)	<0·0001

Data are n/N (%), median (IQR), and p value. *Data were only collected from 543 individuals in 2022. Age of onset of seizures was 8·0 (IQR 6·0–9·0) years for the 181 people with nodding syndrome. †Nodular pruritic skin; leopard skin; dry, thickened, or wrinkled skin; or itching. ‡Thoracic or spinal abnormalities, no external signs of secondary sexual development and stunted growth in individuals older than 16 years old.

Table 1: **Clinical characteristics of people with epilepsy in 2018 and 2022**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In 2018, 2511 households of 17 652 individuals were visited, whereas in 2022, 2254 households of 14 402 individuals were visited. The median age of the study population was 17·0 (IQR 8·0–30·0) years in 2018 and 16·0 (8·0–30·0) years in 2022. A similar gender distribution was identified in 2018 and 2022, with 52·2% (9206 of 17 652) female and 47·8% (8446 of 17 652) male in 2018, and 52·4% (7525 of 14 374) female and 47·6% (6849 of 14 374) male in 2022.

The median household size was seven (IQR 5–9) people in 2018 and six (4–8) people in 2022, with a maximum of 20 individuals. Ethnicity was only captured in 2022, but was diverse (appendix p 14): mainly Baka, Muro, Zande, Mundu, and Avokaya. Most families were native to their village of residence (82·0% in 2018 and 82·5% in 2022; p=0·83). In 2022, farming was the most common livelihood activity for 85·1% of households, followed by cattle rearing (5·0%) and fishing (1·5%).

The overall epilepsy prevalence in 2022 was 40·7 (95% CI 37·6–44·1) per 1000 (appendix p 15), which was a decrease from the 43·8 (40·9–47·0) per 1000 prevalence observed in 2018, albeit non-significant (p=0·17). Similarly, the probable nodding syndrome prevalence reduced from 17·7 (15·8–19·8) per 1000 in 2018 to 12·9 (11·1–14·9) per 1000 in 2022 (p=0·0005).

The epilepsy prevalence was higher in the first-line sites (51·8 per 1000 in 2018 *vs* 28·0 per 1000 in 2022; p<0·0001), which were closer to the Maridi dam, especially Kazana-2 (87·0 per 1000). Epilepsy prevalence was higher among males, both in 2018 (51·8 per 1000 for males *vs* 36·6 per 1000 for females; p<0·0001) and in 2022 (45·5 per 1000 for males *vs* 36·6 per 1000 for females; p<0·0001).

Epilepsy prevalence did not vary on the basis of household livelihood activity; meanwhile there was a

disparity in epilepsy prevalence across ethnicities (appendix p 14). From 2018 to 2022, there was a 16·4% (95% CI 11·3–21·5) decrease in the prevalence of epilepsy in the population of individuals aged 20 years and younger (appendix p 16). An increase in epilepsy prevalence (16·3%, 95% CI 11·1–23·5) was observed among people older than 20 years.

Clinical characteristics were described for 736 people with epilepsy in 2018 and 586 people with epilepsy in 2022 (table 1). Baseline and follow-up populations had a similar gender distribution, but the 2018 group was slightly younger (median age of 18 years *vs* 20 years in 2022; p<0·0001). At both timepoints, the most reported seizure type was generalised tonic-clonic and the median age of epilepsy onset was 10 years. In 2018, a higher proportion of people with epilepsy met the criteria for onchocerciasis-associated epilepsy (p=0·0034) and probable nodding syndrome (p<0·0001) than in 2022. Although the proportion of people with epilepsy with Nakalanga features was similar between surveys (16·1% in 2018 and 14·8% in 2022), the median age of Nakalanga cases was 19·0 years (IQR 18·0–21·0) in 2018 and 22·0 years (20·0–25·0) in 2022 (p=0·0004).

Of the 129 people with epilepsy who did not meet the onchocerciasis-associated epilepsy criteria in 2022, 87 (67·4%) matched all requirements but had not lived in the village where they settled for at least 3 years. The remaining people with epilepsy not meeting the onchocerciasis-associated epilepsy criteria developed epilepsy during adulthood (n=8, 6·2%), had an obvious cause of epilepsy (n=2, 1·6%), or provided insufficient information to determine their onchocerciasis-associated epilepsy status (n=32, 24·8%). In 2022, the median age of people with onchocerciasis-associated skin lesions was 20·0 (IQR 13·3–23·8) years, of whom 73·3% (44 of 60) lived in first-line sites. In the same year, the median age for those with blindness was 28·0 (IQR 24·0–29·5) years, of whom 90·0% (nine of ten) lived in first-line sites.

Significantly fewer people with epilepsy reported disabilities in 2022 compared with 2018 (p<0·0001). Moreover, the proportion of people with epilepsy on anti-seizure medication increased by 39·7% (95% CI 35·3–44·2) from 2018 to 2022, with almost every person with epilepsy on regular anti-seizure medication in 2022.

Ivermectin coverage increased by 15·7% (95% CI 14·6–16·8) from 2017 to 2021 (table 2). Ivermectin intake doubled in children aged 5–10 years but remained lower than in those aged 11–20 years (p<0·0001). Coverage was higher in second-line sites in 2017 and in first-line sites in 2021 (p<0·0001).

In the preintervention period, monthly biting rates were highest at the Maridi dam (6038·6 bites per person), followed by Kazana-2 (4697·2 bites per person) and Hai-Matara (3660·0 bites per person; figure 1). Biting rates decreased by over 99% after implementing the first round of slash and clear, except for a spike in biting rates observed in January, 2020, 2 weeks after the first slash and clear. Subsequent rounds of the intervention yielded similar effects in reducing monthly biting rates. The seasonal precipitation pattern from November, 2019, to December, 2021, was similar, with average temperatures in the range 18·9–39·2°C.

Follow-up Ov16 seroprevalence in children aged 3 years was 8·8% (3 of 34) in 2023, compared with the 12·5% (3 of 24) registered in 2019 (p=0·651).

We found a significant decrease in the incidence of epilepsy with the resumption of community-directed treatment with ivermectin in 2017 and the subsequent strengthening of the onchocerciasis control interventions in Maridi (figure 2). Before these interventions, the incidence of overall epilepsy was 348·8 (95% CI 307·2–395·8) per 100 000 person-years and was

	2017	2021	p value
Gender			
Female	3794/9206 (41·2%)	4180/7512 (55·6%)	<0·0001
Male	3406/8445 (40·3%)	3928/6833 (57·5%)	<0·0001
Age groups at risk of onchocerciasis-associated epilepsy onset			
5–10 years	904/3485 (25·9%)	1683/3243 (51·9%)	<0·0001
11–20 years	2450/4872 (50·3%)	2640/3866 (68·3%)	<0·0001
Study site			
First-line sites	2043/5524 (37·0%)	4518/7668 (58·9%)	<0·0001
Second-line sites	5215/11 575 (45·1%)	3593/6689 (53·7%)	<0·0001
Overall	7209/17 652 (40·8%)	8134/14 378 (56·6%)	<0·0001

Data are n/N (%) and p value.

Table 2: **Ivermectin coverage in 2017 and 2022 in the overall population, by gender and in the younger population**

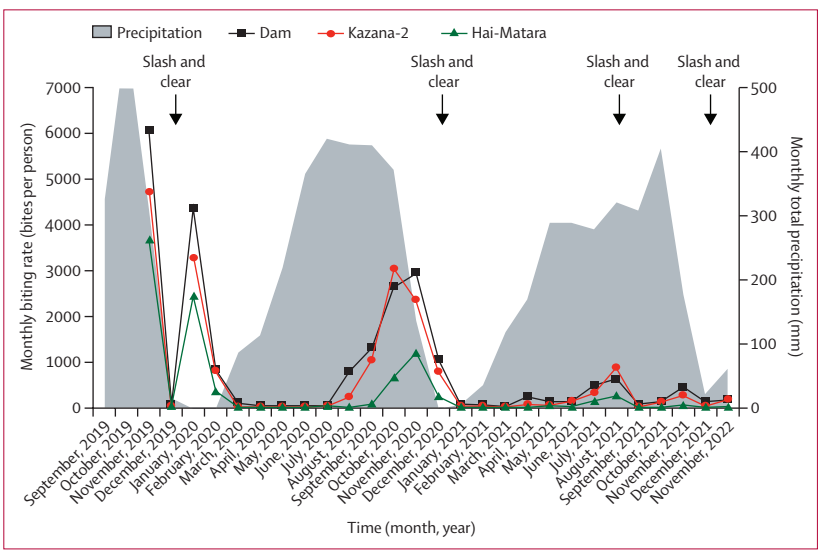

Figure 1: **Effect of the slash and clear vector control method on blackfly biting rates at the Maridi dam, Kazana-2 and Hai-Matara**

Entomological data (ie, biting rates) were not collecting between January and October, 2022.

154·7 (127·6–187·3) for probable nodding syndrome (table 3). A non-significant downward trend in epilepsy incidence was already observed before implementing onchocerciasis interventions in 2017. In 2017–18, epilepsy incidence (per 100 000 person-years) significantly decreased to 157·2 (95% CI 106·3–230·9), as did probable nodding syndrome to 19·1 (5·4–57·2); these numbers remained low through 2020. Following implementation of biannual community-directed treatment with ivermectin in 2021 and slash and clear since 2019, there was another significant reduction in the incidence of epilepsy to 41·7 (22·6–75·0) per 100 000 person-years. Almost all (98·3%) new cases of epilepsy between March, 2018, and March, 2022 were developed before the age of 18 years.

12 people with epilepsy developed the disease between March, 2020, and March, 2022, with a median age at onset of 12·0 (IQR 6·5–15·5) years. These individuals either had their first seizures when ivermectin was not distributed in 2021 (nine of 12, 75·0%), or had never taken ivermectin before (three of 12, 25·0%). 11 individuals met the criteria for onchocerciasis-associated epilepsy; the remaining individual had cerebral malaria as a possible cause of epilepsy. The incidence of epilepsy decreased in all study areas from May, 2013, to March, 2022, although not always significantly (appendix p 17). Mudubai, the site furthest away from the dam, did not have any new cases of epilepsy between 2018 and 2022.

In the multivariable analysis, epilepsy was associated with being male, being aged between 6 years and 40 years, not taking ivermectin, and living in settlements closer to the blackfly breeding site (table 4). Ethnicity was significantly associated with epilepsy in the univariable analysis (p<0·0001) but was correlated with study site, farming family, and immigrant family (appendix p 14). Adding an interaction effect between any of these three variables and ethnicity rendered the association between ethnicity and epilepsy prevalence non-significant.

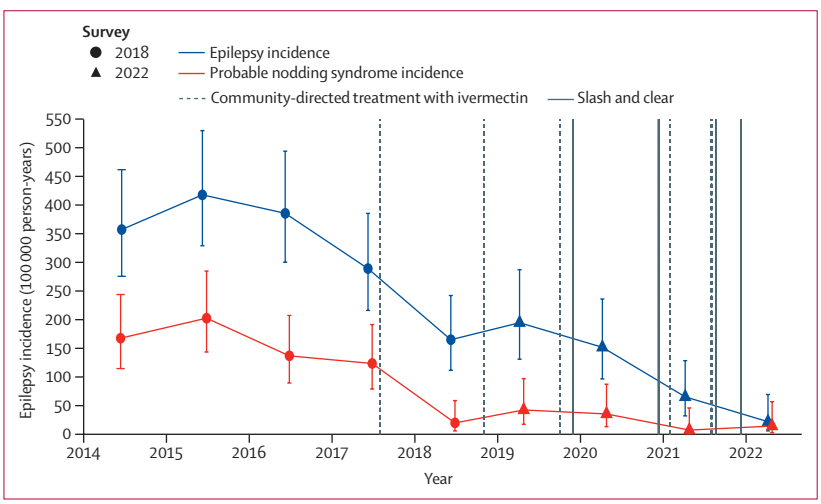

Figure 2: **Epilepsy and probable nodding syndrome incidence**
Error bars represent 95% CIs.

Discussion

A significant decrease in epilepsy incidence and probable nodding syndrome incidence was observed after introducing biannual community-directed treatment with ivermectin and slash and clear in the study sites. The decreasing trend in Ov16 seropositivity among children aged 3 years suggests that these interventions also hampered onchocerciasis transmission.

Although not significant, the incidence of epilepsy oscillated before the reintroduction of community-directed treatment with ivermectin. The underlying cause for this fluctuation is not clear, but there are a couple of potential explanations. First, some individuals could have received ivermectin from a source other than the community-directed programme in 2016. Additionally, unreliable reporting could have had a role as, until 2018, epilepsy treatment was not yet provided for free by Amref Health Africa and the high level of epilepsy-related

	Epilepsy			Probable nodding syndrome		
	New cases	Total person-years	Incidence per 100 000 person-years (95% CI)	New cases	Total person-years	Incidence per 100 000 person-years (95% CI)
June, 2013, to May, 2017 (data from survey 1; no onchocerciasis control)*	221	70 608	348·8 (307·2–395·8)*	85	70 608	154·7 (127·6–187·3)*
June, 2017, to May, 2018 (data from survey 1; annual community-directed treatment with ivermectin)*†	23	17 652	157·2 (106·3–230·9)*	2	17 652	19·1 (5·4–57·2)*
April, 2018, to March, 2020 (data from survey 2; annual community-directed treatment with ivermectin)†	47	28 804	163·2 (121·3–218·9)	11	28 800	38·2 (20·1–70·6)
April, 2020, to March, 2022 (data from survey 2; biannual community-directed treatment with ivermectin and potential effect of slash and clear)	12	28 804	41·7 (22·6–75·0)	3	28 800	10·4 (2·7–33·2)

Data are n, total person years unless otherwise specified. *Incidence values of survey 1 (2018) adjusted using rake weighting technique to account for different proportions of first-line and second-line sites during the two surveys. †Although encompassed within the same intervention, these periods were calculated separately as they were obtained from distinct surveys and overlap between the time periods of April and May 2018.

Table 3: **Incidence of epilepsy and probable nodding syndrome from 2013 to 2022**

stigma[28] could have led some families to only report known people with longstanding, well-known epilepsy, neglecting to include instances of new-onset epilepsy. Therefore, there could have been an underestimation of recent cases during survey 1. During the second survey in 2022, most people with epilepsy (including very recent cases) had been identified and registered at the clinic for free treatment, yielding more reliable incidence estimates.

For the first time, using a prospective design, our study confirms the results of previous retrospective studies,[15,16,26] which found that strengthening onchocerciasis elimination efforts decreases the incidence of epilepsy, including nodding syndrome. This sharp decrease in epilepsy incidence is probably because community-directed treatment with ivermectin coverage in 2021 doubled among children aged 5–10 years and also substantially increased among those aged 11–20 years from 2017 to 2021. The higher coverage might have decreased the microfilarial load in many children to below the threshold that would put them at risk of developing onchocerciasis-associated epilepsy. Additionally, the slash and clear intervention initiated in 2019 drastically decreased blackfly biting rates by over 99%. This reduction was sustained when slash and clear was done twice instead of once in 2021. The spike in biting rate in January, 2020, shortly after the first slash and clear, was probably due to remaining mature larvae and pupae missed from scraping the concrete dam spillway, which later hatched.[25] This slash and clear method, which is ecologically harmless compared with chemical larviciding, was effective in depleting blackfly biting rates in northern Uganda.[29] Continuing vector control in Maridi is essential to complement the still suboptimal coverage of community-directed treatment with ivermectin and could also limit onchocerciasis transmission to young children prone to onchocerciasis-associated epilepsy.

Overall epilepsy prevalence substantially decreased between the two surveys, although this was not significant in the first-line sites. As these sites are more endemic for onchocerciasis, a higher coverage of community-directed treatment with ivermectin, a longer follow-up period, or both would probably be necessary to detect a significant decrease. This phenomenon was observed in an onchocerciasis-endemic area in western Uganda.[16] Furthermore, the highest epilepsy prevalence in 2018 was recorded in the group aged 11–20 years, while in 2022, the highest prevalence was in the group aged 21–30 years. This age shift in epilepsy prevalence has been seen in other settings after implementing onchocerciasis control interventions[4,15] and is explained by the decreased epilepsy incidence in the 11–20 year age group and the anti-seizure treatment initiated in Maridi in 2019. Lastly, the probable nodding syndrome prevalence significantly reduced between 2018 and 2022. This reduction might be because of higher mortality among people with nodding syndrome, a more severe form of onchocerciasis-associated epilepsy associated with serious disabilities.[5,14]

	Adjusted odds ratio	p value
Age (years)		
0–5	Ref	Ref
6–10	3·11 (1·77–5·71)	0·0003
11–20	18·20 (11·40–31·12)	<0·0001
21–30	16·43 (10·12–28·45)	<0·0001
31–40	2·24 (1·14–4·42)	0·019
>40	1·65 (0·81–3·34)	0·16
Gender		
Male	1·43 (1·20–1·70)	<0·0001
Female	Ref	Ref
Ethnicity		
Avokaya, Baka, Mundo, and Muro*	Ref	Ref
Zande	0·68 (0·40–1·10)	0·68
Minor ethnicities†	0·89 (0·50–1·49)	0·14
Immigrant family settled <20 years	0·92 (0·73–1·15)	0·43
Farming family	0·92 (0·72–1·18)	0·50
Cattle rearing family	1·11 (0·75–1·59)	0·58
Study site		
Second-line sites	Ref	Ref
Other first-line sites	1·96 (1·59–2·43)	<0·0001
Kazana-2	3·52 (2·61–4·73)	<0·0001
Interaction effect ethnicity and study site		
Zande and other first-line sites	0·75 (0·39–1·49)	0·40
Zande and Kazana-2	0·89 (0·30–2·33)	0·82
Minor ethnicities and other first-line sites	0·51 (0·20–1·20)	0·13
Minor ethnicities and Kazana-2	0·39 (0·39–1·47)	0·39
Ivermectin intake	0·73 (0·61–0·88)	0·0007

Data are adjusted odds ratio (95% CI) and p value. First-line sites were closer to the Maridi dam: Kazana-1, Hai-Matara, and Kwanga. Second-line sites were further from the Maridi dam: Hai-Gabat, Mudubai, Nagbaka, and Hai-Tarawa. Kazana-2 was the site closest to the Maridi dam. *All the major ethnicities (>1000 individuals) with the exception of Zande had similar epilepsy prevalence and characteristics. †Ethnicities with less than 200 individuals surveyed.

Table 4: **Multivariable analysis of factors associated with epilepsy in Maridi**

The clinical presentation of people with epilepsy slightly changed between the two surveys. People with epilepsy in 2022 were older and less often met the onchocerciasis-associated epilepsy criteria. This could be because people with onchocerciasis-associated epilepsy died (particularly those with probable nodding syndrome) and the incidence of onchocerciasis-associated epilepsy declined between the two surveys. Moreover, people with epilepsy were also less cognitively impaired in 2022, possibly because of the epilepsy treatment programme initiated in Maridi. Risk factors for epilepsy included being male, being aged between 6 years and 40 years, not taking ivermectin, and residing in a first-line village.

Our study had several limitations. During the 2022 survey, fewer households of second-line and more households of first-line study sites were included than in the 2018 survey to facilitate follow-up studies that will focus only on these highly endemic communities.

Although the population per study site varied between the surveys, the overall study population for both surveys was most likely representative of the communities since we used door-to-door approaches for recruitment. Moreover, we weighted the 2018 epilepsy incidence values before comparing them with the 2022 findings.

Second, we did not validate the epilepsy screening questionnaire for use in our study population. However, previous validation studies of this questionnaire revealed that it had very high sensitivity (95%)[19] and could reliably be used in sub-Saharan Africa.[30] Epilepsy confirmation by clinicians ensured optimum specificity.

Finally, epilepsy incidence was assessed based on the self-reported onset of first seizures and were therefore subject to recall bias. The bias was minimised by calculating the epilepsy incidence using only data from the 4 years preceding each survey. Additionally, the creation of 2-year to 3-year timeframes to regroup new-onset epilepsy cases into periods (before, during, and after implementation of onchocerciasis measures) probably decreased the errors introduced by wrong estimation and reporting of the exact year of seizure onset. Also, as the seizure onset data were on the basis of only on living people with epilepsy, we might have slightly underestimated the true disease-incidence rates by not including people with epilepsy who died before the surveys took place.

Overall, this study confirms the epidemiological association between onchocerciasis and epilepsy and that strengthening onchocerciasis elimination efforts can significantly decrease the incidence of epilepsy, including nodding syndrome. More research is warranted to establish the individual contributions of each onchocerciasis intervention to preventing onchocerciasis-associated epilepsy in endemic communities.

Contributors

SRJ and RC conceptualised the study. LJ-A, RC, and SRJ accessed and verified the data and curated the data. LJ-A did the formal analysis and made the figures. LJ-A, RC, JR, and JYC acquired funding and resources. SRJ, RC, JYC, TL, AHa, and JNSF did the investigation. SRJ, RC, TL, and LJ-A designed the method. SRJ and JYC did the project administration. YYB, MYL, and AHo provided advice and facilitated the research. LJ-A used the required software. RC and JYC supervised the study. RC validated the study. LJ-A and RC wrote the original draft. LJ-A, RC, JYC, TL, JR, YYB, MYL, AHo, AHa, and JNSF reviewed and edited the draft. RC had the final responsibility for the decision to submit for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

After de-identification (text, tables, figures, and appendices), all individual participant data underlying the results reported in this Article will be made available immediately and indefinitely via the Zenodo repository following publication for anyone who wishes to access the data for any purpose.

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