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Research article

Epidemiology of epilepsy in Wulu County, an onchocerciasis-endemic area in South Sudan

Joseph Nelson Siewe Fodjo [a,*,1], Stephen Raimon Jada [b,1], Abraham Taban [c], John Bebe [b], Yak Yak Bol [d], Jane Y. Carter [e], Robert Colebunders [a,f]

[a] Global Health Institute, University of Antwerp, Antwerp, Belgium
[b] Amref Health Africa, Juba, South Sudan
[c] Wulu County Neglected Tropical Diseases Unit, South Sudan
[d] Neglected Tropical Diseases Unit, Ministry of Health, Juba, South Sudan
[e] Amref Health Africa Headquarters, Nairobi, Kenya
[f] Department of Tropical Disease Biology, Liverpool School of Tropical Diseases, Liverpool, United Kingdom

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ABSTRACT

Background: We sought to investigate the epidemiology of epilepsy in Wulu County (Lakes State, South Sudan), and document the onchocerciasis transmission status in the study villages.
Methods: In February 2024, a community-based epilepsy study was conducted Wulu County and participants were surveyed via a door-to-door approach in five villages, namely: Kombi, Makundi Center, Tonjo, War-Pac, and Woko. All village residents were asked about ivermectin intake during the 2023 round of community-directed treatment with ivermectin (CDTI). In addition, children aged 3–9 years were tested for Ov16 antibodies using a rapid diagnostic test. Epilepsy diagnosis in screened individuals was confirmed by a physician.
Results: We surveyed 1355 persons in the five study sites. The overall CDTI coverage in 2023 was 67.4 %. Fifty-five persons with epilepsy (PWE) were identified (prevalence 4.1 %) and a history of nodding seizures was noted in 11/55 (20 %) PWE. The mean age of PWE was 21.5 ± 9.6 years, with 32 (58.2 %) being males. Epilepsy onset frequently occurred under 5 years of age (38.6 % of cases). In two PWE, seizure onset occurred during the past 12 months (annual incidence: 147.6 per 100,000 persons). Twenty-nine PWE (52.7 %) were taking anti-seizure medicines, but only five were taking them daily. Overall, Ov16 seroprevalence in children aged 3–9 years (n = 119) was 15.1 % and differed across villages, peaking at 30.9 % in Woko village where epilepsy prevalence was also highest (7.1 %). Of the 35 recorded deaths during the past two years, 9 (25.7 %) occurred in PWE. Annual estimates for epilepsy mortality and fatality rates were 323.7 per 100,000 persons and 7031.3 per 100,000 PWE, respectively.
Conclusion: High epilepsy prevalence was found in Wulu, particularly in villages with persistent onchocerciasis transmission. Frequent epilepsy onset among under-fives suggests that perinatal/early childhood etiologies are common. Appropriate measures should be instituted to prevent and treat epilepsy in Wulu villages.

* Corresponding author. Global Health Institute, University of Antwerp, Gouverneur Kinsbergen Center, Doornstraat 331, 2610, Wilrijk, Belgium.
E-mail address: josephnelson.siewefodjo@uantwerpen.be (J.N. Siewe Fodjo).
[1] Equal contribution.

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1. Background

Epilepsy is a frequent neurological condition, currently affecting an estimated 50 million individuals worldwide [1]. However, these epilepsy cases are unequally distributed across the globe with low- and middle-income countries (LMICs) experiencing a greater burden than high-income countries (HICs) [2]. Indeed, a meta-analysis estimated a pooled epilepsy prevalence of 8.75 per 1000 persons in LMICs compared to 5.18 per 1000 in HICs [3]. In the sub-Saharan Africa (SSA) region, the median epilepsy prevalence was estimated at 1.4 % [4] although this value can exceed 10 % in some villages of South Sudan [5]. Among other causes, parasitic infections such as malaria, toxoplasmosis, neurocysticercosis and onchocerciasis constitute the most important risk factors for epilepsy in tropical Africa [4,6–8].

Onchocerciasis is a neglected tropical disease caused by the filarial parasite *Onchocerca volvulus* and transmitted by blackfly vectors (*Simulium*) [9]. The cornerstone of onchocerciasis elimination programs is the annual community-directed treatment with ivermectin (CDTI), which requires that at least 80 % of the population takes the drug every year to yield significant results [10]. Because ivermectin kills the *O. volvulus* microfilariae but does not kill adult worms, endemic communities need to implement CDTI for 10–15 years, which is the average lifespan of the adult worms [9]. During the past decades, increasing evidence has demonstrated an association between onchocerciasis and epilepsy, giving rise to the term "onchocerciasis-associated epilepsy" (OAE) in recent literature [11–13]. A high epilepsy prevalence has been reported in onchocerciasis-endemic areas with high ongoing or past *O. volvulus* transmission [14]. Two prospective studies conducted in two different onchocerciasis-endemic sites in Cameroon, showed that the level of *O. volvulus* microfilarial load in young children determined the risk of developing epilepsy later in life [15,16]. It has been further demonstrated that addressing onchocerciasis transmission can significantly curb the epilepsy prevalence and incidence in endemic foci [17–20], In western Uganda, OAE stopped appearing when onchocerciasis was eliminated through vector control and annual CDTI [17]. Longitudinal studies showed that strengthening the onchocerciasis elimination program in Maridi (South Sudan) [20] and in Mahenge (Tanzania) [21] reduced the incidence of epilepsy including nodding syndrome. All these studies suggest that OAE is indeed a major etiology of epilepsy in such onchocerciasis-endemic settings [12]. The pathophysiological mechanisms of OAE remain unclear, but there are suggested hypotheses about the possible direct passage of the *O. volvulus* parasite or its derivatives into the central nervous system under certain conditions [22].

South Sudan is currently among the countries in Africa with persistently high onchocerciasis endemicity, mostly because of sub-

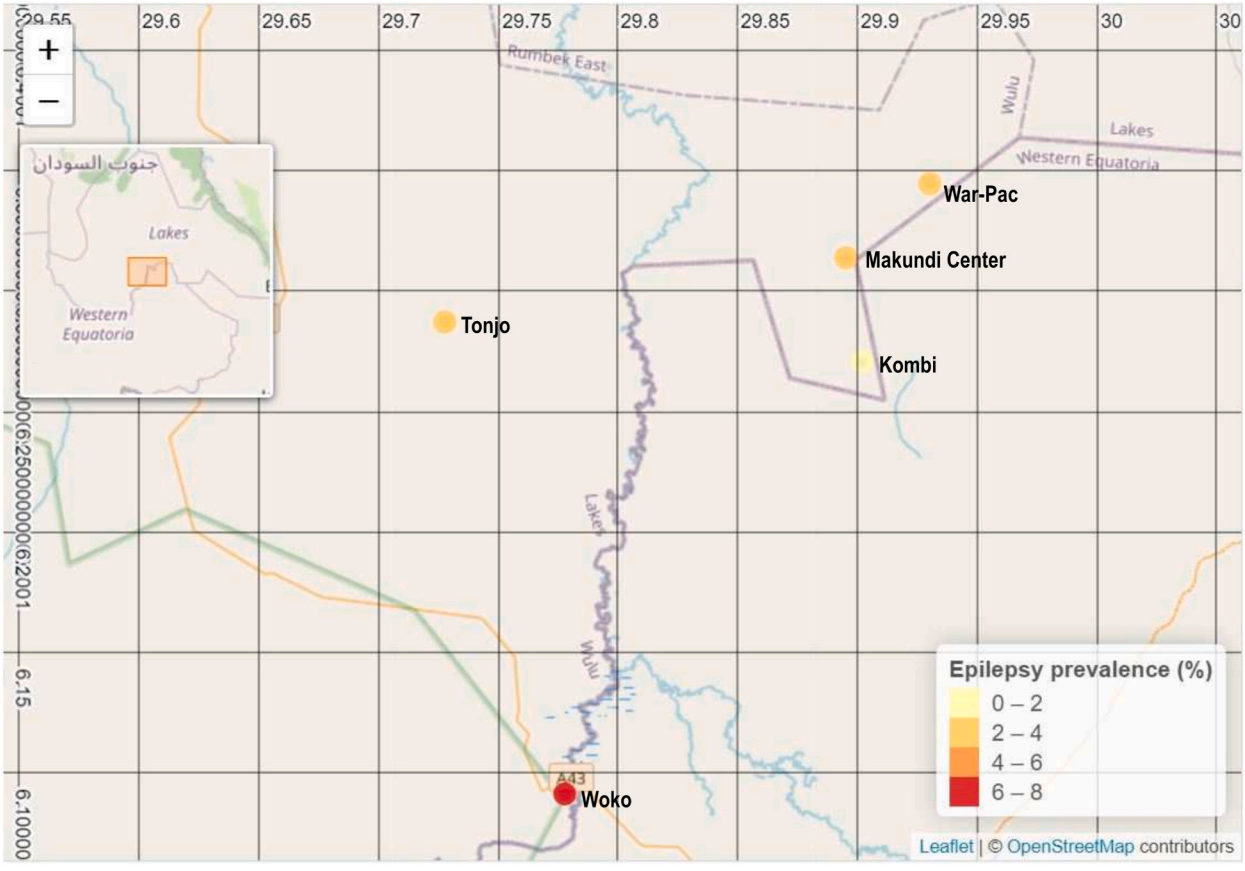

Fig. 1. Map of the study area in Wulu County, South Sudan.

optimal implementation of elimination measures over the years owing to longstanding conflicts and insecurity. Previous studies in South Sudanese onchocerciasis foci have documented the occurrence of epilepsy including nodding syndrome (a form of OAE characterized by head nodding seizures, stunted growth and cognitive impairment), with prevalence above 3 % in villages of Maridi, Mundri, and Mvolo Counties [5,23,24]. However, the epilepsy situation in many other endemic villages in South Sudan remain unexplored. The goal of the present study was to document epilepsy prevalence in villages in Wulu County, Lakes State, which is endemic for onchocerciasis and where cases of nodding syndrome have been observed in the past [25]. We also sought to determine the presence of Ov16 antibodies in children which can serve as a proxy for onchocerciasis transmission in the community. Ultimately, this study will contribute to identifying OAE hotspots that require onchocerciasis elimination measures to be urgently strengthened. As we witnessed a switch from annual to biannual CDTI in another South Sudanese county (Maridi) after our research revealed the high onchocerciasis burden (including OAE) in that area [26], it is expected that documenting the OAE burden in Wulu will help convince public health officials and funders to scale up the preventive measures aimed at eliminating onchocerciasis and to provide sufficient and free access to anti-seizure medications (ASM) for persons with epilepsy in Wulu.

2. Methods

2.1. Study setting and population

The study was conducted from the 1st to the 5th February 2024, in Wulu County, a known onchocerciasis focus in Lakes State, South Sudan. Five rural villages were selected for the study: Kombi, Makundi Center, Tonjo, War-Pac, and Woko. All the study sites were located at various distances from the blackfly-infested Naam River [27], which forms the border between Wulu County and Mvolo County in Western Equatoria State (see Fig. 1). Wulu County is characterized by a hot tropical climate and open savannah woodlands dominated by shrubs and small trees. The main activities include farming (sorghum, millet, sweet potatoes, groundnuts), animal husbandry (cows, goats, chickens), fishing, and honey production.

A pre-control assessment by nodule palpation (1996–2008) revealed that Wulu County was meso-endemic for onchocerciasis [28]. Although CDTI was initiated in the early 2000s, therapeutic coverage has been sub-optimal and there have been several interruptions in treatment. All individuals residing permanently in the villages were eligible to participate in the study.

2.2. Study design and procedures

We conducted a cross-sectional community-based survey using a door-to-door approach, considered to be the gold standard for epidemiological studies on epilepsy [29]. A few weeks prior to data collection, the lead researchers held a meeting with the administrative and health authorities of the community, as well as the traditional chiefs, during which the research project was explained and their collaboration obtained. They were also asked to sensitize the villagers to be available in their homes for the upcoming door-to-door study, with precise dates as per the agreed planning. Before the study, selected community health workers were trained on the door-to-door exercise and teamed up with members of the research team.

The research team deployed for data collection consisted of two physicians (JNSF, SRJ), five clinical officers, and ten community health workers. The community health workers of each study village served as local guides to facilitate access to households and interpret the household interviews when required. Households were visited one after the other and given a unique identification code by the investigators. In case the research team found a household empty at the time of survey, a second visit was planned either during the same day or the following day. One adult member from each household was selected to provide the required information for all the residents (age, sex, ivermectin intake during the last CDTI campaign, epilepsy screening), with additional inputs from other household members as required. The research team distinguished immigrant households (that is, families who are not natives from the village but moved in for residence) from native households. Household information was collected on paper questionnaires.

Identification of epilepsy cases was done in two steps: firstly, we administered a validated 5-item epilepsy screening questionnaire [30] to screen all household members for potential epilepsy (see Supplementary File 1). The second step was reserved for individuals who answered "yes" to one or more of the epilepsy screening questions. For such individuals (termed "suspected cases of epilepsy" or SCE), a second more detailed questionnaire (see Supplementary File 2) was administered by the study physicians who also conducted a thorough physical examination, to confirm or exclude the diagnosis of epilepsy including nodding syndrome. Epilepsy confirmation data were collected using electronic questionnaires in tablets via the Open Data Kit (ODK) platform.

Regarding the onchocerciasis serosurvey procedures, children aged 3–9 years encountered in the households were finger-pricked to obtain a drop of blood and an Ov16 rapid diagnostic test (RDT) performed as per the manufacturer's instructions (prototype C Biplex test, DDTD San Diego, USA). A positive RDT result, indicating the presence of the Ov16 antibodies (IgG) in children <10 years old, will be interpreted as a proof for recent/ongoing transmission of *O. volvulus* in the study area.

2.3. Data processing and analysis

At the end of each survey day, all questionnaires (paper and electronic) were cross-checked by the clinical epidemiologist and any inconsistencies were resolved by discussing with the rest of the team or by returning to the household in question the following day as needed. The verified data were then compiled in a Microsoft Excel spreadsheet, cleaned, and analyzed using R version 4.3.3. Continuous variables were summarized as means with standard deviation (SD) or as medians and compared across groups using non-parametric statistical tests. Categorical variables were expressed as percentages and compared using the Chi-squared test or Fisher

exact test as appropriate. We applied the published epidemiological OAE criteria [31] on all confirmed PWE to estimate the proportion of epilepsy cases in the study villages that could potentially be related to onchocerciasis. For all statistical testing, a two-sided p-value below 0.05 was considered statistically significant.

Annual mortality per 100,000 persons per year was calculated based on the number of deaths (among both PWE and the general population) recorded during the past two years in the study area as follows:

$$Mortality = \frac{Number\ of\ deaths\ recorded\ during\ the\ past\ two\ years}{(Total\ population + number\ of\ deaths) \times 2\ years} \times 100,000$$

Annual epilepsy incidence was calculated as a proportion of the total study population represented by PWE whose seizure onset occurred during the past 12 months and expressed per 100,000 persons per year. Calculation of epilepsy mortality and incidence assumed a stable population size during the period of study.

To investigate risk factors for epilepsy at household level, we created a dichotomous dependent variable which was coded as "1" for every individual belonging to a household with a confirmed epilepsy case or in which a PWE death was reported during the past two years, and coded as "0" otherwise. A mixed effects logistic regression model was constructed and included purposefully selected covariates in its fixed portion (age, sex, native vs immigrant household, farming profession, fishing profession, cattle rearing practice, ivermectin intake in 2023, and blindness) while the variable "village" was introduced in the random portion of the model.

2.4. Ethical considerations

This study received ethical approval from the Ministry of Health of South Sudan (MOH/RERP/P/35/15/05/2023-MOH/RERP/A/35/2023) and from the ethics committee of the Antwerp University Hospital, Belgium (Ref: B300201940004). Written informed consent was obtained from all household heads and study participants with epilepsy, including from the parents or guardians of participating children with epilepsy. All collected data were treated with absolute confidentiality.

3. Results

3.1. Study villages and participants

Overall, we surveyed 1355 individuals in 214 households. The median household size was six, with Tonjo village having the highest proportion of immigrant households; see Table 1. Farming was the most common occupation. Some families also reared animals, mainly chickens, cows, and goats; no pig-rearing household was identified. In total, 48 households had PWE; only in Woko village was more than one PWE identified in the same household (five households with two PWE; one household with three PWE). There were 42/168 (25.0 %) native households with at least one PWE, compared to 6/46 (19.6 %) immigrant households with PWE ($\chi^2 = 0.577$; p-value = 0.447). Although this was not specifically assessed, the investigators observed that in all villages, about one in every three households had a pregnant woman.

The overall mean age of village residents was 20.1 ± 16.2 years. There were slightly more females (53.9 %) than male participants (46.1 %). PWE were identified in all five villages, although the prevalence differed significantly across sites (p = 0.004); see Table 2. Combining data from all villages, overall ivermectin coverage for the previous CDTI round of 2023 was 67.4 % (77.9 % when considering only those aged ≥5 years, and 81.2 % among those aged 5–14 years), with Woko village having the lowest coverage (Table 2). Reasons for missing ivermectin treatment in 2023 were collected from 378 participants, as follows: age below 5 years (n = 165); absent from home during CDTI (n = 106); refusal (n = 36); sickness at the time of distribution (n = 24); pregnancy (n = 18); fear of side effects (n = 15); distribution did not reach my home (n = 10); and breastfeeding (n = 4).

Table 1
Household characteristics in the study villages.

N° of households	KOMBI	MAKUNDI CENTER	TONJO	WAR-PAC	WOKO	P-value
	***n* = 19**	***n* = 21**	***n* = 71**	***n* = 33**	***n* = 70**	***N* = 214**
Native households	15 (78.9 %)	13 (61.9 %)	43 (60.6 %)	31 (93.9 %)	66 (94.3 %)	<0.001
Immigrant households	4 (21.1 %)	8 (38.1 %)	28 (39.4 %)	2 (6.1 %)	4 (5.7 %)	
Duration in years for immigrants: Mean (SD)	4.8 (5.2)	3.4 (0.7)	3.1 (1.9)	4.0 (1.4)	10.2 (8.9)	0.004
Household occupation						
Farming	18 (94.7 %)	18 (85.7 %)	65 (91.5 %)	32 (97.0 %)	65 (92.9 %)	0.668
Fishing	0 (0 %)	0 (0 %)	11 (15.5 %)	0 (0 %)	21 (30.0 %)	<0.001
Cattle rearing	0 (0 %)	0 (0 %)	3 (4.2 %)	0 (0 %)	5 (7.1 %)	0.469
Employed	1 (5.3 %)	2 (9.5 %)	6 (8.5 %)	1 (3.0 %)	4 (5.7 %)	0.858
Households with at least one PWE	2 (10.5 %)	4 (19.5 %)	11 (15.5 %)	5 (15.2 %)	26 (37.1 %)	<0.001
Households with one or more deaths in the past 2 years	2 (10.5 %)	2 (9.5 %)	3 (4.2 %)	7 (21.2 %)	20 (28.6 %)	0.001

PWE: Person with Epilepsy; SD: Standard Deviation.

Table 2
Characteristics of the individual study participants.

N° of participants	KOMBI	MAKUNDI CENTER	TONJO	WAR-PAC	WOKO	P-value
	n = 110	***n = 153***	***n = 419***	***n = 211***	***n = 462***	***N = 1355***
Age: Mean (SD)	19.5 (18.6)	19.4 (16.3)	19.8 (14.8)	19.4 (16.7)	21.0 (16.5)	0.656
Sex: n (%)						0.263
Female	54 (49.1 %)	86 (56.2 %)	237 (56.6 %)	102 (48.3 %)	252 (54.5 %)	
Male	56 (50.9 %)	67 (43.8 %)	182 (43.4 %)	109 (51.7 %)	210 (45.5 %)	
Ivermectin in 2023:						<0.001
Yes	76 (69.1 %)	131 (85.6 %)	289 (69.0 %)	148 (70.1 %)	269 (58.2 %)	
No	34 (30.9 %)	22 (14.4 %)	117 (27.9 %)	59 (28.0 %)	182 (39.4 %)	
Don't know[a]	0 (0 %)	0 (0 %)	13 (3.1 %)	4 (1.9 %)	11 (2.4 %)	
Blindness:	0 (0 %)	1 (0.7 %)	1 (0.2 %)	1 (0.5 %)	8 (1.7 %)	0.227
Suspected epilepsy	2 (1.8 %)	4 (2.6 %)	17 (4.1 %)	5 (2.4 %)	46 (9.9 %)	<0.001
Confirmed epilepsy	2 (1.8 %)	4 (2.6 %)	11 (2.6 %)	5 (2.4 %)	33 (7.1 %)	0.004

SD: Standard Deviation.
[a] For participants who were not at home during the door-to-door survey and no one could confirm their ivermectin intake.

3.2. Description of persons with epilepsy

The 5-item screening tool identified 74 participants as suspected cases of epilepsy (SCE). More detailed information was obtained for 72 of these SCE; for the remaining two, it was impossible to obtain further details because they were absent and no one else in the household could provide the required information. Of the 72 SCE who underwent further investigation, the physicians concluded that 55 had epilepsy, giving an overall epilepsy prevalence of 4.1 % (95 % CI: 3.1–5.3). Of the 17 SCE who were not confirmed with epilepsy, alternative diagnoses included: febrile seizures (n = 11), dizziness/syncope (n = 3), only one seizure (n = 2), and psychogenic non-epileptic seizures in one participant.

The overall mean age of PWE was 21.5 ± 9.6 years (range: 4–45). The majority of PWE (n = 32, representing 58.2 %) were males. The gender-specific prevalence of epilepsy was 32/625 (5.1 %) for males and 23/730 (3.2 %) for females; p = 0.067. The median age at seizure onset (available in n = 44 PWE) was 8 years (IQR: 4–12), range 0–23 years. Seizure onset was most frequent in the 0–5 years age group (17/44 PWE, 38.6 %) and became less frequent with increasing age (Fig. 2). The median duration of epilepsy among PWE was 10.5 years (IQR: 5.0–18.3), range: 0–30.

Of the 44 PWE with available data on age at seizure onset, we applied the criteria for the OAE epidemiological definition and noted that 27/44 (61.4 %) could be classified as persons meeting the OAE criteria. The proportion of persons meeting the OAE criteria was lowest in Kombi village, where the lone PWE with data on age at epilepsy onset did not fulfil the OAE criteria, while it was highest at Woko village (Table 3). Twelve (21.8 %) PWE had never taken ivermectin in their lifetime, while 25 (45.5 %) did not take the drug prior to seizure onset. The reasons for not taking ivermectin before the onset of seizures were mostly related to the absence of CDTI during those years; 12 PWE reported that ivermectin was not distributed during the period preceding their epilepsy onset. Considering only PWE who experienced their first epileptic seizure at the age of 6 years and above (implying that they were eligible for ivermectin during the year prior to seizure onset), we found that 10/18 (55.6 %) of those meeting OAE criteria, and 6/9 (66.7 %) of those not meeting the OAE criteria had taken ivermectin before epilepsy onset (p = 0.587).

Only one PWE had been born in a health facility with skilled health attendants; the remainder (98.2 %) were born either at home or in a traditional delivery house. Of the 55 PWE, 13 (23.6 %) reportedly had a delayed cry at birth (proxy for perinatal asphyxia) according to their mothers; see Table 3.

Fig. 2. Age at seizure onset among persons with epilepsy in Wulu County.

Table 3
Personal and family history of persons with epilepsy in Wulu County.

	Kombi (n = 2)	Makundi Center (n = 4)	Tonjo (n = 11)	War-Pac (n = 5)	Woko (n = 33)	N
Age in years: Mean (SD)	18.0 (19.8)	26.2 (6.1)	15.9 (11.0)	19.6 (5.7)	23.2 (8.9)	55
Sex:						55
Female	1 (50.0 %)	0 (0 %)	3 (27.3 %)	2 (40.0 %)	17 (51.5 %)	
Male	1 (50.0 %)	4 (100 %)	8 (72.7 %)	3 (60.0 %)	16 (48.5 %)	
Family history of epilepsy						55
Father	0 (0 %)	0 (0 %)	1 (16.7 %)	0 (0 %)	1 (5.6 %)	
Mother	0 (0 %)	0 (0 %)	2 (33.3 %)	0 (0 %)	0 (0 %)	
Sibling	1 (100 %)	0 (0 %)	5 (83.3 %)	1 (100 %)	12 (66.7 %)	
Place of birth:						55
At home or in a house	2 (100 %)	4 (100 %)	11 (100 %)	5 (100 %)	32 (97.0 %)	
In a hospital or health facility	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	1 (3.0 %)	
Delayed cry at birth:						55
Yes	2 (100 %)	1 (25.0 %)	2 (18.2 %)	2 (40.0 %)	6 (18.2 %)	
No	0 (0 %)	3 (75.0 %)	8 (72.7 %)	2 (40.0 %)	20 (60.6 %)	
Not known	0 (0 %)	0 (0 %)	1 (9.1 %)	1 (20.0 %)	7 (21.2 %)	
Diagnosis						55
Epilepsy with history of nodding seizures	0 (0 %)	3 (75.0 %)	1 (9.1 %)	2 (40.0 %)	5 (15.2 %)	
Epilepsy without a history of nodding seizures		1 (25.0 %)	10 (90.9 %)	3 (60.0 %)	28 (84.8 %)	
Seizure onset during the last 12 months:	0 (0 %)	0 (0 %)	1 (9.1 %)	0 (0 %)	1 (3.0 %)	55
Fulfil the OAE criteria:	0/1 (0 %)	2/4 (50.0 %)	4/9 (44.4 %)	3/5 (60.0 %)	18/25 (72.0 %)	44
Ivermectin intake during lifetime	2 (100 %)	4 (100 %)	7 (63.6 %)	3 (60.0 %)	27 (81.8 %)	55
Ivermectin intake before seizure onset	1 (50.0 %)	0 (0 %)	6 (54.5 %)	3 (60.0 %)	20 (60.6 %)	55

3.2.1. Clinical features of the identified persons with epilepsy

More than half of the PWE in Wulu experienced at least one seizure every month. The most frequent seizure type at the time of the survey was generalized tonic-clonic convulsions, reported by 41 (74.5 %) PWE. Next came nodding seizures in 11/55 (20.0 %) of PWE (Table 4). Absences, focal, and sensory seizures were not properly assessed and hence will not be reported. No PWE with delayed secondary sexual development were identified, and despite the presence of a thoracic or spinal deformity in five PWE, none of them presented with the full clinical picture of Nakalanga syndrome [32]. Regarding epilepsy treatment, 29 PWE (52.7 %) admitted to taking anti-seizure medicines (ASM) but only five PWE (9.1 %) took them on a daily basis.

Table 4
Clinical features of persons with epilepsy in Wulu County.

Clinical characteristics	Findings	N
Most frequent seizure type: n (%)		55
Tonic-clonic convulsions	41 (74.5 %)	
Nodding seizures	11 (20.0 %)	
History of nodding seizures		55
Still occurring	6 (10.9 %)	
Occurred in the past	5 (9.1 %)	
Treatment		55
Anti-seizure medications	29 (52.7 %)	
Traditional medicine	6 (10.9 %)	
No treatment	25 (45.5 %)	
Age at seizure onset: Mean (SD)	8.6 (5.9)	44
Duration of epilepsy: Mean (SD)	12.3 (8.2)	44
Visual acuity		40
Normal	28 (70.0 %)	
Reduced	10 (25.0 %)	
Blind in both eyes	2 (5.00 %)	
Thoracic or spinal deformity	5 (12.5 %)	40
Delayed sexual development	0 (0 %)	9[a]
Cognitive assessment		40
Oriented in space	25 (62.5 %)	
Oriented in time	20 (50.0 %)	
Skin examination		40
Normal	31 (77.5 %)	
Nodules	9 (22.5 %)	
Itching with no lesion	10 (25.0 %)	
Papular pruritic lesions	3 (7.5 %)	
Leopard skin	0 (0 %)	
Lizard skin	1 (2.5 %)	
Scars from wounds or burns	3 (7.5 %)	

[a] Only 9 participants accepted examination of their external genitalia.

3.3. Mortality of epilepsy

Verbal autopsy found that a total of 35 persons had died in the study villages during the past 24 months, nine (27.5 %) of whom had epilepsy. This yielded an estimated annual epilepsy mortality rate of 323.7 per 100,000 persons. The median age at death was not significantly different between PWE (20 years old; IQR: 3–35) and their deceased non-epileptic peers (24 years old; IQR: 18–25); $p = 0.639$. Based on these nine deaths among PWE during the past two years, we estimated the annual epilepsy fatality rate as 7031.3 per 100,000 PWE. The relative risk of dying among PWE compared to the non-epileptic population was 7.2. The causes of death by epilepsy status are detailed in Table 5.

3.4. Incidence of epilepsy

The onset of seizures in two PWE occurred within the previous 12 months (incident cases); the incidence of epilepsy was therefore calculated as 147.6 per 100,000 persons per year in the Wulu villages.

3.5. Risk factors for epilepsy in the village households

The multivariable regression analysis found that having farming as household occupation was associated with increased odds of having a PWE (alive or died during the past 24 months) in the household. Meanwhile, being a village native or practicing fishing were protective of epilepsy in the households (Table 6). The village variable, introduced in the random part of the model, accounted for 56.6 % of the variance which could be explained by the full model.

3.6. Ov16 seroprevalence in children aged 3–9 years

A total of 119 children were tested with Ov16 antibodies detected in 18 (15.1 %). While in some villages the Ov16 seroprevalence was zero, a peak value of 30.9 % was observed in Woko village. Ov16 seropositivity varied significantly across villages, but not by age (Table 7).

4. Discussion

Our survey found a prevalence of epilepsy (including nodding syndrome) of 4.1 % in Wulu, which is significantly higher than the median 1.4 % prevalence reported in the SSA region [4]. This prevalence is similar to what was observed in other onchocerciasis-endemic areas of South Sudan using similar methodologies, notably 4.4 % in Maridi [5], 3.3 % in Mundri [23] and 5.1 % in Mvolo [24]. As expected, epilepsy prevalence was highest in Woko village, where Ov16 seroprevalence was also the highest, indicating ongoing onchocerciasis transmission. Woko village had the highest prevalence of individuals meeting the OAE criteria and the highest prevalence of blindness. Furthermore, Woko was the only study site in which PWE were clustered within the same household. Located on the banks of the Naam River, a likely blackfly breeding site, Woko village also recorded the lowest ivermectin coverage (58.2 % in 2023). To address this low CDTI coverage, it is crucial to increase ivermectin intake in this village, ideally administering it to children twice a year. An extra round of ivermectin distribution was undertaken using a school-based approach to increase ivermectin use in this vulnerable population [26].

Our study findings suggest that among a panoply of seizure etiologies, persistent onchocerciasis transmission still contributes to a fair share of the community's epilepsy burden in endemic sites. For instance, in an onchocerciasis focus in Cameroon, among other causes of epilepsy, the population attributable fraction of epilepsy due to onchocerciasis was estimated between 80 and 90 % [15]. A previous meta-analysis by Pion et al. reported that on average, every 10 % increase in onchocerciasis prevalence results in a 0.4 %

Table 5
Causes of death in Wulu County in 2022–2023.

Cause of death	Persons with epilepsy	Persons without epilepsy
N = 35	n = 9	n = 26
Accident	1	1
Childbirth complications	0	1
Dog bite	0	1
Epilepsy/Seizure	5	0
Gastro-intestinal illness	0	3
Gunshot wound	0	1
Heart attack	0	1
Malaria	0	4
Neonatal death	0	1
Pneumonia	0	3
Unspecified illness	0	6
Wandering away from home	2	0
Wound	0	1
Unknown	1	3

Table 6
Risk factors for belonging to a household with epilepsy.

Covariates	Odds Ratio (95 % CI)	P-value
Age	1.007 (0.9990–1.015)	0.087
Male sex	1.223 (0.950–1.574)	0.118
Native household	0.703 (0.499–0.988)	0.042
Farming	4.542 (2.296–8.989)	<0.001
Fishing	0.480 (0.309–0.747)	0.001
Cattle rearing	1.105 (0.494–2.474)	0.808
Blindness	1.973 (0.530–7.340)	0.311
Ivermectin intake in 2023	1.174 (0.879–1.567)	0.278

CI: Confidence Interval.
R-squared, fixed part of model = 8.10 %.
R-squared, full model (fixed part + random part) = 18.67 %.
Intra-cluster correlation coefficient (ICC) for the clustering variable "village" = 0.115.

Table 7
Ov16 serological findings in children by rapid diagnostic testing.

By village	Ov16 seroprevalence	P-value	By age	Ov16 seroprevalence	P-value
Kombi	0/11 (0 %)	0.001	3 years	4/24 (16.7 %)	0.588
Makundi Center	0/15 (0 %)		4 years	3/18 (16.7 %)	
Tonjo	0/13 (0 %)		5 years	4/13 (30.8 %)	
War-Pac	1/25 (4.0 %)		6 years	3/21 (14.3 %)	
Woko	17/55 (30.9 %)		7 years	3/19 (15.8 %)	
			8 years	1/13 (7.7 %)	
			9 years	0/11 (0 %)	
Total	18/119 (15.1 %)		Total	18/119 (15.1 %)	

increase in epilepsy prevalence [11].

We found that 61 % of the PWE in our study met the clinical and epidemiological criteria of OAE, lower than in other South Sudanese sites where it is generally >75 % [23,24,33]. This suggests that other epilepsy etiologies are largely at play in the Wulu villages. Considering that home delivery by unskilled attendants is the norm in Wulu, the fact that almost one-quarter of PWE experienced delayed cry at birth, and the frequent seizure onset reported during their first years of life, poor perinatal practices could indeed constitute a major cause of epilepsy in this community. Additional studies are needed to understand the full scope of the causes of epilepsy in Wulu, preferably using a longitudinal approach that would investigate births and epilepsy onset prospectively. In the meantime, Wulu County would certainly benefit from interventions that meet the reproductive health needs of women, including contraception and safe delivery practices.

Nodding syndrome cases were identified in Wulu County, as in other endemic areas within South Sudan [23,24,33,34] and beyond [18,35–38]. It is worth noting that in Kombi and Tonjo villages where Ov16 seroprevalence was 0 %, nodding syndrome was also scarce. This concurs with observations from Kabarole (Western Uganda) where nodding syndrome stopped appearing after elimination of onchocerciasis [17]. However, that Ugandan study still found persons with nodding syndrome who were carry-overs from the period of high endemicity in the area [17]. Similarly, the occurrence of nodding syndrome even in the absence of any Ov16 seropositivity in some villages such as Makundi Center could imply high onchocerciasis transmission in the past, which has been declining in recent years. No person with a full clinical picture of Nakalanga syndrome was identified, possibly because the latter typically occurs in places with prolonged and ongoing hyperendemic status and also disappears when elimination measures are put in place. A similar finding was made in the Mbam valley of Cameroon, where only one case of Nakalanga syndrome was identified despite a meso-endemic onchocerciasis status at the time of the study [36]. This person with Nakalanga features (aged 35 years at the time of the survey) was most likely a survivor from the hyper-endemic pre-CDTI era when she and her household were highly exposed to onchocerciasis [36].

The proportion of PWE in Wulu having access to ASM was low (52.7 %), and even fewer PWE (<10 %) could afford daily ASM treatment. These numbers are not different from those observed in Maridi, South Sudan, where only 51.4 % of PWE were taking ASM prior to implementing an epilepsy treatment program [33]. When taken together, these reports attest to the wide treatment gap that still exists in this part of the world, in line with a meta-analysis that reported a treatment gap of 68.5 % in SSA [39]. A major factor that limits access to epilepsy care in South Sudan is the high cost of ASM which was estimated at 12.0 USD per month in Maridi, constituting the largest proportion of epilepsy direct costs [40]. In the absence of treatment, seizures are likely to persist thereby perpetuating a vicious cycle of poverty, poor health outcomes and stigma [40]. Therefore, it is expedient that initiatives to freely provide uninterrupted ASM to PWE in Wulu be established. Indeed, free ASM provision would increase the proportion of treated PWE to >90 % as observed in Maridi [20] and Mundri [23]. A community-based model of PWE follow-up and ASM delivery could greatly improve the quality of life of affected individuals, as recently demonstrated in Maridi [41].

The high rate of ivermectin intake (55.6 %) prior to epilepsy onset in persons meeting the OAE criteria was unexpected, considering previous data suggesting that ivermectin intake in onchocerciasis-endemic areas may protect children from developing epilepsy [42,

43]. This could mean that indeed in some of these children classified as probable OAE, the epilepsy may not be associated with onchocerciasis. It also could be that the first seizures occurred before ivermectin intake but were initially not recognised by the family. Moreover, although ivermectin can rapidly deplete the *O. volvulus* microfilarial load, it does not kill the adult worms. In fact, it was shown that after ivermectin treatment, the production of microfilariae by the female adult worms resumes within six months [44]. Therefore, with the inconsistency in ivermectin intake during subsequent CDTI rounds, the microfilarial load may rebuild after missed treatments and could eventually reach levels sufficient to directly or indirectly induce epilepsy.

The epilepsy mortality rate of 323.7 per 100,000 persons per year in our study is similar to previous observations in South Sudan (Maridi: 342.9 per 100,000 person-years) [45]. The 7-fold mortality risk for PWE compared to the general population in Wulu is similar to the 7.4 reported by Kaiser in Uganda [46] and the 6.2 found by Kamgno et al. in Cameroon [47], but still lower than the 11.9 mortality risk in Mundri, South Sudan [45]. Looking at the epilepsy fatality rate of 7031.3 per 100,000 PWE per year in our study, it is extremely high compared to previous findings which range between 19.3 and 208.6 per 100,000 in other onchocerciasis-endemic areas [45]. This could be related to the huge treatment gap, but there are certainly other reasons to explain such high mortality in PWE. The fact that several PWE in Wulu most likely acquire seizures perinatally would dampen their prognosis, possibly causing more frequent and earlier deaths among PWE.

The CDTI coverage in the study villages was 67.4 %, falling short of the 80 % goal set by the World Health Organization and the Ministry of Health [48]. However, among the vulnerable 5–14 years age group who are more susceptible to developing OAE, coverage was >80 % indicating their willingness to take the drug. To sustain high coverage, it is important to devise innovative ways of distributing ivermectin in such settings. A bi-annual CDTI scheme could be considered to ensure that the maximum number of eligible individuals receive ivermectin at least once a year as was done in Maridi County [20]. A less costly alternative to bi-annual CDTI is school-based administration of ivermectin to children, in combination with other chemoprophylaxis interventions like albendazole or praziquantel treatment [43]. Such an intervention is underway in Wulu [26].

Unexpectedly, the Ov16 seroprevalence in children seemed to decrease with age especially after the age of 5 years (Table 7), contrary to previous observations in South Sudan [49] and the Democratic Republic of the Congo [50]. A possible explanation could be the high ivermectin coverage among children aged 5 years and above, which prevents any further *O. volvulus* infection in older children. Indeed, a recent study in Guatemala demonstrated that in case of no new onchocerciasis (re)infection, the Ov16 antibody response gradually decreases with a half-life of 3.3 years [51].

In the regression analysis (Table 6), the farming profession was found to be a risk factor for epilepsy in the household. The exact reasons for this finding are unclear, but it could be that farming mothers carry the young children on their back when going to the farm, thereby exposing them to more blackfly bites outdoors, possibly contributing to high Ov16 positivity among children up to 5 years old, since most older children attend school instead. Also, farming families sometimes camp at the farmlands (often close to rivers and blackfly breeding sites) for several days, especially during the harvesting season. Therefore, children from farming homes may be more at risk of early onchocerciasis infection which makes them more prone to developing OAE [15]. Meanwhile, fishing was associated with lower odds of having an epileptic household member, most likely because fishermen (mainly adult males, as observed in the study area) do not take children with them when going to the river daily, and the family spends less time in the farmlands thereby limiting their exposure to blackfly bites. The fact that native families had lower odds for an epileptic household member was unexpected and contrasts with previous findings in the Maridi onchocerciasis focus of South Sudan [5]. While this deserves to be investigated further, a plausible explanation is that immigrant households may be more likely to occupy areas close to the rivers for farming and fishing opportunities thereby heightening their onchocerciasis exposure and consequently OAE risk. A similar pattern was observed in western Uganda, with native populations settling at a distance from the river because the riverbanks were considered to be “cursed by evil spirits bringing diseases” (including epilepsy), while immigrants are prompt to occupy these available farmlands with high onchocerciasis transmission [17].

Our study had several limitations. Although we used a door-to-door approach, not all household residents were present in all the visited homes. Consequently, information about the absent individuals were obtained second-hand from another household member. It is also possible that stigma and social desirability bias influenced the responses to some of the survey questions, particularly those pertaining to epilepsy and ivermectin intake. We were unable to perform any additional tests (such as brain imaging or genetic investigations) to identify the etiologies of the epilepsy. Brain imaging is particularly useful to detect neurocysticercosis-related lesions as a cause of epilepsy. However, given the scarcity of pigs in Wulu, it is very unlikely that neurocysticercosis is a major epilepsy etiology in this area.

5. Conclusion

We found a high prevalence of epilepsy in Wulu County, with significant differences across villages. Notably, Woko village (close to Naam River and having the highest onchocerciasis transmission) had the highest epilepsy prevalence. Besides onchocerciasis as a possible risk factor for epilepsy, frequent epilepsy onset among the under-five age group points towards a possible perinatal etiology of seizures in many cases. Ongoing onchocerciasis transmission, poor childbirth practices, and a wide treatment gap are among the most crucial elements to be addressed by potential epilepsy prevention and care programs in Wulu.

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Ethics approval and consent to participate

Ethical approvals were obtained from Ministry of Health of South Sudan (MOH/RERP/P/35/15/05/2023-MOH/RERP/A/35/2023) and from the ethics committee of Antwerp University Hospital, Belgium (Ref: B300201940004). Informed consent was obtained from all study participants, and confidentiality was observed.

Consent for publication

Written informed consent was obtained from all participants described in this paper.

Data availability statement

The data presented in this study have not been deposited in a public repository. However, they are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Joseph Nelson Siewe Fodjo: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Stephen Raimon Jada:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Abraham Taban:** Writing – review & editing, Supervision, Investigation. **John Bebe:** Project administration, Supervision, Writing – review & editing. **Yak Yak Bol:** Writing – review & editing, Supervision, Resources. **Jane Y. Carter:** Writing – review & editing, Resources, Funding acquisition. **Robert Colebunders:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

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