The prevalence of onchocerciasis-associated epilepsy in Mundri West and East Counties, South Sudan:

a door to door survey

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Abstract

A two phase survey of epilepsy was conducted in selected villages in Mundri West and East Counties (26 June–8 July, 2021), an onchocerciasis-endemic area in Western Equatoria State in South Sudan. In the first phase, households were visited by a trained research team to identify persons suspected to have epilepsy. In the second phase, persons suspected to have epilepsy were interviewed and examined by a clinician to confirm the diagnosis.

 A total of 364 households agreed to participate in the survey, amounting to 2,588 individuals. The epilepsy screening questionnaire identified 91 (3.5%) persons suspected to have epilepsy, of whom in 86 (94.5%) the diagnosis of epilepsy was confirmed by a clinician. The overall prevalence of confirmed epilepsy was 3.3% (95% CI: 2.7-4.1%), and of nodding syndrome 0.9% (95% CI: 0.6-1.4%). In 61 (16.8%) households there was at least one person with epilepsy. Only 1,212 (46.9%) of 2,583 people took ivermectin during the last distribution round in 2021. The annual epilepsy incidence was 77.3/100.000 (95% CI: 9.4-278.9/100,000) and the annual epilepsy mortality 251.2/100,000 (95% CI: 133.8-428.7/100,000). In conclusion, a high prevalence and incidence of epilepsy was observed in villages in

Mundri. Urgent action is needed to prevent children from developing onchocerciasis-associated epilepsy by strengthening the local onchocerciasis elimination programme.

1. Introduction

A high prevalence of epilepsy is observed in many onchocerciasis-endemic areas, where persons with nodding syndrome and Nakalanga syndrome are reported [1]. Recent studies have shown that nodding syndrome and Nakalanga features are phenotypic presentations of onchocerciasis-associated epilepsy (OAE) [1]. Indeed, children with nodding syndrome and others meeting OAE criteria without nodding syndrome live in the same families and in villages located close to rapid flowing rivers with blackfly breeding sites [1]. A recent post-mortem study showed that brains of persons who died with nodding syndrome or another form of OAE have similar pathological findings [2]. Both nodding syndrome and other forms of OAE appear in areas with high *Onchocerca volvulus* transmission and stop appearing when onchocerciasis is eliminated [3,4].

Between 2001 and 2002, three small case control studies were performed in Greater Mundri in Western Equatoria, South Sudan, to identify potential risk factors for the development of nodding syndrome [5]. These studies, performed in Mundri Centre, Lui and Amadi Payams, three administrative divisions close to the Yei River, showed a strong positive association between nodding syndrome and onchocerciasis. Indeed, *O. volvulus* microfilariae were observed in 92.3% of skin snips from epilepsy cases compared with 43.7% of controls (OR 15.4; 95% CI: 1.60- 148.82 (P=0.008)) [5]. At that time, the prevalence of nodding syndrome was estimated at 2.3% (41/1783) in Lui and 6.7% (57/854) in Amadi, with the first cases of nodding syndrome estimated to have appeared in Mundri in the 1990s [5].

In 2018, in a door-to-door survey performed in onchocerciasis-endemic villages in Maridi, Western Equatoria state, South Sudan, an epilepsy prevalence of 4.4% was documented with a prevalence of 11.9% in a village close to the Maridi dam, the only known blackfly breeding site in the area [6]. In this survey,

85.2% of persons with epilepsy (PWE) met the criteria of OAE and 45.5% met the criteria of nodding syndrome [7]. In June 2020 a similar survey in Mvolo County documented an epilepsy prevalence of 5.1%, whereby 78.4% of PWE met the criteria of OAE and 44.1% of PWE had a history of nodding seizures [8].

Recent cross-sectional studies suggest that strengthening an onchocerciasis elimination programme is able to reduce the incidence of nodding syndrome and OAE [3,4]. However, this has not yet been demonstrated in a prospective study and it is also not known which onchocerciasis elimination measures are most effective. To investigate these questions we initiated a prospective study comparing the effect of bi-annual community directed treatment with ivermectin (CDTI) together with community-based vector control using a "slash and clear" method in Maridi [9] with annual CDTI in Mvolo and Mundri on the incidence of nodding syndrome and other forms of epilepsy [10]. As part of this initiative, a baseline epilepsy survey was completed in Maridi [6] and Mvolo [8]. In this paper we present the results of a baseline survey carried out in the Greater Mundri area.

2. Methodology

2.1. Study setting

The study was conducted in Mundri West and East Counties in Western Equatoria State of South Sudan (Figure 1)
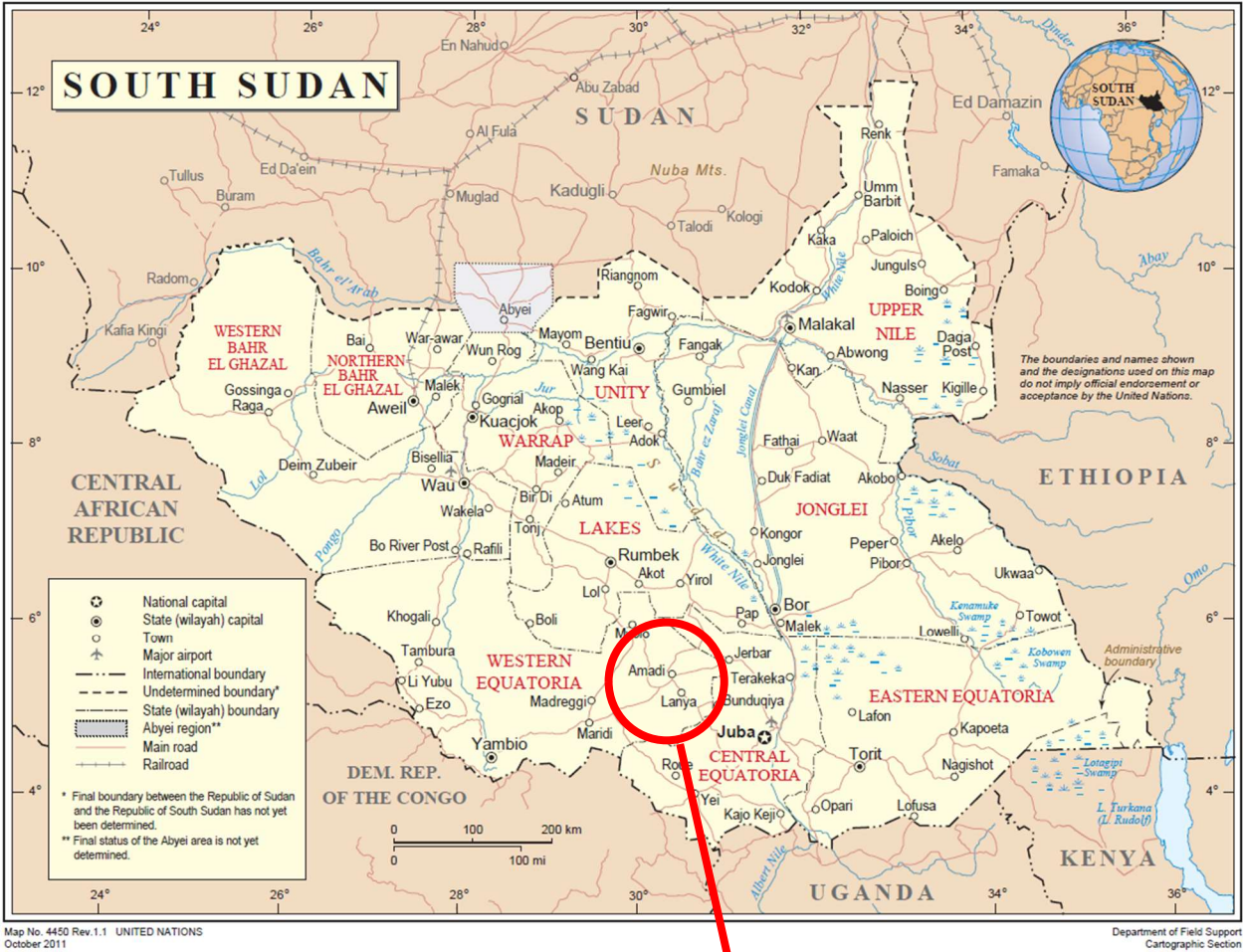
Figure 1. Map of South Sudan and map of Western Equatoria State with Mundri West and Mundri East

Counties.

An epilepsy survey was conducted in selected villages in Amadi and Mundri Payams (Mundri West County) and Lui Payam (Mundri East County) between 26 June–8 July, 2021, in Western Equatoria State, South Sudan. Villages, with the exception of Lui town, were chosen because of their proximity to the Yei River (Figure 2)
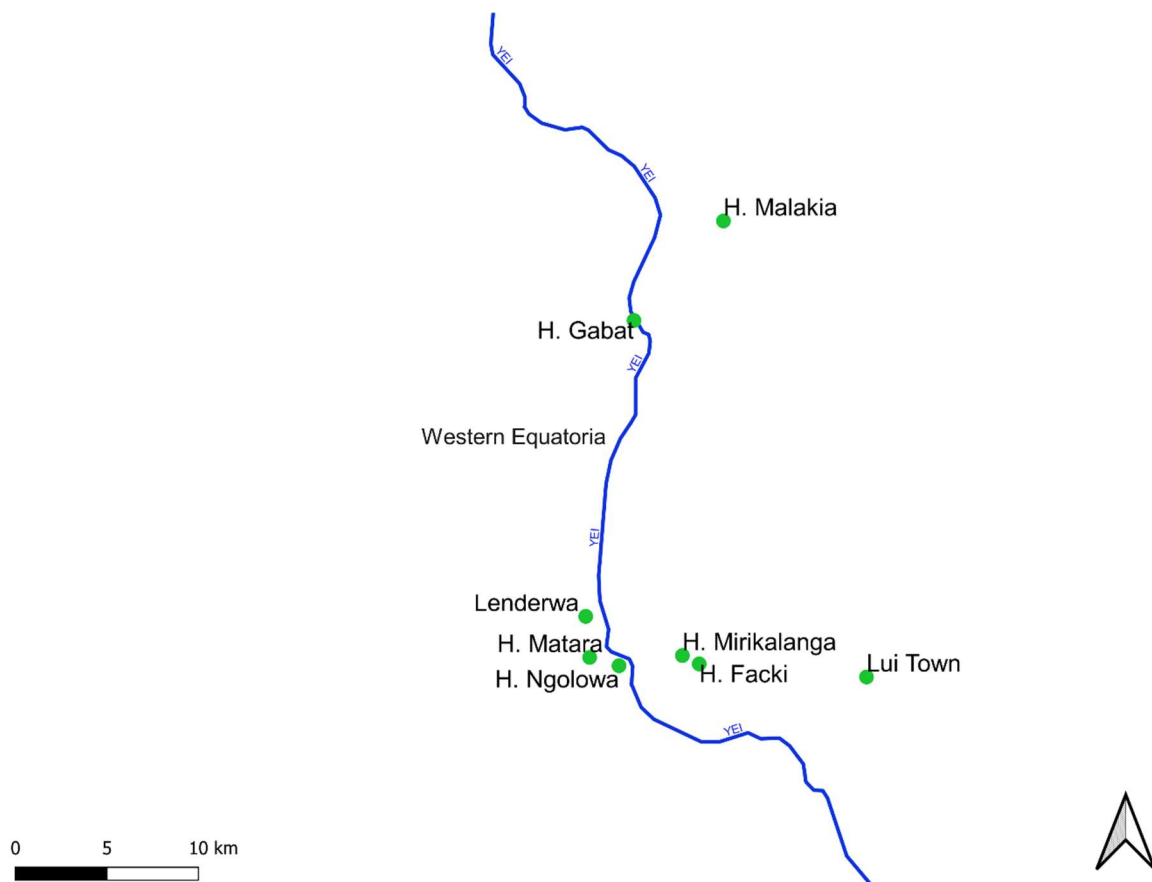
Figure 2. Map showing locations of villages included in the study and their positions relative to the Yei

These villages were expected to have a high OAE incidence and therefore priority villages for inclusion in a prospective study to demonstrate the impact of an intervention to decrease OAE incidence.

The projected population of the Greater Mundri area is estimated at 115,717 (47,853 Mundri West; 67,864 Mundri East Counties). Muru is the dominant ethnic group in the Greater Mundri area; other

ethnic groups include Muru-Kodo and Avukaya. Muru is the dominant language in both Mundri East and Mundri West, but the common language of communication is local Arabic.

Farming is the main economic and livelihood activity; the main crops grown in Mundri are sorghum, *simsim* (sesame), cassava, sweet potatoes, groundnuts, vegetables, maize and millet. Fishing is also a viable supplementary livelihood activity in Mundri West. Water is mainly accessed from the Yei and Mori Rivers, which are fast flowing with several shallow rapids. Goats and chickens are the main livestock in Mundri West and Mundri East. No pigs are kept in the area.

2.2. Study design

A door-to-door survey was conducted in seven selected villages in Mundri West and East Counties. A two step survey was used to identify PWE. In the first phase, households were visited by a trained research team of ten locally recruited research assistants (each household was visited by a single research assistant). After obtaining informed consent, family members were interviewed using a validated questionnaire translated into the local language [11]. In the second phase, persons suspected by the research assistants of having epilepsy were referred for interview and examination by five clinical officers trained to diagnose epilepsy according to International League against Epilepsy (ILAE) definitions [12]. These clinical officers confirmed the diagnosis of epilepsy or suggested an alternative diagnosis. These ten research assistants and five clinical officers were selected by the local health authorities from the Mundri West and Mundri East County Health Departments. Research assistants were chosen from among the county community drug distributors who had at least secondary school education level. The research assistants were trained for one full day on the use of the screening questionnaire for suspected epilepsy. In addition, five clinical officers from primary healthcare centres in the counties were trained on how to confirm the diagnosis of epilepsy. Both the research assistants and clinical officers pilot tested the data collection tools prior to data collection. The training was organized by two medical doctors (SR

and GA). During the home visits, SR supervised the research assistants and clinical officers and also

interviewed and examined selected persons with suspected epilepsy.

2.3. Definitions

In accordance with the ILAE, a case of epilepsy was defined as an individual with at least two

unprovoked seizures with at least 24 hours separating the two episodes [13].

Nodding seizures were defined as the head dropping forward repeatedly in a person during a brief

period of reduced consciousness. Nodding syndrome was defined according to the World Health

Organization consensus definition [14]. OAE was defined as a person meeting all the following six

criteria: i) a history of at least two unprovoked epileptic seizures at least 24 hours apart; ii) living for at

least 3 years in an onchocerciasis endemic region; iii) living in a village with a high number of persons

with epilepsy (epilepsy well known by the community) and with families with more than one child with

epilepsy; iv) no other obvious cause of epilepsy as determined by the history; v) onset of epilepsy

between the ages of 3 and 18 years; and vi) normal psychomotor development before the onset of

epilepsy as reported by the parents [1].

As potential "obvious causes of epilepsy" we considered a history of a perinatal event, severe malaria,

encephalitis or meningitis and head injury with loss of consciousness in the 5 years preceding the onset

of epileptic seizures. Nakalanga features were defined as an association of growth retardation without

obvious cause, delay or absence of external signs of secondary sexual development, severe learning

difficulties, epilepsy, and often facial, thoracic, and spinal abnormalities[15]. A "permanent household"

was defined as a family who had lived in the village for at least 20 years. An "immigrant household"

referred to a family who had lived in the village for less than 20 years.

2.4. Data collection, management

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Screening of households by research assistants to identify persons with suspected epilepsy was performed using a paper-based questionnaire (supplementary material 1) addressed to each family member. If nobody or only children were present in a house, this house was revisited at least one further time. For every household member it was noted whether a person was present or absent. If a person was absent information about him/her was obtained from the other household members. This questionnaire included five epilepsy screening questions adapted from a questionnaire that was previously validated in Mauritania [11]. After these five questions had been used during an epilepsy survey in Maridi, South Sudan [6] we decided to remove the question "Sudden onset of brief body sensations, hallucinations or illusions be they visual, auditory or olfactory" from the previously validated questionnaire because we experienced that this question was difficult to translate into the local language, was poorly understood, and it was exceptional that a person with confirmed epilepsy would be identified only by a positive answer to this question. We replaced this question with a question about head nodding episodes. If the answer to one of the five epilepsy questions was positive, this person was considered to have suspected epilepsy and was referred to one of the clinicians. Each household member was also asked whether he/she experienced skin itching and/or problems with vision (blindness or blurred vision), and whether they had taken the drug ivermectin during the previous distribution in 2021. The questionnaire also contained questions about duration of residence, ethnicity, main income generating activity of the family, exposure to cattle or pigs, whether family members had recently developed epilepsy and whether family members with epilepsy recently had died (when and at what age). For confirmation of epilepsy, clinical officers and medical doctors used a questionnaire deployed on the KoBo toolbox, a free open-source tool for mobile data collection (https://www.kobotoolbox.org/) with unique codes assigned to each suspected case. Clinicians assessed the type of epilepsy, triggers of seizures, causes of epilepsy, epilepsy related co-morbidities (cognitive impairment, behavioural problems, burn scars). Cognitive function was evaluated by determining whether the participant was

well orientated in time and space, whether he/she could remember his/her name, was coherent in speech, and was obedient to orders. PWE were also examined for onchocerciasis related clinical signs (skin lesions, vision problems). Blurred vision or blindness was considered if a person was not able to see the five fingers of his hand. Level of autonomy was assessed using a modified Rankin scale 1–5 [16]. Questions were asked about current and past anti-seizure medication and ivermectin intake in 2021.

2.5. Onchocerciasis antibody testing of children

A total of 224 children aged between 3–9 years, living in Amadi and Mundri Centre, were tested for IgG antibodies to *O. volvulus* using the Ov16 rapid diagnostic test (Standard Diagnostics, Inc., Yongin-si, South Korea) as an indicator of the degree of recent *O. volvulus* transmission. Blood was obtained via finger prick and the test was performed according to the manufacturer's instructions. Among these Ov16-tested children, we investigated ivermectin use during the last CDTI round in 2021.

2.6. Data analysis

Continuous variables were summarized with median and interquartile range (IQR), while the absolute and relative frequencies were used to summarize categorical variables. Chi-squared Exact test was used to compare categorical variables and Wilcoxon signed-rank tests were used for continuous variables. The epilepsy prevalence in a village was calculated by summing up all the epilepsy confirmed cases in the village, divided by the total number of persons residing in that village who had participated in the survey. The corresponding 95% Clopper-Pearson confidence interval (exact interval) was used. This interval was preferred to the Wald confidence interval because it is based on the exact binomial distribution rather than the normal approximation of the Wald confidence interval. The overall epilepsy incidence in the total population was calculated by summing up all the cases of epilepsy in whom the seizures started within the previous 5 years (epilepsy duration between 0 and 5 years), and dividing by

the total population at risk during this period and by five to obtain the annual incidence. Epilepsy related mortality was calculated by dividing the number of persons known to have epilepsy who died in the previous 12 months by the summed person-years of the population at risk in this period. Ivermectin coverage was defined as the percentage of the population that reported taking ivermectin in 2021. A two level hierarchical generalized linear mixed model (GLMM) with logit link was considered to assess variables associated with epilepsy. A household was considered as the first hierarchical level to account for the similarity among individuals living in the same house, and a village was considered as the second hierarchical level to account for the similarity among individuals residing in the same village. Adjusted odds ratios with 95% confidence intervals (CI) in multivariable analysis were determined. All two-way interactions between variables were considered in the model and a likelihood ratio test was used to identify potential interactions.

3. Results

3.1. Households participating in the survey

In total, 364 households containing 2,588 individuals were visited, of whom 526 (20.3%) were not present at the time of the interview, but the interviewer obtained information about them from their family members. The median number of individuals living in the same house was four (IQR: 2−6), with a maximum of 20 individuals living in the same house. Three hundred and forty six (95.1%) families belonged to the Moro ethnic group and 18 (4.9%) families belonged to other ethnic groups including Nyamosa and Pojulu. Reported income generating activities included farming by 305 (83.8%) families, fishing by 50 (13.7%), cattle keeping by 19 (5.5%), trading by 18 (4.9%) trading, working for the local government by 102 (28.0%). Two hundred and ninety four (80.8%) families originated from the selected villages while 70 (19.2%) were immigrant families with a median (IQR) period of residence in the village of seven (3.0−10.0) years.
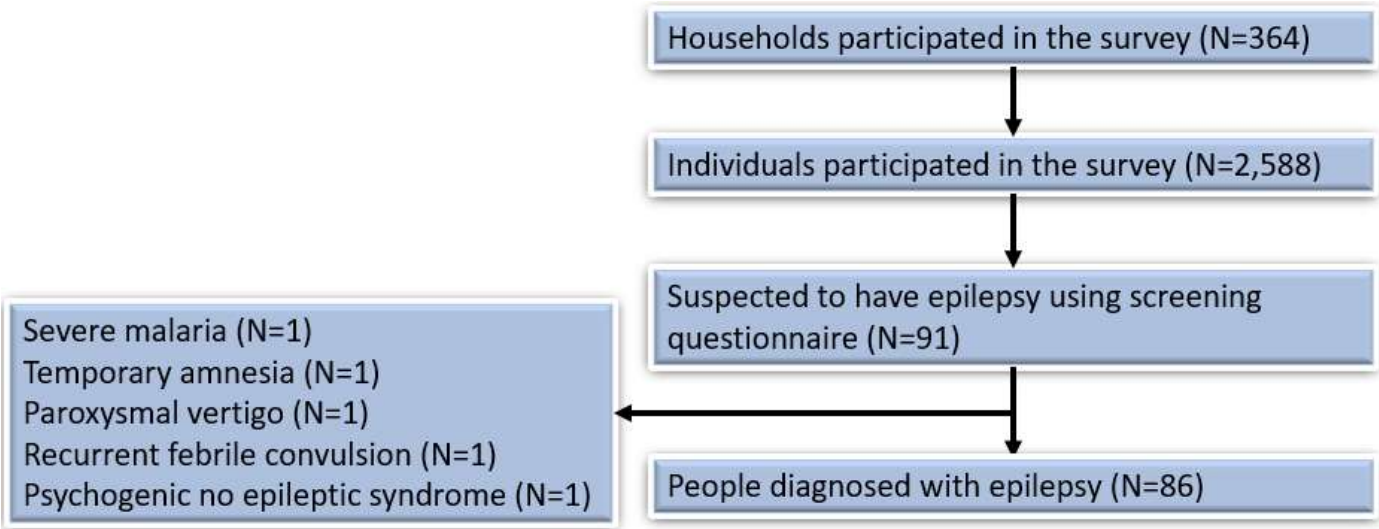
Figure 3. Overview of the survey participants

3.2. Prevalence of epilepsy and potential onchocerciasis-associated co-morbidities

Of the 2,588 individuals included in the survey, 91 (3.5%) were identified in the screening questionnaire

as persons with suspected epilepsy and were referred to the clinician. In 86 individuals (95.5%) the

diagnosis of epilepsy was confirmed by the clinical officer and/or a medical doctor (SR). Five persons

with suspected epilepsy were diagnosed with another condition: severe malaria (N=1), temporary

amnesia (N=1), paroxysmal vertigo (N=1), recurrent febrile convulsions (N=1), and psychogenic seizures

(N=1) (Figure 3). The overall prevalence of confirmed epilepsy was 3.3%, (95% CI: 2.7-4.1%). Itching was

reported in 1,041 (40.2%) individuals and blindness or blurred vision in at least one eye in 70 (2.7%)

(Table 1). The highest number of PWE were observed in Hai Lenderwa: 10 (6.6%) and Hai Gabat village:

14 (4.3%).

Table 1. Number of persons with potential onchocercisis related conditions and ivermectin use by study
village

Village	Participants in survey, n	Epilepsy confirmed cases, n (%)	Itching, n (%)	Blindness, n (%)	Ivermectin use, n (%)	Approximate distance to Yei River in km
Mundri West						
Amadi Payam						
Hai Gabat	328	14 (4.3)	231 (70.4)	18 (5.5)	155 (47.3)	<2km
Hai Malakia	256	3 (1.2)	174 (67.9)	10 (3.9)	140 (54.7)	>2km
Mundri Centre Payam						
Hai Facki	332	12 (3.6)	155 (46.7)	14 (4.2)	213 (64.2)	>2km
Hai Ngulawa	286	10 (3.5)	88 (30.8)	7 (2.4)	136 (47.5)	<2km
Hai Lenderwa	151	10 (6.6)	46 (30.5)	4 (2.6)	85 (56.3)	<2km
Hai Mirikalanga	372	8 (2.2)	133 (35.7)	10 (2.7)	202 (54.3)	>2km
Mundri East						
Lui town	862	28 (3.2)	214 (2.5)	7 (0.8)	295 (34.2)	>2km
Overall East and West Mundri	2588	85 (3.3)	1041 (40.2)	70 (2.7)	1226 (47.4)	

In 61 (16.8%) of 364 households who participated in the survey there was at least one household member with PWE, in 19 (5.2%) of 364 households there were two PWE and in one household there were three PWE.

3.3. Characteristics of persons with epilepsy

Of the 86 PWE, 43 (50.0%) were female (Table3). The median age of PWE was 25.0 (20.0-29.0) years. Of the 81 PWE for which the age of onset of seizures was known, the first seizures most frequently appeared between the ages 5–15 years (Figure 4).
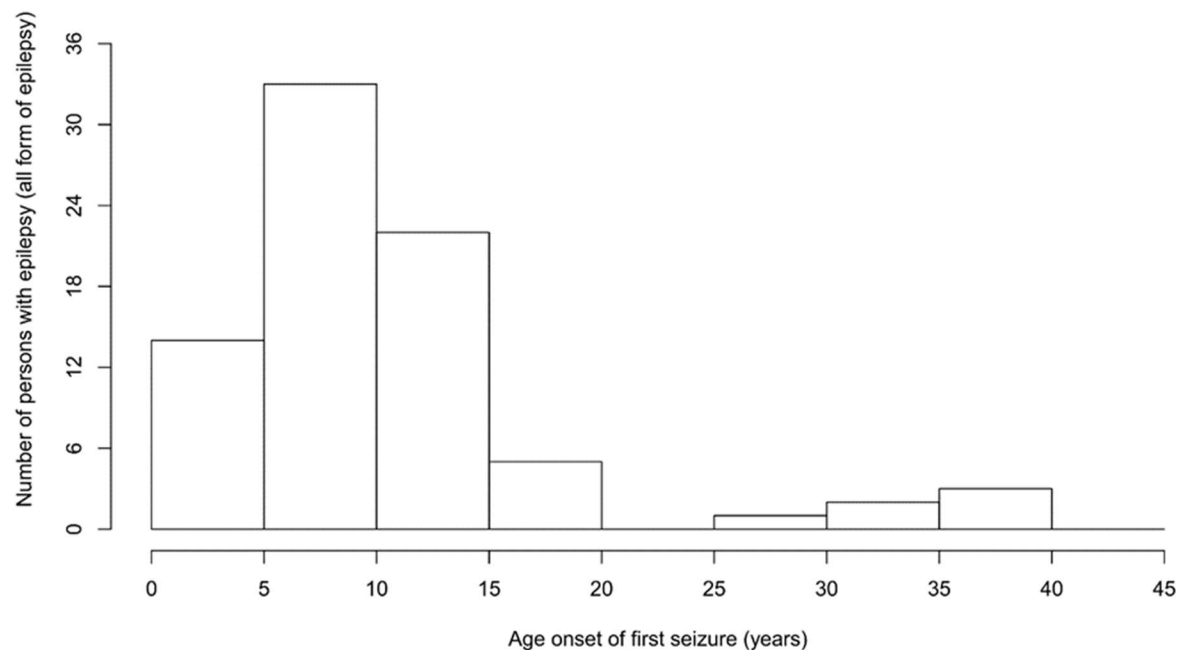
Figure 4: Age of onset of seizures

The median age of onset was 10.0 (IQR 8.0-15.0) years. The most frequent seizure type in PWE was

generalised convulsive seizures in 61 (72.6%). Twenty three (26.7%) of the 86 PWE met the criteria of

probable nodding syndrome including seven (8.1%) who only experienced nodding seizures and 16

(18.6%) who experienced both nodding and convulsive seizures. In three individuals (3.5%) there was a

history of blurred vision or blindness in at least one eye. In 67 (79.8%) PWE, there was no specific trigger

that caused the seizures but in 8 (9.5%) seizures were precipitated by the sight of food and in 9 (10.7%)

by cold weather. According to family members 6 (7.1%) PWE were severely cognitively impaired.

Papular-nodular pruritic lesions were present in 12 (14.3%) PWE, and burn scars in 14 (16.7); itching was

reported in 20 (23.8%). Overall, 65 (75.6%) of 86 PWE met the OAE criteria. Two (2.5%) PWE presented

with Nakalanga features. Eighty two (95.4%) PWE had been treated with anti-seizure medication and

were currently taking the medication, mainly carbamazepine 55 (67.1%). Fifty eight (67.4%) PWE

reported having ever taken ivermectin but only 39.3% had taken ivermectin in 2021. In 45 PWE there

was a history of epilepsy in the family and in 37 of hem (97.5%) this was a sibling (Table 2).

Table 2. Characteristics of the 86 persons with epilepsy (PWE) examined by clinicians

Participants characteristics	
Female sex, n (%)	43 (50.0)
Age (years), median (IQR)	25.0 (20.0-29.0)
Born in the study village, n (%)	48 (57.1)
Period (years) of residing in the survey area, median (IQR)	20.0 (10.0-25.0)
Epilepsy features	
Age of onset of the first seizure in all PWE, median (IQR)*	10.0 (8.0-15.0)
Age of onset of the first nodding seizure, median (IQR)	8.0 (5.0-12.0)
Onset of the first seizure last year, n (%)	2 (2.4)
Onset of the first seizure in last 5 years, n (%)	4 (5.0)
Experienced absence(s) or sudden loss of contact with surroundings, for a short duration of time, n (%)	1 (1.2)
Experienced sudden, uncontrollable twitching or shaking of arms, legs or head, for a period of a few minutes, with amnesia, n (%)	76 (90.5)
History of head nodding, n (%)	23 (27.4)
Loss of bladder control, n (%)	58 (69.1)
Foaming at the mouth, n (%)	77 (91.7)
Biting of the tongue, n (%)	68 (80.9)
Most frequent seizure types	
Generalized convulsive seizures only, n (%)	61 (72.6)
Only nodding seizures, n (%)	7 (8.3)
Nodding and convulsive seizures, n (%)	16 (19.1)
Frequency of seizures	
Daily seizure, n (%)	1 (1.2)
Weekly seizure, n (%)	13 (15.5)
Monthly seizure, n (%)	55 (63.1)
Yearly seizure, n (%)	86 (100)
Experienced seizure in the last 12 months, n (%)	72 (83.7)
Seizures/head nodding triggers	
Spontaneous (no obvious trigger), n (%)	67 (79.8)

Sight of food, n (%)	8 (9.5)
Cold weather, n (%)	9 (10.7)
Severe diseases preceding the onset of seizures	
Measles, n (%)	1 (1.2)
Malaria, n (%)	1 (1.2)
Physical examination/symptoms [&]	
Reduced vision or blind in at least one eye, n (%)	3 (3.6)
Thoracic/spinal abnormalities, n (%)	2 (2.4)
Cervical lymph nodes, n (%)	10 (11.9)
Nakalanga manifestations, n (%)	
Itching, n (%)	20 (23.8)
Burn lesions, n (%)	14 (16.7)
Papular/nodular pruritic skin, n (%)	12 (14.3)
Neurological examination [&]	
Severe cognitive impairment, n (%)	6 (7.1)
Paresis, n (%)	3 (3.6)
Behavioural problem, n (%)	1 (1.2)
Level of autonomy assessed with a modified Rankin scale	
No significant disability despite symptoms (able to carry out all usual duties and activities)	67 (79.8)
Slight disability (unable to carry out all previous activities, but able to look after own affairs without assistance)	8 (9.5)
Moderate disability (requiring some help, but able to walk without assistance)	5 (5.9)
Moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs without assistance)	4 (4.8)
Epilepsy classification	
Epilepsy without head nodding, n (%)	63 (73.2)
Head nodding only, n (%)	7 (8.1)
Head nodding with other seizure types, n (%)	16 (18.6)
Meeting OAE criteria, n (%)*	65 (81.3)
Family members with epilepsy	
Family history of seizures, n (%)	45 (53.6)
Siblings (brother/sister), n (%)	37 (82.2)
Father/Mother, n (%)	7 (15.7)
Grandparent, n (%)	1 (2.2)
History of anti-seizure medication	
Never used an anti-seizure medication, n (%)	4 (4.6)
Currently taking an anti-seizure medication, n (%)	82 (95.4)
Type of anti-seizure medication [T]	
Phenobarbital, n (%)	24 (29.4)
Phenytoin, n (%)	1 (1.2)
Carbamazepine, n (%)	55 (67.1)
Sodium valproate, n (%)	1 (1.2)

Ivermectin intake	
Ever received ivermectin, n (%)[#]	58/74 (78.4)
Ivermectin intake in 2021, n (%)[$]	33/79 (41.7)
Ivermectin intake in 2021 not known, n (%)	7 (8.9)

N: count; IQR: Interquartile range; ^ : 2 missing ; * : the age onset of the first seizure of 6 PWE was not known ; &: 34 missing; T: 4 missing; # : 12 did not remember whether they had ever taken ivermectin; $: 7 PWE did not know their ivermectin intake status.

P: The denominator=Family with seizure history (n=45);

N: Missing information on: age of onset of the first seizure, severe diseases preceding the onset of seizure, or psychomotor problem.

Epilepsy was most frequent in the age group 21–25 years 25/247 (10.1%) (Figure 5).
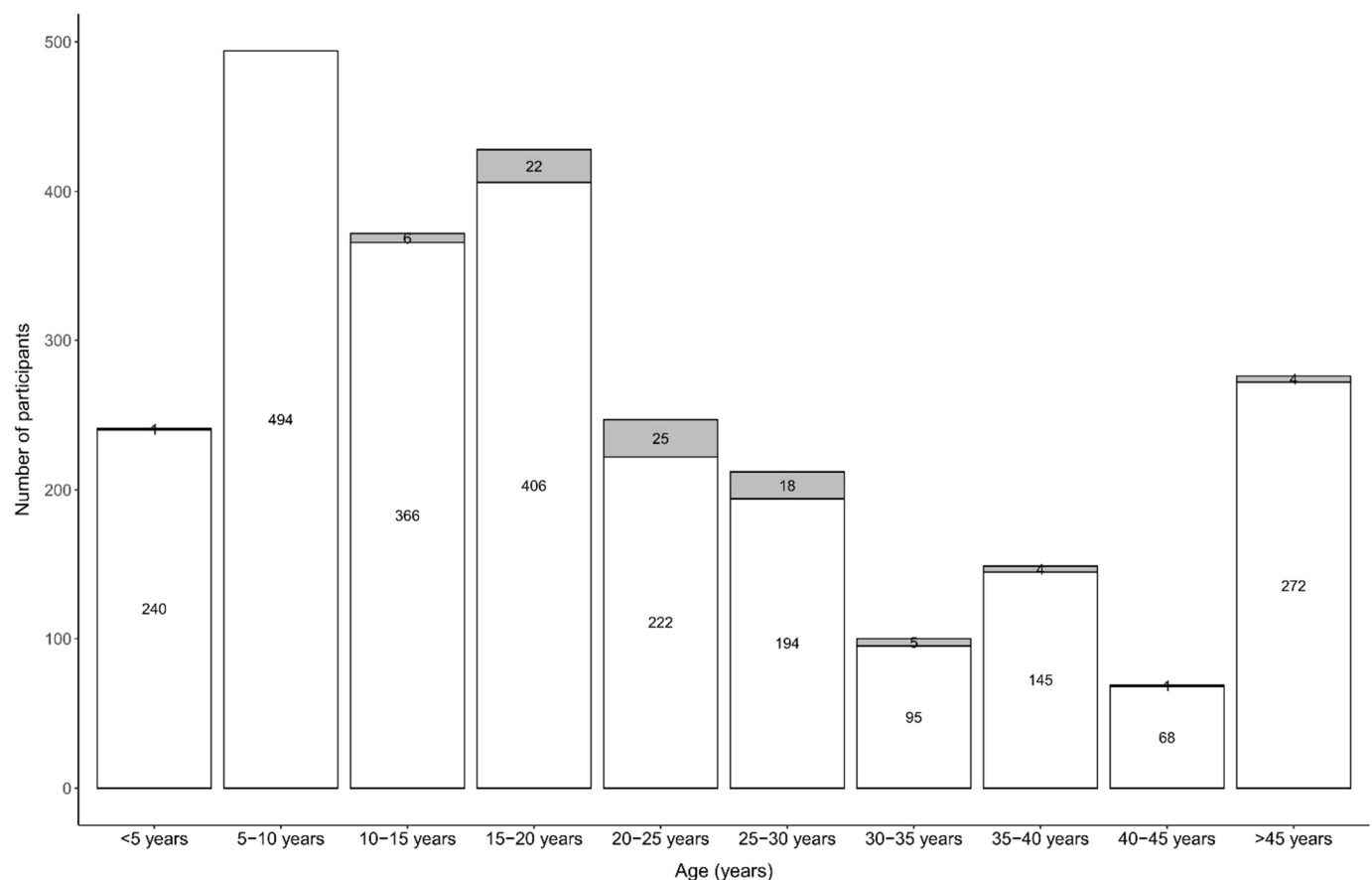
Figure 5. House-to-house survey in Mundri West and East with number of confirmed epilepsy cases per age group.

Twenty three PWE were diagnosed with probable nodding syndrome. The overall prevalence of probable nodding syndrome was therefore 0.9%. Persons with nodding syndrome were younger, presented their first sizures at a younger age and their seizures were more ofthen triggered by sight of food or cold compared with persons with other forms of epilepsy (Table 3).

Table 3. Characteristics of persons with epilepsy with and without nodding syndrome

	Epilepsy without nodding syndrome (N=63)	Nodding syndrome (N=23)	P-value
Female, n (%)	31 (50.8)	13 (56.5)	0.825
Age (years), median (IQR)	25.0 (20.0-32.0)	24.0 (20.0-28.0)	0.012
Age of onset of first seizures (years)	10.0 (8.0-15.0)	8.0 (5.0-12.0)	0.007
Triggers of seizures			
Sight of food, n (%)	0 (0.0)	8 (34.8)	NA
Cold weather, n (%)	1 (1.6)	7 (30.4)	<0.001
Spontaneous (no obvious trigger), n (%)	60 (95.2)	8 (34.8)	<0.001
Itching, n (%)	13 (20.6)	7 (30.4)	0.556
Burn lesion (s), n (%)	5 (7.9)	5 (21.7)	0.183
Papular/nodular pruritic skin, n (%)	8 (12.7)	4 (17.3)	0.881
Moderate and severe disabilities, n (%)	5 (7.9)	4 (17.4)	0.384

NA = not applicable

3.4. Incidence of epilepsy

Two PWE developed their first seizures in the 12 months preceding the survey (annual incidence of 77.3/100.000, 95% CI: 9.4-278.9/100,000) and four PWE developed their first seizures in the previous 5 years, corresponding to an incidence of 154.6/100.000, 95% CI: 42.1-395.3/100.000 per 5 years.

3.5. Onchocerciasis related morbidity in the family

In 21 (5.8%) households there was at least one person with a history of nodding syndrome or nodding syndrome plus other seizure types. In 244 (67.0%) households, there was at least one person with skin itching, and in 61 (17.0%) households there was at least one person with blindness or blurred vision with 8 (2.2%) families with more the one person with blindness or blurred vision. The median age of persons with skin itching was 18.0, (IQR: 10.0-30.0) and blindness or blurred vision was 54.5, (IQR:40.0-66.0) years.

3.6. Mortality of persons with suspected epilepsy

Overall, 41 persons died during the previous 24 months; of these 13 (36.6%) were persons with epilepsy according to the family. This corresponds to 251.2/100,000 (95% CI: 133.9-428.7/100,000) deaths of persons suspected to have epilepsy per year. The median age of death of people with suspected epilepsy was 22.0 (IQR 15.0–35.0) years, range 20–35 years.

3.7. Risk factors for epilepsy

The variance of the random effect attributed to the village was zero. Therefore, we only considered a family as the random effect in the GLMM model. This model revealed that the probability of living with epilepsy increased with increasing age up to 29.9 years but decreased above this age (Table 4 & Figure 7). Moreover, the probability of living with epilepsy was high among people living in a family with a household member with blindness or blurred vision in at least one eye but the association was insignificant (p-value=0.067).

Table 4. Generalized linear mixed model to assess characteristics associatiated with epilepsy in Mundri West and East.

Characteristics	aOR	95% CI		P-value
Age (years)	1.450	1.286	1.636	<.0001
Age*Age	0.994	0.992	0.996	<.0001
Male vs female sex	1.143	0.712	1.836	0.580

Family income from activities related to the river vs from other activities[&]	1.178	0.520	2.670	0.694
Village <2km from the Yei River vs >2km from the Yei River	1.692	0.918	3.117	0.092
Ivermectin taken during last round vs no ivermectin taken	0.638	0.376	1.083	0.096
Skin itching vs no itching in the family	1.014	0.543	1.893	0.965
Blindness/blurred vision vs no blindness in the family	1.940	0.956	3.940	0.067
$Var[b0](se)$	1.685 (0.767)			

*aOR: adjusted odds ratio; CI: confidence limits, age*age : Quandratic quadratic effect of age. &: Activities related to the river include fishing and agriculture closer to the river and other activities include employment, trading and military. $Var[b0]$: Variance of random intercept. se: Standard error.*
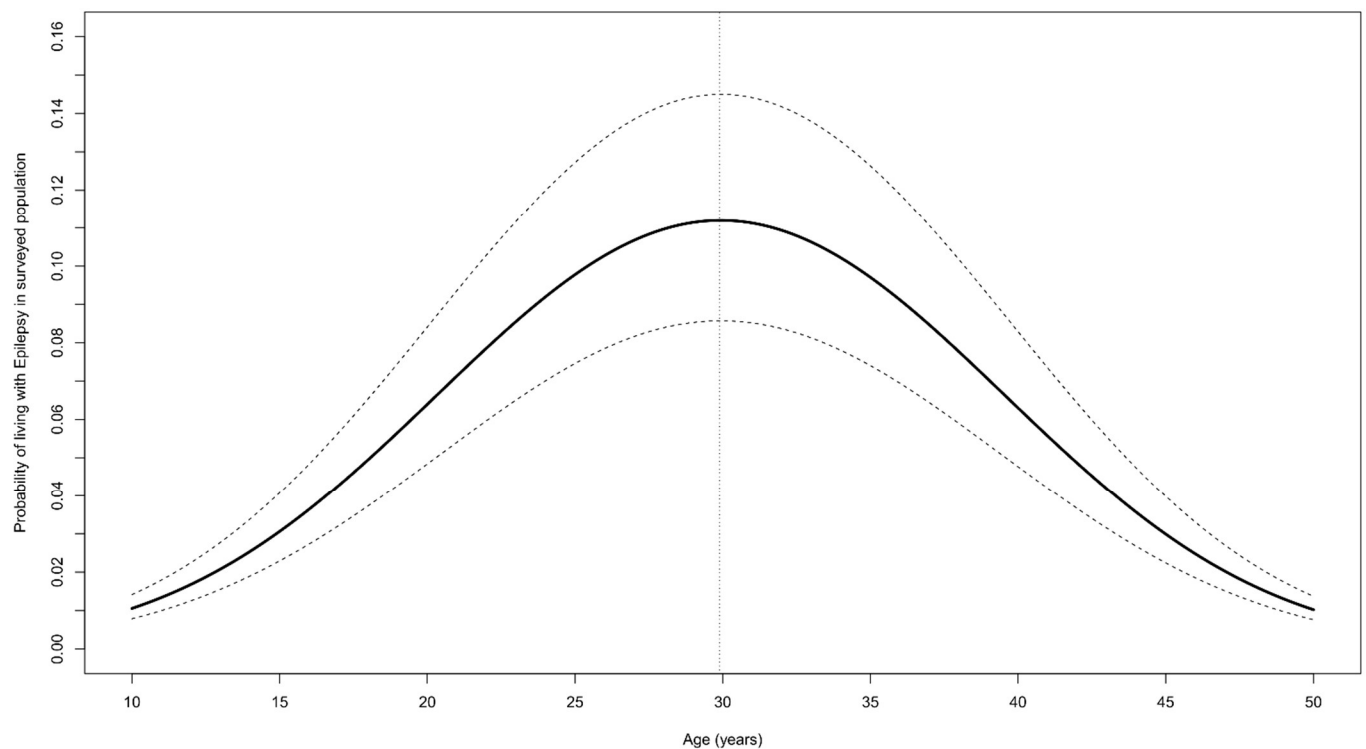

Figure 7. Probability of living with epilepsy according to age (years) estimated from GLMM by keeping other variables as fixed (male person living in a family located close to the Yei River, with income from farming, and with itching and blindness present in the family).

Including all villages in the analysis, distance to the Yei River was not found to be a risk factor for epilepsy. However, excludeding Lui town, the site where the epilepsy treatment centre is located, from the analysis, a higher prevalence of epilepsy was observed in villages very close to the Yei River (Hai Gabat, Hai

Ngulawa, Hai Lenderwa) compared to those located further away from the Yei River (Hai Malakia, Hai

Facki, Hai Mirikalanga) (p-value=0.041) (Table 5).

Table 5. Generalized linear mixed model to assess characteristics associatiated with epilepsy in Mundri

West and East (excluding Lui town).

Variables	aOR	95% CI		P-value
Age (years)	1.635	1.353	1.975	<.0001
Age*Age	0.991	0.988	0.995	<.0001
Male vs female sex	0.990	0.546	1.797	0.975
Family income from activities related to the river vs from other activities&	1.184	0.459	3.054	0.727
Village <2km from the Yei River vs >2km from the Yei River	2.241	1.034	4.861	0.041
$Var[b0](se)$	2.419 (1.338)			

*aOR: adjusted odds ratio; CI: confidence limits, age*age : Quandratic quadratic effect of age. &: Activities related to the river include fishing and agriculture closer to the river and other activities include employment, trading and military. $Var[b0]$: Variance of random intercept. se: Standard error.*

A proportion of 41.8% of the PWE had taken ivermectin in 2021, and this proportion was comparable to

the overall study population (46.9) (Table 6).

Table 6. Ivermectin use in the total study population and among persons with epilepsy (PWE) per age group

Age group (years)	Ivermectin use in the total study population, n (%)#	Ivermectin use among PWE, n (%)*	P-value&
<5 years	0/240 (0.0)	0 (0.0)	NA
5-10 years	235/492 (48.0)	0 (0.0)	NA
10-15 years	183/369 (49.6)	1/4 (25.0)	0.691
15-20 years	235/426 (55.2)	10/23 (43.5)	0.998
20-25 years	138/245 (56.3)	9/24 (37.5)	0.534
25-30 years	115/211 (54.5)	8/20 (40.0)	0.295
30-35 years	56/99 (56.6)	3/6 (50.0)	0.775
35-40 years	72/149 (48.3)	1/2 (50.0)	0.999
40-45 years	29/69 (42.0)	0/2 (0.0)	NA
>45 years	142/276 (51.4)	1/4 (25.0)	0.584
Overall	1212/2583 (46.9)	33/79 (41.8)	0.706

*Denominator=number of PWE in each age group who took ivermectin (missing=7); # : denominator=number of survey participants in each age group (missing=10); &: Exact-chi-square test for the differences in ivermectin use among PWE and the total population. NA = not aplicable

In total, 224 children (74 from Hai Gabat village in Amadi Payam and 150 from Hai Milikanga, Hai Ngolawa and Hai Matara village in Mundri Centre Payam) aged between 3−9 years were tested for IgG antibodies to *O. volvulus* using the Ov16 rapid diagnostic test to evaluate the degree of onchocerciasis transmission. Of those children eligible for ivermectin (5 years and above), only 22/62 (35.5%) in Amadi and 21/109 (19.3%) in Mundri Centre taken ivermectin during the last CDTI round (Table 7).

Table 7. Ov16 seroprevalence among children in Amadi and Mundri Centre

Study site	Ov16 IgG4 seroprevalence							Ivermectin coverage*
	3 years	4 years	5 years	6 years	7 years	8 years	9 years	
Amadi	3/8 (37.5%)	0/4 (0.0%)	3/18 (16.7%)	2/7 (28.5%)	1/11 (9.1%)	4/14 (28.6%)	6/12 (50.0%)	22/62 (35.5%)
Mundri Centre	1/24 (4.2%)	0/17 (0.0%)	1/26 (3.8%)	1/18 (5.5%)	0/26 (0.0%)	1/23 (4.3%)	0/16 (0.0%)	21/109 (19.3%)

* : The denominator = children eligible for ivermectin (5 years and above).

4. Discussion

Our study confirms the high prevalence of epilepsy (3.3%) in villages in Mundri East and West Counties in Western Equatoria State, South Sudan. This prevalence is slightly lower than the 4.4% epilepsy prevalence in Maridi [6] and the 5.1% prevalence in Mvolo. A very high percentage (97.8%) of persons with suspected epilepsy, based on answers to the five epilepsy screening questions [11], were confirmed to have epilepsy. This has also been observed in other areas with high epilepsy prevalence, where the affected population is generally well informed about epilepsy [6,17], in contrast to areas of low epilepsy prevalence [18]. In Maridi, the diagnosis of epilepsy was confirmed in 92.1% of persons with suspected epilepsy. The higher percentage of confirmed cases in Mundri is explained by the fact that in Mundri we did not include the screening question "sudden onset of brief body sensations, hallucinations or illusions be they visual, auditory or olfactory". This question was previously noted as having the lowest specificity

for the diagnosis of epilepsy [14]. In only one of the suspected epilepsy cases a diagnosis of febrile seizures was made. The raison why not more children with febrile seizures were considered as suspected perons with epilepsy is because the local population of Mundri generally considers febrile seizures as malaria and not as potentially epilepsy. This however may have led to an underestimation of th number of epilepsy cases in the < 5 years old.

Of the PWE, 75.6% met the OAE criteria and in 26.7% of PWE there was a history of nodding seizures. These percentages were lower than in Maridi, where 91.8% of PWE met the OAE criteria and 45.5 % were classified as having probable nodding syndrome [7]. The overall prevalence of probable nodding syndrome 0.9% is lower than the previously reported 2.3% prevalence in Lui town and 6.7% in Amadi [5]. It may be that there has been a decrease in the incidence of nodding syndrome because of the re-introduction of CDTI sinds 2017. However, given the low therapeutic coverage of ivermectin, most likely previously certain persons with other forms of epilepsy have been considered as persons with nodding syndrome.

The annual incidence of epilepsy in Mundri was 77.3/100.000, 95% CI: 21.2-281.3/100,000, which is lower than the 373.9/100.000 annual incidence in Maridi [6]. A very high proportions of recent deaths (36.6%) reported by families occurred in persons considered to have epilepsy. The 231.8/100,000 annual mortality of persons with suspected epilepsy in Mundri was similar with the 294.6/100,000 reported mortality in Maridi [6]. A large proportion of our study population reported itching (40.2%) and in 2.7% blindness or blurred vision of at least one eye was reported. These findings suggest a very high level of past and ongoing *O. volvulus* transmission explained by the low coverage of CDTI (46.9%). This percentage is much lower than the coverage percentages reported by the community directed distributors (84.7% in Mundri West and 80.2% Mundri East), and the coverage percentages calculated using the National Bureau of Statistics projected population as denominators (83.4% in Mundri West and 70.2% in Mundri East) (MY Logora, peronnal communication).

More PWE were observed in families with a member who was blind or had blurred vision. This suggests that both epilepsy and blindness may have a common aetiology. In contrast to the findings from Maridi, belonging to a farmer family, was not found to be a risk factor for epilepsy [6]. Including all study villages in the analysis, in contrast to Maridi [6] and Mvolo [8], living in a village close to a river was not found to be a risk factor for developing epilepsy. However, excluding Lui town from the analysis, living close to the river was also found to be a risk for developing epilepsy. The high prevalence of epilepsy in Lui town, despite it's location more than 7km from the Yei River, most likely is explained by the fact that the only epilepsy treatment centre in the region is located in Lui hospital. This may have attracted families with members affected by epilepsy to live in Lui town. Indeed, during the survey in Lui town several PWE reported that they originally were not from Lui town and that they presented their first seizures in another village (S Raimon, personal communication).

The OV16 seroprevalence in children below the age of 10 years was higher in Amadi than in Mundri Centre, suggesting higher ongoing *O. volvulus* transmission in areas closer to the river. The OV16 seropositivity of the 3 year-old children may be related to the presence of *O. volvulus* antibodies acquired from the mother. However, the presence of such antibodies in 5-9-years-old children is indicative of ongoing *O. volvulus* transmission in the area.

The strength of our study is that this was a population-based epilepsy survey in which all households were visited by the research team and information was obtained on each household member concerning potential onchocrciasis-related symptoms and signs, and ivermectin use. However, there were also several limitations of the study. First, our study villages are not representative of all villages in the Greater Mundri area because we selected those located close to the Yei River. Moreover, the diagnoses of epilepsy were not confirmed by a neurologist and no EEGs were performed. Neither laboratory studies nor imaging investigations were performed to identify the causes of epilepsy. However, as there are no pigs in the Mundri area, neurocysticercosis cannot explain the high epilepsy

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prevalence. Clinicians only examined persons with suspected epilepsy referred by the research assistants and did not visit households where no PWE were reported. However, given the very high epilepsy prevalence we do not expect that additional PWE were missed. A large percentage (20.3%) of the study population was not present during the home visits and information about them was only obtained from family members. However, as most persons away from their homes were working in the fields, they were likely to be healthier than those who were present at home. The diagnosis of cognitive impairment, behavioural problems and blindness were only assessed by interview. Important to note is that none of the children with epilepsy were below the age of five years and no deaths of children with epilepsy were reported in this age group. This is in contrast with population-based epilepsy surveys in non-onchocerciasis endemic regions in Africa where epilepsy due to perinatal anoxia and cerebral palsy is an important cause of epilepsy in this age group [22,23]. It may be that in some children below the age of five, epileptic seizures were considered as febrile seizures. Given the cross-sectional study design, epilepsy-related mortality could only be estimated retrospectively by interview and the information obtained could have been influenced by recall bias. We only obtained information from families on whether a family member with epilepsy died in the previous year but we do not know whether the diagnosis of epilepsy was confirmed by a medical doctor and no verbal autopsies were done.

5. Conclusion

This study confirms the high prevalence of epilepsy including nodding syndrome in onchocerciasis-endemic areas where the onchocerciasis-elimination programme is working sub-optimally. The ivermectin coverage in villages in Mundri in 2021 was very low (47.4%). Ideally bi-annual distribution of ivermectin, as was successfully implemented in northern Uganda [3], is needed to reduce the incidence of epilepsy and interrupt the development of OAE. Urgent international solidarity is needed to prevent children in Mundri from developing epilepsy and other irreversible neurological abnormalities and to provide uninterrupted anti-seizure medication to all those affected by epilepsy.

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Institutional Review Board Statement

Ethical approval was obtained from the ethics committee of the Ministry of Health of South Sudan (January 2018, MOH/ERB 3/2018) and from the ethics committee of the Antwerp University Hospital, Belgium (April 2019, B300201940004).

Informed Consent Statement

The study aims and procedures were explained to all participants in the language of their choice; and signed or thumb-printed informed consent was obtained from participants, parents or care-givers, and assent obtained from adolescents (aged 12–18 years).

Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

Conflicts of Interest:

The authors declare no conflicts of interest.

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