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Mortality among persons with epilepsy in onchocerciasis-endemic and non-endemic areas of sub-Saharan Africa: A systematic review and meta-analysis

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ABSTRACT

Purpose: To document epilepsy-related mortality in sub-Saharan Africa (SSA) and investigate possible associations with onchocerciasis endemicity.

Methods: Systematic review with meta-analysis. Searches were performed in PubMed and Google Scholar (search terms: 'epilepsy'; 'mortality/death'; 'sub-Saharan Africa'). Included studies were classified as high-risk or low-risk for onchocerciasis based on documented endemicity data. Pooled mortality rates and annual case fatality rates (CFR) were calculated, and risk factors for mortality among persons with epilepsy (PWE) were investigated using meta-regression analysis.

Results: The 28 eligible studies reported 30 epilepsy surveys, of which 9 (30.0%) were conducted in onchocerciasis high-risk sites. The pooled epilepsy mortality rate was 20.9 (95% CI: 5.9–74.4) per 100,000 person-years, and the pooled CFR was 36.2 (95% CI: 23.9–54.4) per 1,000 PWE per year, albeit with substantial between-study heterogeneity. Compared to onchocerciasis low-risk sites, high-risk sites had higher pooled mortality (342.9 versus 10.0 per 100,000 PY; $p<0.001$) and CFR (57.0 versus 26.6 per 1,000 PWE per year; $p = 0.001$). Mortality of PWE was almost five-fold that of people without epilepsy (mortality risk ratio: 4.9; 95% CI: 3.5–6.8). Studies in onchocerciasis high-risk sites and the study which recruited only PWE with nodding syndrome were associated with higher CFR ($p = 0.044$ and $p = 0.002$, respectively). The leading causes of epilepsy-related death were status epilepticus (58.5%), drowning (15.7%), and sudden unexpected death in epilepsy (10.1%).

Conclusion: Epilepsy mortality remains high in SSA. Most reported causes of death among PWE might be averted by improving seizure control. Better epilepsy prevention and care are urgently needed, particularly in onchocerciasis-endemic settings.

1. Introduction

Epilepsy is among the most prevalent neurological diseases globally, with a greater burden of disease in low- and middle-income countries (LMICs) compared to high-income countries (HICs) [1]. Mortality among persons with epilepsy (PWE) is also significantly higher than in the general population, with standardised mortality ratios (SMRs) reaching 3.0 in HICs and 19.8 in LMICs [1]. Although sub-Saharan Africa (SSA) is particularly affected by epilepsy, data on epilepsy mortality remain scarce in most SSA countries. Indeed, a previous systematic review on epilepsy in SSA [2] identified only six small cohort studies reporting mortality data, which is insufficient to represent the entire sub-region. A few well-designed studies have estimated a SMR for epilepsy of 6.5 (95% CI: 5.0–8.3) in Kenya [3] and 2.6 (95% CI: 1.7–3.5) in South Africa [4]. However, these studies recruited only persons with active convulsive epilepsy, whose mortality may differ from PWE with non-convulsive epilepsies [5].

This higher epilepsy mortality in SSA results mainly from weak healthcare systems and a high prevalence of infections that may induce epilepsy [2]. Trained healthcare workers able to treat persons with epilepsy are scarce, and those who have received adequate training are rarely present in rural areas [2]. Moreover, few trained neurologists are available to capacitate and supervise non-specialist healthcare workers. Consequently, delays in epilepsy diagnosis and treatment are common.

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Epilepsy in SSA is a very stigmatised condition and is often considered to be caused by evil spirits [6]. For this reason, PWE often consult traditional healers instead of medical facilities [7]. Furthermore, the irregular availability and elevated cost of anti-seizure medications (ASMs) still pose a challenge in several SSA communities [8].

It has been documented that onchocerciasis foci harbor a specific form of epilepsy, onchocerciasis-associated epilepsy (OAE), characterised by severe seizures, cognitive impairment, and reduced life expectancy [9]. Given that OAE usually occurs in remote onchocerciasis-endemic villages with limited research capacity, its epidemiology, clinical features, and outcomes (including mortality) remain sparsely reported. To fill this knowledge gap, we conducted a systematic review of the published literature on mortality among PWE in onchocerciasis-endemic and non-endemic sites in SSA. Pooling together the available evidence on epilepsy mortality in Africa could lead to the identification of risk factors for fatal outcomes in epilepsy, which can then be addressed.

2. Methods

We followed the PRISMA 2020 guidelines [10].

2.1. Search strategy

We searched PubMed and Google Scholar for published literature (including PhD theses) in French and English indexed until the 31st of January 2023. Key search terms included 'epilepsy', 'mortality' and 'onchocerciasis' in the titles and abstracts (see Supplementary Appendix 1 for full search strings). We also conducted manual searches and reviewed the reference lists of relevant review articles on this topic to identify additional records that were eligible for inclusion.

2.2. Screening and data extraction

Inclusion and exclusion criteria: We included community-based and hospital-based studies conducted in SSA, which documented deaths among populations of PWE. Only original research reporting the number of deaths among PWE and with clear denominators of the study population(s) were eligible. Reviews, opinion papers, and commentaries were excluded. We also excluded studies that focused only on PWE with convulsive status epilepticus, as the latter is already a complication of epilepsy and not representative of PWE populations. Two authors (JNSF and RC) independently performed the screening of articles for inclusion in this review.

Assessment of reports and extraction of data: The risk of bias in selected studies was assessed by two authors (JNSF and GVC) using the "study participation", "study attrition", and "outcome measurement" domains of the Quality in Prognosis Studies (QUIPS) tool [11]. Relevant crude data were extracted from the eligible epilepsy studies into Microsoft Excel spreadsheets. The main outcome variables were the crude number of deaths among PWE and the total number of PWE observed. Additional variables of interest extracted included: year and country of study, study setting (hospital versus community), types of seizures experienced by PWE in the study, number of deaths recorded in the general/control population (if available), causes of death among PWE, and any major epilepsy-related intervention that was implemented during the study.

Onchocerciasis endemicity was estimated in three ways to group included study sites into low- or high-risk. Firstly, we classified study sites countries as low- or high-risk for onchocerciasis based on the prevalence of persons with one or more nodules (palpable onchocercomata) below or above 20% respectively; this information was obtained from the published map generated by a geostatistical analysis of Rapid Epidemiological Mapping of Onchocerciasis (REMO) data [12]. All studies conducted in countries marked as non-endemic on REMO maps, such as Kenya and South Africa, were automatically included in the onchocerciasis low-risk group. In addition, the REMO approach considered that highly urbanised settings like big towns are not conducive for onchocerciasis transmission [12], and we therefore classified such sites as low-risk zones. Secondly, we resorted to freely available data on community-directed treatment with ivermectin (CDTi) from the website of the Expanded Special Programme for Neglected Tropical Diseases (ESPEN) [13], where we could retrieve information about onchocerciasis endemicity for specific sites within the countries that harboured onchocerciasis foci. Lastly, onchocerciasis endemicity data was also obtained from published literature (either the same epilepsy study included in this systematic review or a different study conducted in the site of interest).

2.3. Definition of terms

Annual case fatality rate (CFR) refers to the proportion of PWE who died from any cause within a period of one year and is expressed per 1000 PWE per year. This was calculated by dividing the number of reported PWE deaths by the total number of PWE in a given study (controls excluded). For community-based studies entailing many years of follow-up of a cohort of PWE, we adjusted the total number of PWE deaths by dividing it by the number of years of observation and rounded it to the nearest integer before calculating the annual CFR. For retrospective hospital-based studies which reported the proportion of PWE with fatal outcomes based on hospital registries, we did not divide by the number of years since the denominator (number of PWE consulted or admitted in the hospital) also increased during the observation period.

Mortality rate refers to the number of PWE who died from any cause within a specified observation period, divided by the total person-years observed in the entire population (consisting of both PWE and people without epilepsy). It is expressed per 100,000 person-years (PY).

The mortality risk ratio expresses how manifold PWE are more likely to die compared to their peers without epilepsy. It is obtained by dividing the proportion of deaths in a PWE population by the proportion of deaths in the control population.

Epilepsy-related deaths refers to deaths among PWE for whom the circumstances of demise were clearly documented as one of the following: status epilepticus, after a seizure, sudden unexpected death in epilepsy (SUDEP), drowning, burns, or traumatic injury [14].

Nodding syndrome is an epileptic disorder reported only in onchocerciasis-endemic areas and characterised by repetitive head-nodding fits with altered state of consciousness, stunting, and cognitive impairment. It is considered a typical phenotype of OAE [15].

2.4. Data analysis

Extracted data on epilepsy mortality were transferred to the software R version 4.2.2 for analysis. Mortality rates and CFRs were considered as proportions and pooled using the 'metaprop' function in the R-package 'meta', which implements the inverse variance method with logit transformation and uses the restricted maximum likelihood estimator to calculate the heterogeneity during pooling. We used random-effects models to calculate pooled estimates of epilepsy mortality rates and case fatality rates; the Knapp-Hartung adjustment was used to calculate 95% confidence intervals [16]. Where data were available, we compared the proportions of deaths among PWE and the general population and generated pooled mortality risk ratios using the 'metabin' function of the same R-package. In some study reports which did not clearly state the number of person-years, it was estimated by multiplying the surveyed population size (N) by the number of years of observation reported (y). This approach assumed a stable population throughout the observation period (restricted to studies with a follow-up duration $\leq$1 year to minimize bias). Sensitivity analyses were conducted by excluding outliers to ascertain the pooled estimates.

Subgroup analyses were performed to compare onchocerciasis low-risk versus high-risk areas, and forest plots generated. For pooled estimates, clustering by study country was used to account for possible

intra-country correlations.

We also conducted a meta-regression analysis to investigate the contribution of purposefully selected study covariates (onchocerciasis endemicity, type of seizure disorder in the PWE population, and free provision of ASMs) on the annual CFR among PWE irrespective of the country; therefore, clustering by country was not implemented in the meta-regression model. All p-values were two-sided and considered statistically significant if <0.05.

3. Results

Our database search identified 390 records, plus another six records [17–22] retrieved via reference lists and manual search. Thirty-seven full-text articles from the database search were sought, and 15 were excluded for the following reasons: Full text unavailable for four reports [23–26]; no epilepsy mortality data for three reports [27–29]; same data as another included study for three ([30] same as [31]; [32] same as [33]; and [34] same as [3]); two studies including only cases of convulsive status epilepticus (a complication of epilepsy) [35,36]; and three studies with aggregated data which could not be exploited [37–39]. Data were finally extracted from 28 eligible full-text articles reporting data from 30 surveys (Fig. 1); these data provided mortality information from a total of 8145 PWE and 827,046 controls. The included studies had been conducted in 16 SSA countries, and 9/30 (30.0%) study sites were classified as 'high-risk' for onchocerciasis. Table 1 summarises the findings from the individual studies. One-third (10/30) of the surveys reported the free provision of ASM as epilepsy intervention during the study. Most studies had a low risk of bias (see Supplementary Appendix 2).

3.1. Pooled epilepsy mortality in sub-Saharan Africa

Only seven studies provided exploitable epilepsy mortality data with community person-years as the denominator (total number of person-years: 1572,428). Overall, the pooled epilepsy mortality rate was 20.9 (95% CI: 5.9–74.4) per 100,000 person-years. The mortality rate was significantly higher in the only onchocerciasis high-risk site included in this sub-analysis (South Sudan, mortality: 342.9 per 100,000 PY) compared to the other sites (pooled estimate of mortality: 10.0 per 100,000 PY; $p<0.001$) (Fig. 2). The median epilepsy mortality was 11.2 per 100,000 PY.

Sensitivity analyses were conducted by excluding the mortality data from the South Sudanese study [18], which was considered an outlier. In that scenario, only the onchocerciasis low-risk sites were included, giving a pooled epilepsy mortality rate of 10.0 (95% CI: 8.0–12.6) per 100,000 person-years (Fig. 2).

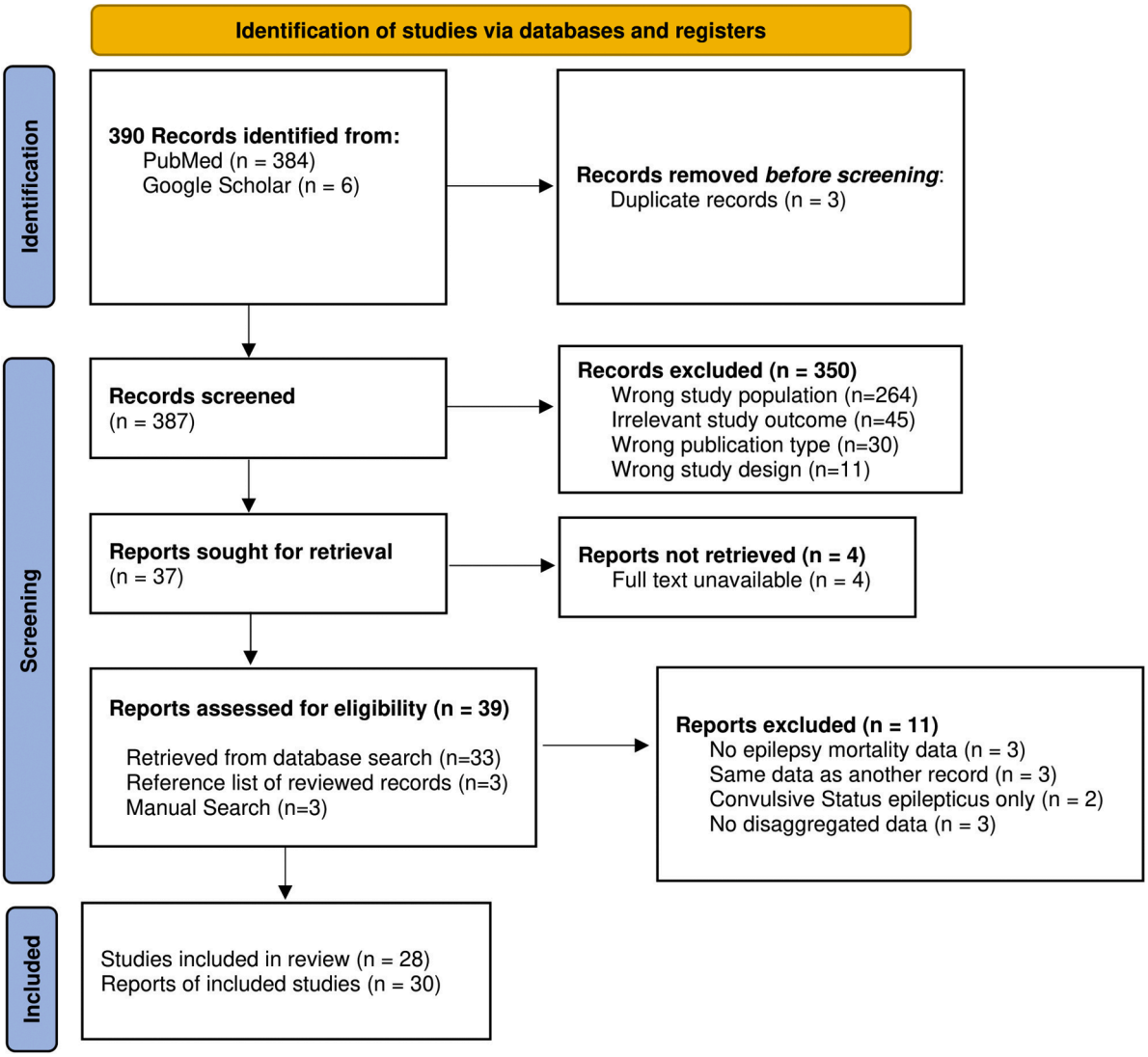

Fig. 1. PRISMA flowchart for the selection of eligible reports.

Table 1
Summarised data of included studies.

First author of included study	Country and publication year	Study setting	Intervention	Epilepsy CFR[a]	Epilepsy mortality[b]	Oncho risk	Number of PWE (seizure disorder)
Angues [40]	Uganda 2018	Community	ASM + Nutrition	208.6	NA	High [12]	326 (NS only)
Carpio [41]	Mali 2005	Community	ASM + Sensitization	32.3	NA	Low [13]	31 (ACE only)
Colebunders [18]	South Sudan 2018	Community	None	76.8	342.9	High [18]	794 (All seizures)
Coleman [21]	Gambia 2002	Community	ASM	95.2	NA	Low [42]	21 (All seizures)
Guinhouya [33]	Togo 2010	Community	ASM	9.8	NA	Low [43]	816 (All seizures)
Houinato [44]	Benin 2013	Community	ASM	18.8	NA	Low [13]	160 (All seizures)
Jada [19]	South Sudan 2022	Community	ASM	70.7	NA	High [19]	99 (All seizures)
Jilek-Aall [45]	Tanzania 1992	Community	ASM	24.4	NA	High [12]	164 (All seizures)
Kaiser [46]	Uganda 2007	Community	ASM	49.2	NA	High [46]	61 (All seizures)
Kamgno [47]	Cameroon 2003	Community	None	31.3	NA	High [48]	128 (All seizures)
Kariuki [49]	Kenya 2015	Hospital	Hospital care	27.2	NA	Low [12]	992 (All seizures)
Kariuki [50]	Kenya 2021	Community	None	7.1	19.6	Low [12]	141 (All seizures)
Kompoliti [51]	Cameroon 2017	Hospital	Hospital care	44.8	NA	Low [12]	223 (All seizures)
Levira [31]	Kenya 2020a	Community	None	17.9	NA	Low [12]	670 (ACE only)
Levira [31]	South Africa 2020	Community	None	20.6	NA	Low [12]	243 (ACE only)
Levira [31]	Tanzania 2020	Community	None	19.3	NA	High [12]	362 (ACE only)
Levira [52]	Tanzania 2019	Community	None	NA	7.4	Low [12]	48* (All seizures)
Mandro [17]	DRC 2020	Community	ASM	60.9	NA	High [17]	197 (All seizures)
Mosser [53]	Tanzania 2007	Community	None	61.5	NA	Low [12]	65 (All seizures)
Munthali [54]	Malawi 2018	Community	None	NA	9.4	Low [12]	2* (All seizures)
Ngugi [3]	Kenya 2014	Community	ASM	26.5	11.2	Low [12]	754 (ACE only)
Nkwi [22]	Cameroon 1989	Community	None	28.6	NA	High [55]	35 (All seizures)
Otubogun [56]	Nigeria 2020	Hospital	Hospital care	43.5	NA	Low [12]	23 (All seizures)
Sarfo [57]	Ghana 2016	Hospital	Hospital care	73.3	NA	Low [58]	314 (All seizures)
Sebera [59]	Rwanda 2020	Hospital	Hospital care	21.3	NA	Low [12]	235 (All seizures)
Tekle-Haimanot [20]	Ethiopia 1990	Community	None	31.7	NA	Low [13]	316 (All seizures)
von Gaudecker [60]	Kenya 2020b	Hospital	Hospital care	23.8	NA	Low [12]	42 (All seizures)
Wagner [4]	South Africa 2015	Community	None	27.0	11.0	Low [12]	296 (ACE only)
Wroe [61]	Malawi 2020	Hospital	Hospital care	12.4	NA	Low [62]	486 (All seizures)
Wroe [63]	Malawi 2022	Community	Hospital care	0	NA	Low [62]	101 (All seizures)

ACE: Active Convulsive Epilepsy; ASM: Anti-seizure medicines; DRC: Democratic Republic of Congo; NA: Not Available; NS: Nodding Syndrome; Oncho: Onchocerciasis; PWE: Person with epilepsy.
*Only the number of PWE who died was available, not the total PWE population.
[a] Annual Case Fatality Rate expressed per 1000 PWE per year.
[b] Mortality rate expressed per 100,000 person-years.

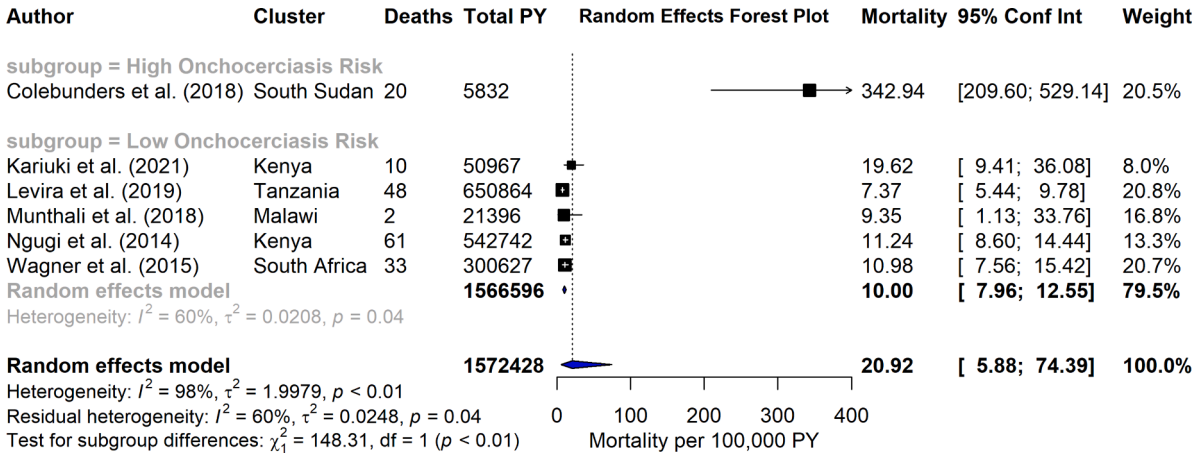

Fig. 2. Pooled Mortality Rate of Epilepsy (per 100,000 Person-years) in SSA. *PY: Person-years; Conf Int: confidence interval.*

3.2. Annual Case Fatality Rates (CFRs) of epilepsy in SSA

The pooled annual case fatality rate (CFR) of epilepsy was 36.2 (95% CI: 23.9–54.4) per 1000 PWE per year (Fig. 3). This was significantly higher in onchocerciasis high-risk sites compared to low-risk sites (57.0 versus 26.6 per 1000 PWE per year; test for subgroup differences, p = 0.014). Further analysis found that the annual CFR was not significantly different in community-based studies compared to hospital-based studies: 35.0 (95% CI: 22.2–54.8) versus 39.6 (95% CI: 21.8–70.9) per 1000 PWE per year (p = 0.672). Considering all the studies with CFR data, the median CFR value was 27.6 per 1000 PWE per year.

The single study with only NS cases as participants [40] reported a significantly higher annual CFR (208.6 per 1000 PWE per year, 95% CI: 165.8–256.8; p<0.001) compared to other studies. Therefore, a sensitivity analysis was conducted by excluding the study by Angues et al. in Uganda [40] from CFR pooling; this yielded a pooled annual epilepsy CFR of 33.0 (95% CI: 23.3–46.6) per 1000 PWE per year, with no significant difference between onchocerciasis low-risk and high-risk sites (p = 0.910); see Supplementary Appendix 3.

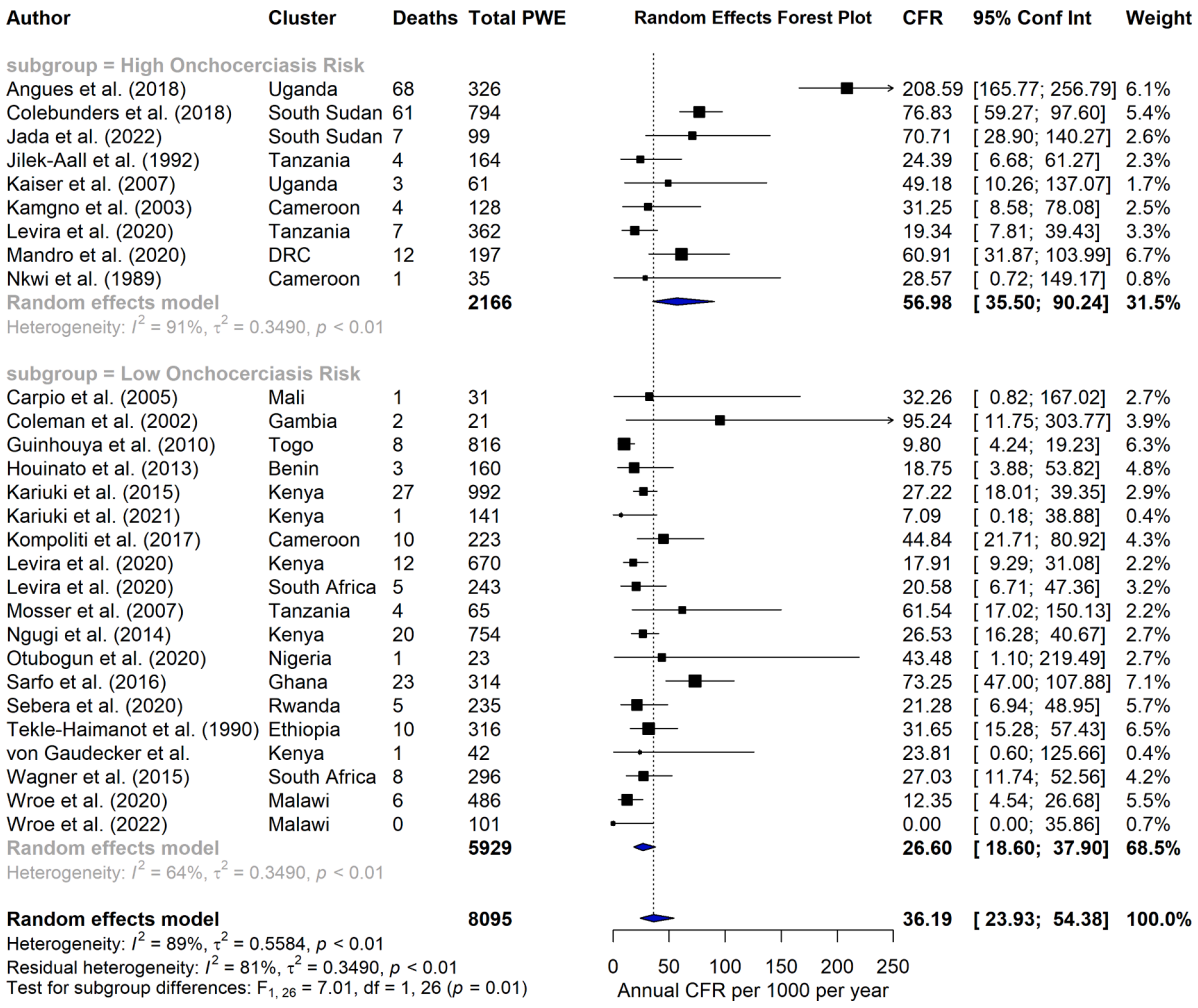

Fig. 3. Annual Pooled Case Fatality Rate of Epilepsy (per 1000 PWE per year) in the included studies. *PWE: Person with Epilepsy; CFR: Annual Case Fatality Ratio per 1000 PWE per year; Conf Int: confidence interval.*

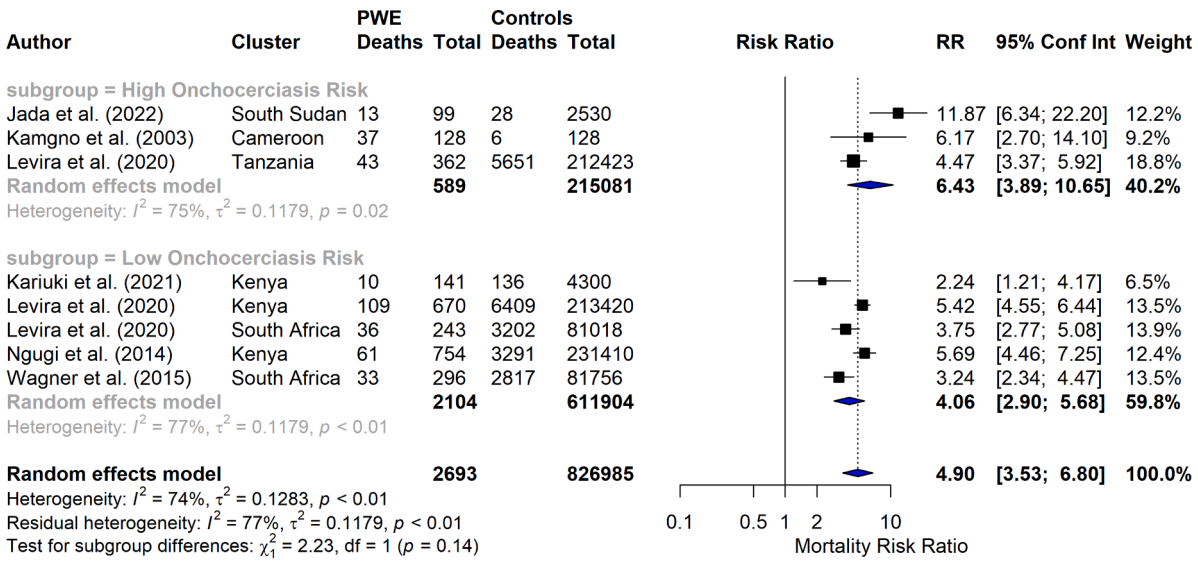

Fig. 4. The Mortality Risk Ratio of PWE versus the general population. *PWE: Person with epilepsy; RR: Risk Ratio; Conf Int: Confidence Interval.*

3.3. Mortality risk ratio (MRR) among PWE versus the general population in SSA

Mortality risks for the individual studies were all significantly higher among PWE compared to the general population (all MRR >1). The pooled MRR was 4.9 (95% CI: 3.5–6.8). The MRR values tended to be higher in onchocerciasis high-risk areas [6.4 (95% CI: 3.9–10.7)] versus low-risk areas [4.1 (95% CI: 2.9–5.7)], but the difference was not statistically significant ($p = 0.136$; Fig. 4).

3.4. Risk factors for fatal outcomes

In the multivariable meta-regression model, both onchocerciasis high-risk and NS populations were significantly associated with increased values of CFR per 1000 PWE ($p = 0.044$ and $p = 0.002$, respectively) (Table 2). The adjusted model predicted that being in an onchocerciasis high-risk site increased the CFR by 0.56 per 1000 PWE per year, and when a population of PWE who all have NS is investigated, the CFR will be higher by 1.75 per 1000 PWE per year on average compared to other PWE populations.

3.5. Causes of mortality among PWE in sub-Saharan Africa

Fourteen studies specified whether the cause of death was related to epilepsy or not, for a total of 357 PWE. Deaths among PWE were epilepsy-related in 172/357 (48.2%) of these cases. Details about the exact cause of epilepsy-related death were provided for 159 PWE (Table 3); status epilepticus accounted for 93/159 (58.5%) of these deaths, followed by drowning in 25 (15.7%), SUDEP in 16 (10.1%), burns in 11 (6.9%), seizures in 9 (5.7%), and traumatic injury in 3 (1.9%).

4. Discussion

The epilepsy mortality rate of 20.9 per 100,000 person-years found in this meta-analysis was derived from a cumulative 1.5 million person-years observed in SSA. We also report an annual CFR of 36.2 per 1000 PWE with a median CFR of 27.6, higher than the previously reported 19.8 median value for annual mortality among PWE in LMICs [64]. Our findings concur with the increasing number of deaths from epilepsy as reported by the Global Burden of Disease study, with epilepsy being the second most important neurological cause of Disability-Adjusted Life Years in SSA as of 2015 [65]. The wide epilepsy treatment gap in SSA (estimated at 69% [66]) certainly contributes to such poor prognoses for PWE in this part of the world, although other factors may be involved. Moreover, the reported deaths among PWE likely underestimate the true epilepsy mortality since epilepsy surveillance systems are often poor in remote African villages, and the prevailing stigma may cause some families not to report their epilepsy-related deaths. More community-based studies should be conducted to ascertain the estimates of the epilepsy burden in SSA by also including data from remote onchocerciasis-endemic settings.

Table 2
Meta-regression model investigating determinants of epilepsy annual case fatality rates.

Model* covariates	Univariate linear estimate (p-value)	Adjusted linear estimate (95% CI)	P-value
Onchocerciasis endemicity			
Low-risk site	Ref	Ref	Ref
High-risk site	0.84 (p=0.011)	0.56 (0.02–1.11)	**0.044**
Seizure types in study population			
All seizure types	Ref	Ref	Ref
Active convulsive seizures only	-0.38 (p=0.221)	-0.31 (-0.88–0.27)	0.279
Nodding syndrome only	2.09 (p<0.001)	1.75 (0.70–2.81)	**0.002**
Free ASM provision			
No	Ref	Ref	Ref
Yes	0.47 (p=0.183)	-0.08 (-0.63–0.48)	0.780

ASM: Anti-Seizure Medicines; Ref: Reference category; CI: Confidence Interval
*N = 28 reports included in meta-regression
*AIC = 123.9
*Residual heterogeneity = $I^2 = 54.8\%$

Pooled epilepsy mortality and pooled annual CFR were higher in the high-risk onchocerciasis study sites. Furthermore, high onchocerciasis endemicity was also associated with increased CFR in the adjusted regression model. In addition to existing evidence on increased prevalence and incidence of epilepsy in onchocerciasis-endemic areas [42,67,68], our findings suggest that onchocerciasis endemicity may also be associated with higher epilepsy mortality. While some of the included reports show a different tendency (i.e. lower CFR despite high onchocerciasis endemicity and vice versa), the pooled estimates and the meta-regression analysis both suggest that overall, onchocerciasis endemicity is associated with increased probability of death among PWE. Onchocerciasis-related excess mortality had already been reported in West Africans under 20 years of age compared to their older peers [69]. However, no explanation was found at the time to rationalize this observation. In retrospect, it is plausible that exposure to onchocerciasis at a young age could have induced OAE in children and adolescents which increased their mortality.

In the meta-regression analysis, the study which recruited only NS had higher CFR than other studies, even after adjusting for onchocerciasis endemicity status and free ASM provision. These findings demonstrate that persons with NS (a typical phenotype of OAE [9,15]) have a much higher risk of dying compared to other forms of epilepsy. The latter aligns with previous reports from Maridi, South Sudan, where NS was reported to be a more severe form of OAE with worse clinical outcomes and potentially higher mortality [70]. Indeed, epidemiological surveys in those South Sudanese study sites found that 85% of PWE satisfied the criteria for OAE, and most had low life expectancies [71].

Among the included studies, those conducted in big cities like Kumasi (Ghana) [57] and Douala (Cameroon) [51], although located in onchocerciasis-endemic areas, were classified as being at low risk for onchocerciasis in line with Noma *et al.* [12] who considered highly urbanised settings as non-transmission zones for onchocerciasis during the mapping exercise. However, we observed that the fatality rate among PWE in these sites was high (range: 44.8–73.3) compared to the pooled annual CFR of 26.6 per 1000 PWE for non-endemic sites. The study by Mosser et al. in Tanzania [53] also reported a CFR of over 60 per 1000 PWE despite being in a non-onchocerciasis zone. We surmise that the epilepsy mortality may be higher for such studies conducted in referral hospitals because they often received critical cases with poor prognoses upon admission. Furthermore, it is likely that residents from neighbouring onchocerciasis-endemic areas would travel to these hospitals for specialised medical care. Therefore, the high mortality reported by these tertiary hospital-based studies should be interpreted with caution.

In contrast with observations from rural China, where epilepsy deaths were caused mainly by injuries (indirectly related to epilepsy) [72], we found that status epilepticus and drowning were responsible for the majority of epilepsy deaths in SSA (see Table 3). Status epilepticus, drowning, and burns have previously been cited as major causes of death among PWE in Africa, in relation to poorly controlled epilepsy [73]. This suggests that epilepsy deaths may be prevented to a great extent in SSA by achieving seizure control via continuous treatment with ASM. Although epilepsy treatment did not emerge as a significant determinant of CFR in the regression analysis (possibly due to our limited sample size, $n = 28$ data points), it is well established that the availability of, and compliance to ASM significantly reduce the frequency of seizures and improves prognosis [74]. In fact, proper treatment with ASM can

Table 3
Causes of death among persons with epilepsy (crude numbers).

Authors	Status epilepticus	Seizure	Drowning	Burns	SUDEP	Traumatic injury	Epilepsy related	Not epilepsy-related or not known
Houinato et al. [44]	1	1	1	0	0	0	3	2
Kamgno et al. [47]	21	0	4	0	7	0	32	5
Mandro et al. [17]	0	2	2	0	0	0	4	8
Tekle-Haimanot et al. [20]	8	0	0	1	0	0	9	11
Ngugi et al. [3]	23	0	0	0	4	0	27	34
Carpio et al. [41]	3	2	0	0	0	0	5	8
Sebera et al. [59]	0	0	0	0	3	1	4	3
Wagner et al. [4]	11	0	0	0	0	2	13	20
Jilek-Aall et al. [45]	16	3	14	6	0	0	39	71
Mosser et al. [53]	0	1	0	2	0	0	3	0
Guinhouya et al. [33]	6	0	2	0	0	0	8	0
Kaiser et al. [46]	4	0	1	2	2	0	9	9
Coleman et al. [21]	0	0	1	0	0	0	1	2
Kariuki et al. [49]	NA	NA	NA	NA	NA	NA	15	12
Total: n (%)*	**93 (26.1%)**	**9 (2.5%)**	**25 (7.0%)**	**11 (3.1%)**	**16 (4.5%)**	**3 (0.8%)**	**172 (48.2%)**	**185 (51.8%)**

NA: Not Available.
SUDEP: Sudden Unexpected Death in Epilepsy.
* Percentages calculated using $N = 357$ as the denominator for all the causes of death.

achieve seizure freedom in up to 70% of PWE [74]. Therefore, interventions geared towards decreasing the epilepsy treatment gap and ensuring proper care for PWE in SSA should be prioritised, particularly in onchocerciasis-endemic settings [75]. Such an intervention is ongoing in Maridi (South Sudan), where an OAE epidemic was observed [76]. Currently, in Maridi, increased access to epilepsy treatment is ensured by free ASM provision, and onchocerciasis elimination strategies (biannual CDTi and "Slash and Clear" vector control method) have been deployed for over two years. An evaluation is underway to determine the impact of these strategies on the epidemiology of onchocerciasis and epilepsy in Maridi.

Our study has some limitations. There was substantial heterogeneity among the included studies due to the widely different methodologies, and we could not adjust for each subpopulation socio-demographics. We also acknowledge that the REMO maps used to classify the endemicity status for some study sites may not always agree in time and space with the exact communities where the epilepsy surveys were conducted. Notwithstanding, REMO maps provide reliable information regarding the communities' exposure to onchocerciasis at a given time. Also, our analysis did not account for individual delays in the diagnostic and therapeutic management of PWE, which still constitute a major concern in SSA and could have influenced the mortality/fatality rates of the included PWE populations. Furthermore, we did not calculate standardized mortality ratios due to the paucity of demographic data from many sites. We nevertheless report a 4.9-fold relative risk of dying among PWE, confirming that epilepsy significantly contributes to excess mortality in SSA.

Another limitation was the scarcity of data about ivermectin use by PWE in the included reports; in fact, in some endemic sites included in this review, ivermectin treatment had not yet been initiated by the time the epilepsy survey was being conducted. While there is some indication that ivermectin may reduce the frequency of seizures [17,77], empirical evidence about its impact on mortality is still lacking. This aspect deserves to be investigated further. Lastly, the still low number of studies reporting epilepsy mortality in SSA (particularly in onchocerciasis-endemic areas) and the disparities in the mortality data from individual studies limit the generalisability of the pooled findings presented in the review. The fact that pooled estimates and sub-group differences varied significantly in sensitivity analysis suggests that some studies with outlier findings introduced bias in our analysis. This is the case specifically for the pooled analysis comparing epilepsy mortality rate across onchocerciasis high-risk and low-risk sites, whereby only one high-risk site had data (possibly an outlier study).

The numerous limitations of this systematic review warrant that we highlight some gaps and research priorities regarding epilepsy mortality in SSA. While routine mortality surveys are not always feasible, promptly recording all epilepsy deaths in an electronic register would provide timely and precise estimates of epilepsy mortality in a particular place, as it was experimented in the Malawi 2018 study [54]. Similar initiatives have been developed on a global scale [78] and should be utilised by health actors in SSA. In onchocerciasis-endemic settings, community distributors of ivermectin can be trained to identify epilepsy cases in their respective villages [79], and eventually contribute to a community-based surveillance system to identify/report epilepsy deaths. Full demographic information should be obtained from participants in epilepsy studies, including a history of the places of residence (if endemic for onchocerciasis or not) and ivermectin intake; this is particularly useful in hospital-based studies which recruit people from different places who consult at the health facility. Furthermore, epilepsy surveys should be conducted according to international standards to ease comparison [80] and should focus on collecting more precise information about the exact causes of death as well as obtaining all relevant population denominators (total number of epilepsy cases and total population). With the growing evidence on the epidemiological association between onchocerciasis and epilepsy [9], future epilepsy surveys in endemic foci should consider simultaneously assessing the onchocerciasis status at the study sites via simple approaches like the REMO assessment [12] and/or rapid diagnostic testing of Ov16 antibodies in children [81].

In conclusion, our study provides updated numbers regarding the mortality and fatality rates of epilepsy in SSA that suggest that onchocerciasis-endemic areas are most affected. Therefore, strengthening onchocerciasis elimination programmes in communities with a high burden of OAE (including NS) should become a priority. Additional research is required to shed more light on epilepsy-related mortality by seizure types in onchocerciasis-endemic settings and further investigate the prognosis of persons with OAE (particularly NS).

5. Author statements

5.1. Registration of the study protocol

A protocol was drafted to guide the authors' procedures in developing this systematic review, but it was neither registered nor published.

Ethics approval and consent to participate

Not applicable

5.3. Availability of data and materials

The data analysed in this paper are available from the cited references. The Excel sheet containing the extracted data and the analysis codes in R are available from the authors upon reasonable request.

Competing interests

The authors declare no competing interests.

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Conceptualisation by JNSF and RC; review and screening of reports by JNSF, GVC and RC; formal analysis by JNSF; writing – original draft by JNSF; writing – review & editing by JNSF, GVC, L-JA, and RC.

Declaration of Competing Interest

The authors declare no Conflict of Interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2023.07.006.

References

[1] Beghi E. The epidemiology of epilepsy. Neuroepidemiology 2020;54:185–91. https://doi.org/10.1159/000503831.
[2] Ba-Diop A, Marin B, Druet-Cabanac M, Ngoungou EB, Newton CR, Preux P-M. Epidemiology, causes, and treatment of epilepsy in sub-Saharan Africa. Lancet Neurol 2014;13:1029–44. https://doi.org/10.1016/S1474-4422(14)70114-0.
[3] Ngugi AK, Bottomley C, Fegan G, Chengo E, Odhiambo R, Bauni E, et al. Premature mortality in active convulsive epilepsy in rural Kenya: causes and associated factors. Neurology 2014;82:582–9. https://doi.org/10.1212/WNL.0000000000000123.
[4] Wagner RG, Bottomley C, Ngugi AK, Ibinda F, Gómez-Olivé FX, Kahn K, et al. Incidence, remission and mortality of convulsive epilepsy in rural Northeast South Africa. PLoS ONE 2015;10:e0129097. https://doi.org/10.1371/journal.pone.0129097.
[5] Forsgren L, Hauser WA, Olafsson E, Sander JWAS, Sillanpaa M, Tomson T. Mortality of epilepsy in developed countries: a review. Epilepsia 2005;46:18–27. https://doi.org/10.1111/j.1528-1167.2005.00403.x.
[6] Baskind R, Birbeck GL. Epilepsy-associated stigma in sub-Saharan Africa: the social landscape of a disease. Epilepsy Behav 2005;7:68–73. https://doi.org/10.1016/j.yebeh.2005.04.009.
[7] Kija E. Traditional healers and the treatment of epilepsy: an african perspective. Epigraph 2015:17.
[8] Siewe Fodjo JN, Mandro M, Wonya'rossi D, Inaç Y, Ngave F, Lokonda R, et al. Economic burden of epilepsy in rural ituri, democratic republic of congo. EClinicalMedicine 2019;9:60–6. https://doi.org/10.1016/j.eclinm.2019.03.010.
[9] Colebunders R, Njamnshi AK, Menon S, Newton CR, Hotterbeekx A, Preux P-M, et al. *Onchocerca volvulus* and epilepsy: a comprehensive review using the Bradford Hill criteria for causation. PLoS Negl Trop Dis 2021;15:e0008965. https://doi.org/10.1371/journal.pntd.0008965.
[10] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.
[11] Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;158:280. https://doi.org/10.7326/0003-4819-158-4-201302190-00009.
[12] Noma M, Zouré HG, Tekle AH, Enyong PA, Nwoke BE, Remme JH. The geographic distribution of onchocerciasis in the 20 participating countries of the African Programme for Onchocerciasis Control: (1) priority areas for ivermectin treatment. Parasit Vectors 2014;7:325. https://doi.org/10.1186/1756-3305-7-325.
[13] Onchocerciasis | ESPEN n.d. https://espen.afro.who.int/diseases/onchocerciasis (accessed November 7, 2021).
[14] Diop AG, Hesdorffer DC, Logroscino G, Hauser WA. Epilepsy and mortality in Africa: a review of the literature. Epilepsia 2005;46:33–5. https://doi.org/10.1111/j.1528-1167.2005.00405.x.
[15] Van Cutsem G, Siewe Fodjo J, Dekker M, Amaral L-J, Njamnshi A, Colebunders R. Case definitions for onchocerciasis-associated epilepsy and nodding syndrome: a focused review. Seizure 2023. https://doi.org/10.1016/j.seizure.2023.03.024.
[16] Schwarzer G, Carpenter JR, Rücker G. Meta-analysis with R. Cham. Springer International Publishing; 2015. https://doi.org/10.1007/978-3-319-21416-0.
[17] Mandro M, Siewe Fodjo JN, Dusabimana A, Mukendi D, Haesendonckx S, Lokonda R, et al. Single versus multiple dose ivermectin regimen in onchocerciasis-infected persons with epilepsy treated with phenobarbital: a randomized clinical trial in the democratic republic of congo. Pathogens 2020;9:205. https://doi.org/10.3390/pathogens9030205.
[18] Colebunders R, Carter JY, Olore PC, Puok K, Bhattacharyya S, Menon S, et al. High prevalence of onchocerciasis-associated epilepsy in villages in Maridi County, Republic of South Sudan: a community-based survey. Seizure 2018;63:93–101. https://doi.org/10.1016/j.seizure.2018.11.004.
[19] Jada SR, Dusabimana A, Abd-Elfarag G, Okaro S, Brusselaers N, Carter JY, et al. The prevalence of Onchocerciasis-Associated Epilepsy in Mundri West and East counties, South Sudan: a Door-to-Door survey. Pathog Basel Switz 2022;11:396. https://doi.org/10.3390/pathogens11040396.
[20] Tekle-Haimanot R, Forsgren L, Abebe M, Gebre-Mariam A, Heijbel J, Holmgren G, et al. Clinical and electroencephalographic characteristics of epilepsy in rural Ethiopia: a community-based study. Epilepsy Res 1990;7:230–9. https://doi.org/10.1016/0920-1211(90)90020-v.
[21] Coleman R, Loppy L, Walraven G. The treatment gap and primary health care for people with epilepsy in rural Gambia. Bull World Health Organ 2002;80:378–83.
[22] Nkwi PN, Ndonko FT. The epileptic among the Bamileke of Maham in the Nde division, west province of Cameroon. Cult Med Psychiatry 1989;13:437–48. https://doi.org/10.1007/BF00052050.
[23] Ndiaye M, Sene-Diouf F, Diop AG, Ndao AK, Ndiaye MM, Ndiaye IP. [Neuropediatrics: epidemiological features and etiologies at the Dakar neurology service]. Dakar Med 1999;44:162–5.
[24] Ndosi NK, Kisesa AF. Causes of death among mental patients at Muhimbili Medical Centre, Dar es Salaam. East Afr Med J 1997;74:82–4.
[25] Snow RW, Williams RE, Rogers JE, Mung'ala VO, Peshu N. The prevalence of epilepsy among a rural Kenyan population. Its association with premature mortality. Trop Geogr Med 1994;46:175–9.
[26] Kwasa TO. The pattern of neurological disease at Kenyatta National Hospital. East Afr Med J 1992;69:236–9.
[27] Tekle-Haimanot R, Forsgren L, Ekstedt J. Incidence of epilepsy in rural central Ethiopia. Epilepsia 1997;38:541–6. https://doi.org/10.1111/j.1528-1157.1997.tb01138.x.
[28] Ae W. The natural history of untreated epilepsy in a rural community in Africa. Epilepsia 1992;33. https://doi.org/10.1111/j.1528-1157.1992.tb01692.x.
[29] Osuntokun BO, Adeuja AO, Schoenberg BS, Bademosi O, Nottidge VA, Olumide AO, et al. Neurological disorders in Nigerian Africans: a community-based study. Acta Neurol Scand 1987;75. https://doi.org/10.1111/j.1600-0404.1987.tb07883.x.
[30] Levira F., Masanja H., Wagner R.G., Tollman S., Odermatt P., Newton C.R. Excess mortality in active convulsive epilepsy and associated risk factors in Sub-Saharan Africa 2019. https://doi.org/10.2139/ssrn.3378693.
[31] Levira F.W. Epilepsy in sub-Saharan Africa : analysis of excess mortality in epilepsy and associated risk factors from cohort studies. Thesis. University_of_Basel, 2018. https://doi.org/10.5451/unibas-007202588.
[32] Koffi BAA, Kodjo GE, Adodo A, Komi A, Mofou B. [Evolution of the epilepsy treatment gap in 6 peripheral care units in Togo]. Mali Med 2009;24:39–43.
[33] Guinhouya KM, Aboki A, Kombaté D, Kumako V, Apétsé K, Belo M, et al. [The epilepsy treatment gap in six primary care centres in Togo (2007-2009)]. Sante Montrouge Fr 2010;20:93–7. https://doi.org/10.1684/san.2010.0193.
[34] Ngugi AK. Prevalence, incidence and mortality of epilepsy in four health and demographic surveillance sites in sub-Saharan Africa. PhD Thesis. London School of Hygiene & Tropical Medicine; 2012.
[35] Reddy Y, Balakrishna Y, Mubaiwa L. Convulsive status epilepticus in a quaternary hospital paediatric intensive care unit (PICU) in South Africa: an 8 year review. Seizure 2017;51:55–60. https://doi.org/10.1016/j.seizure.2017.07.016.
[36] Mbodj I, Ndiaye M, Sene F, Salif Sow P, Sow HD, Diagana M, et al. [Treatment of status epilepticus in a developing country]. Neurophysiol Clin Clin Neurophysiol 2000;30:165–9. https://doi.org/10.1016/s0987-7053(00)00203-3.
[37] Abuga JA, Kariuki SM, Kinyanjui SM, Boele Van Hensbroek M, Newton CR. Premature mortality in children aged 6-9 years with neurological impairments in rural Kenya: a cohort study. Lancet Glob Health 2019;7:e1728–35. https://doi.org/10.1016/S2214-109X(19)30425-5.

[38] Mukendi D, Lilo Kalo J-R, Mpanya A, Minikulu L, Kayembe T, Lutumba P, et al. Clinical spectrum, etiology, and outcome of neurological disorders in the rural hospital of Mosango, the Democratic Republic of Congo. Am J Trop Med Hyg 2017; 97:1454–60. https://doi.org/10.4269/ajtmh.17-0375.

[39] Garenne M, Kahn K, Tollman S, Gear J. Causes of death in a rural area of South Africa: an international perspective. J Trop Pediatr 2000;46:183–90. https://doi.org/10.1093/tropej/46.3.183.

[40] Valdes Angues R, Suits A, Palmer VS, Okot C, Okot RA, Atonywalo C, et al. A real-time medical cartography of epidemic disease (Nodding syndrome) using village-based lay mHealth reporters. PLoS Negl Trop Dis 2018;12:e0006588. https://doi.org/10.1371/journal.pntd.0006588.

[41] Carpio A, Bharucha NE, Jallon P, Beghi E, Campostrini R, Zorzetto S, et al. Mortality of epilepsy in developing countries. Epilepsia 2005;46(Suppl 11):28–32. https://doi.org/10.1111/j.1528-1167.2005.00404.x.

[42] Siewe Fodjo JN, Remme JHF, Preux P-M, Colebunders R. Meta-analysis of epilepsy prevalence in West Africa and its relationship with onchocerciasis endemicity and control. Int Health 2020;12:192–202. https://doi.org/10.1093/inthealth/ihaa012.

[43] Komlan K, Vossberg PS, Gantin RG, Solim T, Korbmacher F, Banla M, et al. *Onchocerca volvulus* infection and serological prevalence, ocular onchocerciasis and parasite transmission in northern and central Togo after decades of Simulium damnosum s.l. vector control and mass drug administration of ivermectin. PLoS Negl Trop Dis 2018;12:e0006312. https://doi.org/10.1371/journal.pntd.0006312.

[44] Houinato D, Yemadje L-P, Glitho G, Adjien C, Avode G, Druet-Cabanac M, et al. Epidemiology of epilepsy in rural Benin: prevalence, incidence, mortality, and follow-up. Epilepsia 2013;54:757–63. https://doi.org/10.1111/epi.12082.

[45] Jilek-Aall L, Rwiza HT. Prognosis of epilepsy in a rural African community: a 30-year follow-up of 164 patients in an outpatient clinic in rural Tanzania. Epilepsia 1992;33:645–50. https://doi.org/10.1111/j.1528-1157.1992.tb02341.x.

[46] Kaiser C, Asaba G, Kasoro S, Rubaale T, Kabagambe G, Mbabazi M. Mortality from epilepsy in an onchocerciasis-endemic area in West Uganda. Trans R Soc Trop Med Hyg 2007;101:48–55. https://doi.org/10.1016/j.trstmh.2006.06.003.

[47] Kamgno J, Pion SDS, Boussinesq M. Demographic impact of epilepsy in Africa: results of a 10-year cohort study in a rural area of Cameroon. Epilepsia 2003;44: 956–63.

[48] Boussinesq M, Pion SD, Ngangue D, Kamgno J. Relationship between onchocerciasis and epilepsy: a matched case-control study in the Mbam Valley, Republic of Cameroon. Trans R Soc Trop Med Hyg 2002;96:537–41.

[49] Kariuki SM, Chengo E, Ibinda F, Odhiambo R, Etyang A, Ngugi AK, et al. Burden, causes, and outcomes of people with epilepsy admitted to a rural hospital in Kenya. Epilepsia 2015;56:577–84. https://doi.org/10.1111/epi.12935.

[50] Kariuki SM, Ngugi AK, Kombe MZ, Kazungu M, Chengo E, Odhiambo R, et al. Prevalence and mortality of epilepsies with convulsive and non-convulsive seizures in Kilifi, Kenya. Seizure 2021;89:51–5. https://doi.org/10.1016/j.seizure.2021.04.028.

[51] Kompoliti K, Doumbe J, Mapoure YN, Nyinyikua T, Ouyang B, Shah H, et al. Mortality and morbidity among hospitalized adult patients with neurological diseases in Cameroon. J Neurol Sci 2017;381:165–8. https://doi.org/10.1016/j.jns.2017.08.3245.

[52] Levira F, Newton CR, Masanja H, Odermatt P. Mortality of neurological disorders in Tanzania: analysis of baseline data from sample vital registration with verbal autopsy (SAVVY). Glob Health Action 2019;12:1596378. https://doi.org/10.1080/16549716.2019.1596378.

[53] Mosser P, Schmutzhard E, Winkler AS. The pattern of epileptic seizures in rural Tanzania. J Neurol Sci 2007;258:33–8. https://doi.org/10.1016/j.jns.2007.02.015.

[54] Munthali CVT, Kang'oma S, Nasasara K, Zaina LM, Lupafya C, Mziya J, et al. Can a village headman use an electronic village register and a simplified community-based verbal autopsy tool to record numbers and causes of death in rural Malawi? Front Public Health 2018;6:246. https://doi.org/10.3389/fpubh.2018.00246.

[55] Kamgno J, Bouchité B, Baldet T, Folefack G, Godin C, Boussinesq M. [Study of the distribution of human filariasis in West Province of Cameroon]. Bull Soc Pathol Exot 1990 1997;90:327–30.

[56] Otubogun FM. Neurological morbidity and mortality in a neurological low-resource setting: a 2-year audit of a Nigerian hospital. Neurologist 2020;25:93–6. https://doi.org/10.1097/NRL.0000000000000279.

[57] Sarfo FS, Awuah DO, Nkyi C, Akassi J, Opare-Sem OK, Ovbiagele B. Recent patterns and predictors of neurological mortality among hospitalized patients in central Ghana. J Neurol Sci 2016;363:217–24. https://doi.org/10.1016/j.jns.2016.02.041.

[58] Biritwum N-K, de Souza DK, Asiedu O, Marfo B, Amazigo UV, Gyapong JO. Onchocerciasis control in Ghana (1974–2016). Parasit Vectors 2021;14:3. https://doi.org/10.1186/s13071-020-04507-2.

[59] Sebera F, Uwacu BH, Nsanzabaganwa W, Umwiringirwa J, Dedeken P, Teuwen DE, et al. Mortality of all causes and sudden unexplained death in epilepsy (SUDEP) in a cohort of 235 persons living with epilepsy in Rwanda using WHO verbal autopsy questionnaire. Epilepsy Behav Rep 2020;14:100383. https://doi.org/10.1016/j.ebr.2020.100383.

[60] von Gaudecker JR, Oduor C, Ofner S, Oyungu E, Said J, Buelow J. Pattern and frequency of neurological and neurosurgical care of adult inpatients and outpatients at a tertiary referral hospital in Kenya. ENeurologicalSci 2020;21: 100286. https://doi.org/10.1016/j.ensci.2020.100286.

[61] Wroe EB, Kalanga N, Dunbar EL, Nazimera L, Price NF, Shah A, et al. Expanding access to non-communicable disease care in rural Malawi: outcomes from a retrospective cohort in an integrated NCD-HIV model. BMJ Open 2020;10: e036836. https://doi.org/10.1136/bmjopen-2020-036836.

[62] Boakye D, Tallant J, Adjami A, Moussa S, Tekle A, Robalo M, et al. Refocusing vector assessment towards the elimination of onchocerciasis from Africa: a review of the current status in selected countries. Int Health 2018;10:i27–32. https://doi.org/10.1093/inthealth/ihx066.

[63] Wroe EB, Mailosi B, Price N, Kachimanga C, Shah A, Kalanga N, et al. Economic evaluation of integrated services for non-communicable diseases and HIV: costs and client outcomes in rural Malawi. BMJ Open 2022;12:e063701. https://doi.org/10.1136/bmjopen-2022-063701.

[64] Levira F, Thurman DJ, Sander JW, Hauser WA, Hesdorffer DC, Masanja H, et al. Premature mortality of epilepsy in low- and middle-income countries: a systematic review from the mortality task force of the international league against epilepsy. Epilepsia 2017;58:6–16. https://doi.org/10.1111/epi.13603.

[65] Feigin VL, Abajobir AA, Abate KH, Abd-Allah F, Abdulle AM, Abera SF, et al. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the global burden of disease study 2015. Lancet Neurol 2017;16:877–97. https://doi.org/10.1016/S1474-4422(17)30299-5.

[66] Owolabi LF, Owolabi SD, Adamu B, Jibo AM, Alhaji ID. Epilepsy treatment gap in Sub-Saharan Africa: meta-analysis of community-based studies. Acta Neurol Scand 2020;142:3–13. https://doi.org/10.1111/ane.13246.

[67] Gumisiriza N, Mubiru F, Siewe Fodjo JN, Mbonye Kayitale M, Hotterbeekx A, Idro R, et al. Prevalence and incidence of nodding syndrome and other forms of epilepsy in onchocerciasis-endemic areas in northern Uganda after the implementation of onchocerciasis control measures. Infect Dis Poverty 2020;9:12. https://doi.org/10.1186/s40249-020-0628-3.

[68] Gumisiriza N, Kaiser C, Asaba G, Onen H, Mubiru F, Kisembo D, et al. Changes in epilepsy burden after onchocerciasis elimination in a hyperendemic focus of western Uganda: a comparison of two population-based, cross-sectional studies. Lancet Infect Dis 2020;20:1315–23. https://doi.org/10.1016/S1473-3099(20)30122-5.

[69] Walker M, Little MP, Wagner KS, Soumbey-Alley EW, Boatin BA, Basáñez M-G. Density-dependent mortality of the human host in onchocerciasis: relationships between microfilarial load and excess mortality. PLoS Negl Trop Dis 2012;6:e1578. https://doi.org/10.1371/journal.pntd.0001578.

[70] Abd-Elfarag G, Carter JY, Raimon S, Sebit W, Suliman A, Fodjo JNS, et al. Persons with onchocerciasis-associated epilepsy and nodding seizures have a more severe form of epilepsy with more cognitive impairment and higher levels of *Onchocerca volvulus* infection. Epileptic Disord Int Epilepsy J Videotape 2020;22:301–8. https://doi.org/10.1684/epd.2020.1164.

[71] Colebunders R, Abd-Elfarag G, Carter JY, Olore PC, Puok K, Menon S, et al. Clinical characteristics of onchocerciasis-associated epilepsy in villages in Maridi County, Republic of South Sudan. Seizure 2018;62:108–15. https://doi.org/10.1016/j.seizure.2018.10.004.

[72] Mu J, Liu L, Zhang Q, Si Y, Hu J, Fang J, et al. Causes of death among people with convulsive epilepsy in rural West China: a prospective study. Neurology 2011;77: 132–7. https://doi.org/10.1212/WNL.0b013e318223c784.

[73] Wilmshurst JM, Kakooza-Mwesige A, Newton CR. The challenges of managing children with Epilepsy in Africa. Semin Pediatr Neurol 2014;21:36–41. https://doi.org/10.1016/j.spen.2014.01.005.

[74] World Health Organization. Epilepsy Fact Sheet 2023. https://www.who.int/news-room/fact-sheets/detail/epilepsy (accessed March 22, 2023).

[75] Siewe Fodjo JN, Dekker MCJ, Idro R, Mandro MN, Preux P-M, Njamnshi AK, et al. Comprehensive management of epilepsy in onchocerciasis-endemic areas: lessons learnt from community-based surveys. Infect Dis Poverty 2019;8. https://doi.org/10.1186/s40249-019-0523-y.

[76] Lakwo TL, Raimon S, Tionga M, Siewe Fodjo JN, Alinda P, Sebit WJ, et al. The role of the Maridi Dam in causing an onchocerciasis-associated epilepsy epidemic in Maridi, South Sudan: an epidemiological, sociological, and entomological study. Pathogens 2020;9:315. https://doi.org/10.3390/pathogens9040315.

[77] Kipp W, Burnham G, Kamugisha J. Improvement in seizures after ivermectin. Lancet Lond Engl 1992;340:789–90.

[78] SUDEP Action. Epilepsy deaths register - making every epilepsy death count. Epilepsy Deaths Regist n.d. https://epilepsydeathsregister.org/ (accessed June 17, 2023).

[79] Kamgno J, Tchatchueng-Mbougua JB, Nana-Djeunga HC, Esso L, Zouré HG, Mackenzie CD, et al. Community-based door to door census of suspected people living with epilepsy: empowering community drug distributors to improve the provision of care to rural communities in Cameroon. BMC Public Health 2020;20: 871. https://doi.org/10.1186/s12889-020-08997-8.

[80] Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 2011;52:2–26. https://doi.org/10.1111/j.1528-1167.2011.03121.x.

[81] World Health Organization. Guidelines for stopping mass drug administration and verifying elimination of human onchocerciasis: criteria and procedures. World Health Organization; 2016. https://apps.who.int/iris/handle/10665/204180 (accessed June 17, 2023).